

THE PSYCHIATRY LETTER

Welcome to our inaugural issue

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For two decades, I've conducted research studies, published in the scientific journals, and written academic and non-academic books. In giving seminars, I've found that many of my clinical colleagues don't have the time to follow journal articles or books, or don't feel qualified to judge on their scientific quality or relevance. Newsletters are a good way to solve these problems, so they ask me which newsletters I'd recommend.

I never could recommend any.

Other newsletters exist, but they aren't written by expert researchers with active clinical practices. They summarize studies but don't provide critiques that are based on well-explained scientific principles. They may criticize the pharmaceutical industry - or not - but they do so simplistically. They accept conventional wisdom, and aren't willing to question the status quo.

That's why we started *The Psychiatry Letter*.

The main columns in each issue are described in the Table of Contents. We'll also have additional material, like guest articles and expert interviews. For Curbside Consults, we will help you think about your cases and answer clinical questions. Please suggest special article topics, tell us if you'd like more or less content, and we'll welcome the feedback.

I'd like to thank Dr. Robert Guerette from the New England Educational Institute, whose courses were the origin for this newsletter idea, and who helped me think it through.

As one of our first subscribers, you are our special inaugural audience, and we appreciate your support. If you like what you see, let your colleagues and friends know.

Let's change psychiatry together, one month at a time.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: Light precautions - Managing winter depression

A few simple behaviors – like adjusting bedroom shades – can make a big difference.

Persons with mood illnesses are more sensitive to light than others (see the current article of the month below): Too much light causes manic symptoms, too little light causes depressive symptoms. In the spring and summer there is too much – in the fall and winter not enough – light. You thus need to modulate light exposure to avoid causing manic symptoms in spring/summer and depressive symptoms in fall/winter. *Mood episodes go together; so if you want to prevent winter depression, you should also try to prevent summer mania.*

For the fall-winter (September-January):

In winter, there is not enough light. Therefore you will sleep in the morning longer than you should, and that will throw off your circadian rhythms. You therefore need to increase your light exposure.

- *Keep shades and curtains open at night, to maximize morning light exposure. This is the simplest thing you can do to reduce risk of winter depression.*

- Don't wear sunglasses in routine activity, or use them less than you normally would (or limit only to driving). Go for walks around noontime, without sunglasses, for up to an hour.

- Go to bed at a regular time at night. Wake up at a regular time in the morning; use an alarm.

For light therapy:

Plan on spending \$100-200. There is no need to spend more. The dose is 10,000 lux (most lightboxes are at that dose). There are many companies – the internet engines will help you.

Use indirect light; do not look into the light box directly (treat it like the sun).

Have it on the table while you read or eat in the morning. Dose is 30 minutes, on average, as long as depression persists. Use the lightbox daily initially, and then reduce use to every other day for prevention. *Use the lightbox in the morning (before 10 AM): remember you're trying to replace the morning sunlight which declines in winter.*

For the spring/summer (March-August): In summer, there's too much light; so you'll sleep in the morning less than you should, throwing off circadian rhythms. To decrease light exposure:

- *Wear sunglasses at all times.*
- *Wear an eyemask to sleep, or get room-darkening shades.*
- *Close curtains at night, to minimize morning light.*
- *Go to bed at a regular time at night. Wake up at a regular time in the morning, but not early.*

The PL Bottom Line

- Lift the shades in the winter
- Pull them down in the spring and summer.
- Use an eyemask (or get room darkening shades) in spring/summer.
- If still depressed in winter despite raising the shades, use a light box in the morning.

Stay tuned for next month's Special article: The use of antipsychotics in bipolar depression

Current study of the month: *Can sunlight cause suicide?*

Vyssoki B, Kapusta ND, Praschak-Rieder N, Dorffner G, Willeit M.

Direct Effect of Sunshine on Suicide. JAMA Psychiatry. 2014;71(11):1231-1237

Too much sun may be harmful for your (mental) health.

So you think good weather makes you feel good? That's what most of us think. Let's go to Florida or California, especially in the winter. The warm weather is the solution for the winter blues. Well, this is partly true. But there is a dark side to this sunny truth.

"SAD"

The whole concept of "seasonal affective disorder" is misunderstood seriously. People act like "SAD" is a new and separate condition from bipolar or unipolar mood illness. It really means *seasonality in affective disorder*.

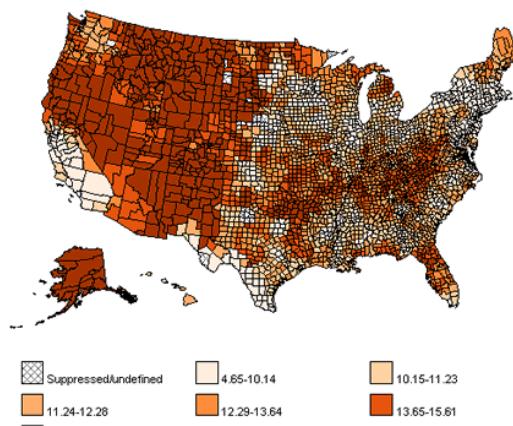
This idea has been well described for over a hundred years: you find it in Kraepelin's textbook, where he described clearly seasonal variation in mood, with more depression in the winter and more mania in the spring and summer.

This seasonality is *not* because of the temperature: it's not cold that makes you sad and heat that makes you happy. It's about light. Too little light triggers depression; too much light triggers mania. People with manic-depression are especially sensitive to light, and thus more likely to have these seasonal mood episodes. In fact, in the first modern studies of "SAD" in the 1980s, winter depression was accompanied by spring hypomania in 92% of

subjects. In other words, "SAD" was the same thing as seasonality in bipolar type II illness.

Don't go West, young man

Now to sunlight causing suicide: For over a hundred years, it has been noticed that the highest suicide rates state-by-state in the US occur in the sunny states of the mountain West and Southwest. Among those states, the highest rates are in the sunniest states. Within states, like California, the highest suicide rates are in the sunniest parts, like San Diego County. These elevated rates have been high for a century, despite major changes in culture and economy (cowboys being replaced by techies); guns are common in the West, and the populations are sparse in

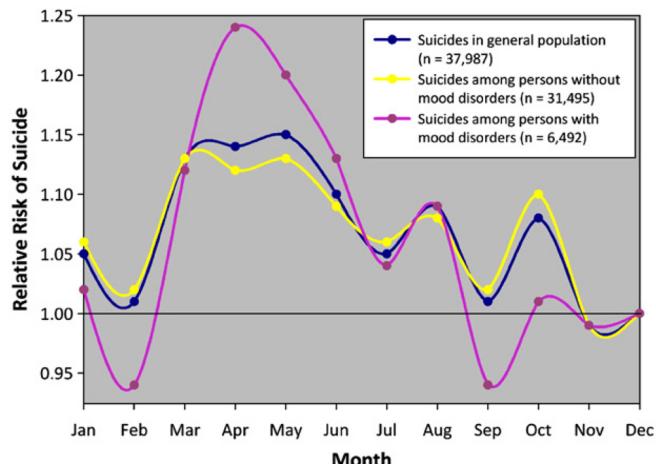


some of those states, with low rates of psychiatrists per capita. Many have raised these other factors are reasons for higher suicide rates, and they certainly have a role.

April is the cruellest month

T. S. Eliot proved it; Kraepelin proved it. In the Northern hemisphere, April has the highest rate of suicide, with a major peak, because, he believed, patient

experience a manic switch from depression to a mixed state as the spring light begins to increase after a long period of low light during wintertime. Kraepelin's classic charts have been confirmed in



modern times, such as in the Danish study below. The effect of seasonality on suicide is pronounced especially in persons with mood illnesses.

The current study of the month (Vysokki et al, JAMA Psychiatry, 2014) confirms the theory of

sunlight increasing the risk of suicide. All suicides in Austria from 1970 to 2014 were studied: 69,462 cases. Daily duration of sunshine was compared to daily number of suicide in different Austrian regions. A moderately strong correlation was found ($r=0.49$). After controlling for the season, the correlation was still there but fell to $r=0.03$, which is a small effect.

The PL Bottom Line

- In sum, the season of the year is a major predictor of suicide (spring being the worst)
- Within any season, sunlight itself has a small but direct effect, which is still present after controlling for other potential clinical risk factors for suicide.
- We all love the sun and its warmth. It feels good. But for people with mood illnesses, there is danger lurking inside those beautiful sunny days.

Further reading: To learn more about high suicide rates in the American West over the past century, a classic source is Howard Kushner, American Suicide, Rutgers University Press, 1991. For the original SAD paper where almost all 29 subjects had bipolar illness: NE Rosenthal et al, Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry. 1984 Jan;41(1):72-80. US suicide map: CDC age-adjusted suicide rates per 100,000 population, by county, 2000–2006. Danish study: J-M Woo et al, Seasonality of suicidal behavior. Int. J. Environ. Res. Public Health 2012, 9(2), 531-547

Clinical tip of the month: Give lithium once daily at night, not multiple times per day.

Most of clinical practice is based on tradition, without a basis in anything but habit. This seems to be the case with the common practice of giving lithium two or even three times daily. There is no basis for giving lithium more than once daily based on its half-life, which is about 24 hours. Further, multiple long-term studies show that there is more long-term kidney impairment with multiple daily dosing, as opposed to once daily. Given at night, many of lithium's short-term cognitive side effects are also minimized when the level peaks after being taken, since people will be asleep. It is well-known that once daily dosing of any drug enhances medication compliance, which is especially important in psychiatric conditions like bipolar illness, where patients often have poor insight or other reasons to avoid or stop taking medications. There is no reason to make an already complex disease more difficult to treat, especially when doing so causes more medical complications. *Do yourself and your patients a favor: Just prescribe lithium once per day!* (Singh LK et al. Improving tolerability of lithium with a once-daily dosing schedule. Am J Ther. 2011;18:288-91)

Classic study of the month: Four diagnostic validators you should use

Eli Robins and Samuel Guze. Establishment of Diagnostic Validity in Psychiatric Illness: Its Application to Schizophrenia. American Journal of Psychiatry. Volume 126 Issue 7, January 1970, pp. 983-987

Relying on symptoms is not enough, no matter what DSM says.

A patient has pneumonia with cough and headache. Another patient has pneumonia without a cough and headache. Are these two different "disorders"? No, you'd say. But why not? Because the symptoms of cough and headache don't represent a different disease.

A patient has depression with mania. Another has depression without mania. Are these two different "disorders". Yes, you'd say. But why? Because mania is a different set of symptoms than depression, you might say. But cough and headache are symptoms, which we said did not represent a different disease.

That's the intuition behind the concept of diagnostic validators. It's not enough to say that symptoms differ and thus we have different "disorders". You have to show that those different symptoms represent some kind of different conditions or diseases. How do you do so? Not by simply referring back to the different symptoms: that would be tautologous. You have to have some different line of evidence, separate from symptoms, that represents a different illness. In the case of pneumonia, you have access to pathology: tests can show evidence of inflammation in the lung, whether or not you have a cough and fever. So those symptoms don't represent a different disease.

In the case of psychiatry, we don't have access to pathology (usually). So what should the independent lines of evidence be?

A diagnostic revolution

This is where this classic article from 1970 revolutionized psychiatry. Eli Robins, the chairman at the Washington University in St Louis, had trained at Massachusetts General Hospital (MGH) in Boston. But in that era, the major US cities were dominated by psychoanalytic thinking. Robins was influenced by Emil Kraepelin, the late 19th century German psychiatrist who taught that "diagnosis is prognosis", that the course of illness tells you which symptoms represent different diseases.

Robins left Boston to go to the smaller city of St Louis, and from there, he trained a series of researchers who produced the change in US psychiatry which led to the third edition of DSM (DSM-III) in 1980 - a change much needed at that time, but which, it may be questioned, has hardened into the new credo of DSM-IV and 5.

With his colleague Samuel Guze, Robins articulated four other diagnostic validators that, along with symptoms, should be used to identify if groups of patients differ from each other enough to justify seeing them as having different diagnoses (their article focused on schizophrenia, but they later applied these principles to all diagnoses). Those validators are shown in the box above. The most important is *course of illness*, Kraepelin's key criterion. Some conditions are chronic, and symptoms are present all the time (like schizophrenia); others are episodic, with symptoms coming and going (like manic-

Modified Robins and Guze Diagnostic Validators

1. Symptoms
2. Course of illness
3. Genetics
4. Treatment effects

depression). The next most important validator is *genetics*: if diagnoses are genetic, you'll find evidence in family members. Next are laboratory tests or biological markers (which are useful in research but not yet in clinical practice, hence we haven't included them in the modified criteria in the box above). Robins and Guze also referred to "delimitation from other disorders", which meant that symptoms were specific to one condition rather than another. This is not always the case, since many symptoms, like anxiety, can occur in many conditions. Since that classic study, instead of delimitation, the diagnostic validator of *treatment effects* has been used, although it should be used cautiously, since many drugs are nonspecific in effect, and some, like amphetamines, are even effective in normal individuals. Treatment effects can also be seen as a proxy for biological markers, but only if treatment effects are specific to an illness (like antidepressant-induced mania).

DSM: Only symptoms

Unfortunately, these diagnostic validators have been suppressed by the evolution of DSM. Originally, these diagnostic validators were the basis for scientific justification for diagnoses in psychiatric research, leading to the original Research Diagnostic Criteria (RDC) that Robins' St. Louis group created. The RDC identified about two dozen scientifically valid diagnoses. DSM-III started with those diagnoses, and added about 270 others. In almost all cases, although the other diagnostic validators were used to justify diagnoses, only symptoms were used in the

"In almost all cases, although the other diagnostic validators were used to justify diagnoses, only symptoms were used in the DSM criteria definitions."

DSM criteria definitions (an exception is schizophrenia, where there is a course criterion of 6 months or longer for psychosis). Now we have about 400 diagnoses in DSM-5, and clinicians are used to only looking at symptoms for definitions. This leads to the perennial arguments: Is the attentional problem ADD or bipolar disorder? Is the anxiety part of major depressive disorder or generalized anxiety disorder? Is the sexual impulsivity mania or a paraphilia or borderline personality? These debates will never end as long as they are conducted on the single dimension of symptoms.

This classic paper reminds us that symptoms only go so far: like cough and fever, we need to look elsewhere to know which symptoms matter diagnostically and which don't. We need to look to course of illness, genetics, and treatment effects.

We'll discuss these diagnostic validators repeatedly throughout clinical discussions of differential diagnosis in PL, so we encourage readers to take the time to read this classic article, and learn to use these four modified diagnostic validators in clinical practice.

The PL Bottom Line

- In a diagnostic dilemma, stop assessing symptoms and turn to the other three diagnostic validators: course of illness, then genetics, then treatment effects.
- Look where those other validators direct you; they matter as much as, if not more than, symptoms to clarify the real diagnosis.

PL Reflection:

Starting with a mistake, a remorseless logic ends in Bedlam.

John Maynard Keynes

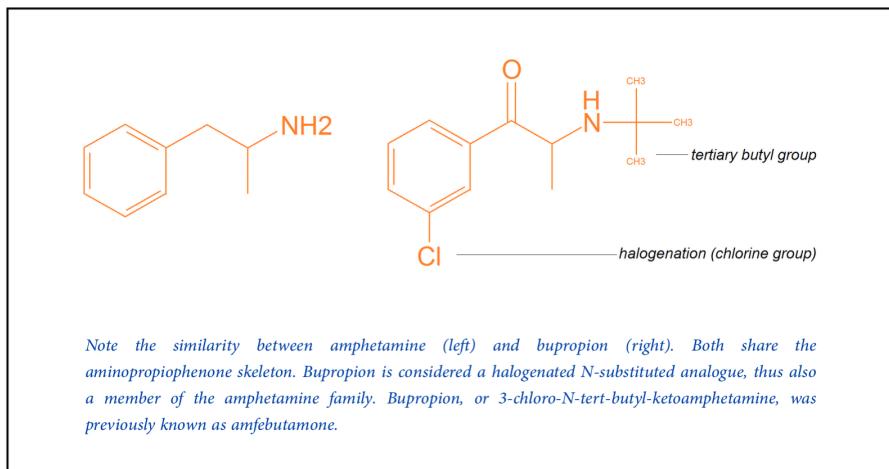
Drug of the Month: *Bupropion (Wellbutrin)*

Surprise: It's just another (mild) amphetamine

This drug has been with us over 25 years now, yet it is still misunderstood. Bupropion was introduced to the US market in 1988, before fluoxetine (Prozac), believe it or not. It was the first of the new generation of post-tricyclic antidepressants; instead of becoming the blockbuster that would be Prozac, it had some bad luck. A few cases of seizures occurred in patients hospitalized at McLean Hospital, and the makers of Prozac used those cases to beat bupropion into submission. Clinicians turned to the new post-TCA agents mainly for safety reasons, not having to worry about overdose toxicity or cardiac arrhythmias. Prozac opened the way for the antidepressant era as other SRIs (serotonin reuptake inhibitors) quickly followed in the early 1990s. For a number of years, clinicians didn't realize that SRIs produced sexual dysfunction, and by the time they found out, the use of SRIs had already become well-established.

Two decades later, after all these agents became generic and the pharmaceutical marketing wars had ended, clinicians can look at these agents more objectively, and bupropion is making a comeback.

We now know more about its benefits: no sexual dysfunction (in fact it enhances sexual drive);



weight loss; and reduction of seizure risk with the slow release formulation (Wellbutrin SR, which is now generic in the US; the seizure rate is 0.1% with wellbutrin SR, which is equivalent to SRIs, as opposed to 0.4% with immediate release bupropion.) Some studies also find low manic switch rates.

Fast Facts: Bupropion

Typical effective dose: 100–300 mg/d (SR formulation, maximum 400 mg/d)

Biological mechanism: Mild dopamine/norepinephrine agonism

Typical side effects: Anxiety, insomnia

Less common but important side effects: Mania, seizures

Clinically proven efficacy: mild/moderate unipolar depressive episodes

Clinically proven inefficacy: bipolar depression

Other proven uses: weight loss, sexual dysfunction, smoking cessation

Bupropion is hot again, too late for its makers to make profits, but not too late to impact many patients. But what many clinicians don't realize is what bupropion is. If you ask most clinicians and

researchers about its mechanisms, they will say it has mild dopamine agonism (also mild norepinephrine agonism). Okay, but what kind of

drug is it? It usually isn't included in any drug class, like SRIs. How does it produce its mild dopamine/norepinephrine agonism?

This mystery shouldn't have persisted for two decades. The solution to the saga of bupropion is: It's just another amphetamine, as is visible in its chemical structure. No wonder it enhances libido and leads to weight loss!

Clinical efficacy and inefficacy

It's just as important to know when a drug doesn't work as when it works. Thus, as noted in the Fast Facts box, clinicians should realize that bupropion has been proven ineffective in bipolar depression, in contrast to unipolar depression (major depressive disorder). In bipolar depression, bupropion was equivalent to placebo, when added to standard mood stabilizers (G Sachs et al, NEJM, 2007, 356:1711-22). In other words it did not improve depression at all. Many researchers emphasize the fact that bupropion did not cause mania more than placebo in that study either, but this is not a justification to use a drug that provides no clinical benefits for depressive symptoms in bipolar illness. Further, although the medium doses used there did not cause more mania than placebo, this does not mean that

bupropion will never cause mania. In fact, like all antidepressants, it can cause mania at a high enough dose. In some who are sensitive to it, bupropion will cause mania even at low doses.

Biological mechanism

This mild dopamine agonism, it should be noted, is less than occurs with sertraline (E Richelson, Mayo Clin Proc, 2001, 76:511-527). This may be why bupropion has avoided being labeled a controlled substance. Yet the drug is still a street drug of value, often ground up and snorted for its addictive properties. The PL impression is that for severe depressive illness of any variety, bupropion is a rather ineffective agent.

The PL Bottom Line

- Bupropion is a mild amphetamine
- It is not effective in bipolar depression
- It does not seem effective in severe depression of any kind
- Its many benefits are amphetamine-like, and it is abused by some persons

Stay tuned for the next drug of the month: Quetiapine

Psychopathology: Defining psychosis

Delusions aren't all-or-nothing phenomena.

Clinicians sometimes use the word "psychotic" loosely. But it is better applied to specific kinds of abnormality: delusions and/or hallucinations. Hallucinations are generally defined as false sensory impressions, like hearing voices. Traditionally, auditory hallucinations are seen as occurring more in psychiatric illness, and visual hallucinations occur more in neurological illness;

but both kinds can occur in both types of illness. Olfactory hallucinations tend to be neurological.

Delusions are more difficult to define. The traditional definition is a fixed, false belief, held against incontrovertible evidence to the contrary. In fact, delusions can be flexible (present some days, and not other days), true (the Othello syndrome: one has a delusion that one's spouse is cheating based on irrelevant reasoning, but in fact

the spouse is cheating), and evidence can be quite strong against a belief despite its truth (e.g., the world seemed flat to almost everyone for a very long time). None of these features, by themselves, are sufficient to qualify for a definition of delusion. But together, the more such features are present (fixity, falsity, evidence against a belief), the more likely a delusion is present. Illogical reasoning is another feature that adds to the weight of delusionality.

Experimental psychology research has shown that all these features are present to some extent in normal non-psychotic individuals (fixity, falsity, illogicality). Delusions are extremes on the dimension of normal to abnormal thinking; they are not completely different psychological experiences from what is normal.

So what is psychosis? It's an extreme of normal thinking where we view an individual as sufficiently out of touch with reality to define delusions or hallucinations. *Many clinicians tend to assume that psychosis is an all-or-nothing phenomenon, contrasting with normality, which is completely different. In fact, psychosis is a more-or-less phenomenon, representing more abnormal thinking than we find in non-psychotic persons.* Since we are all a little abnormal in our thinking, we should be careful when diagnosis psychosis. Our belief that psychosis is present could be false.

For further reading: We recommend a website set up with video and audioconferences of Havens' lectures: www.lestonthavensmd.com as well as L Havens et al, Soundings: A psychological equivalent of medical percussion, Harvard Review of Psychiatry, 2001, 9:147-157

Psychotherapy/interviewing: Don't ask questions

The psychiatrist Leston Havens, a classic teacher of psychotherapy and interviewing at Harvard in

the last half century, had a trademark idea: *The best way to interview patients is to avoid asking questions.* When you ask questions, he'd say, patients avoid giving answers. The more sensitive the question, the more likely you'll get a false, or at least distorted, answer. In early clinical interviews, questions about suicidality are among those that are most likely to lead to misinformation. "Do you think about not being alive?" "No" replies the patient, thinking that if he says yes, he'll get hospitalized. Instead, Havens recommended making statements, not asking questions, and seeing how patients respond. The introductory phrase "I suppose" or "I guess" or "I imagine" is often helpful: "I suppose you sometimes think about not being alive these days." The patient, caught off-guard, might reply, verbally or nonverbally, in a way that raises clinical suspicion: "Not really. What do you mean?" Notice how now the patient is asking the questions, allowing the clinician to decide how to respond. "I suppose you never think about being dead then." Notice how the clinician now has gone to the opposite extreme, to see how the patient responds. "Well, yeah," the patient might say unconvincingly. "Why would you want to be dead? Everything is perfect," the clinician could say, ironically, when it's obvious everything isn't perfect. He thus gives the patient permission to express suicidality as if it makes sense, rather than seeing it as something to hide. This kind of exchange, not a direct yes-or-no question and answer session, is more likely to get at the truth on sensitive topics.

Case of the month:

Your treatment is only as good as your diagnosis

An 80 year-old male seeks consultation for severe treatment-refractory depression. He had been depressed for 7 months, without improvement despite treatment with venlafaxine (Effexor) 150

mg/d for 6 weeks, which was then changed to citalopram (Celexa) 50 mg/d for 9 weeks, which made him more depressed and suicidal. Then olanzapine (Zyprexa) was added to citalopram, up to 15 mg/d, without benefit. Fluoxetine was increased up to 80 mg/d plus olanzapine, and valproate (Depakote, Epival) was added at the same time at 500 mg/d; these last changes made him feel even worse, and valproate was switched to risperidone. At consultation, he was taking fluoxetine (Prozac) 80 mg/d, olanzapine 15 mg/d, and risperidone 3 mg/d, along with multiple cardiological medications.

He complained greatly about anxiety and indecision. "I have a lot of regrets; they bother me a lot. My worry has a basis, but it is overblown." He had a great deal of nihilistic thinking; family reported: "He worries about the least likely thing that could happen." He couldn't function at work.

He had clear discrete depressive episodes in 1968 (his first episode, received ECT), 1975 (recovered in 3-4 months), 1996 (recovered in 3-6 months), 2001 (lasted longer, about 8-9 months, saw a consultant, who diagnosed bipolar illness but didn't stop antidepressants), and the current episode (2013). Unlike prior episodes, there wasn't a major psychosocial trigger for his last episode. In between episodes, his family reported that he was "perfectly normal: very social, very gregarious" and functional as a prominent lawyer.

No prior psychiatrist except for one consultant had observed that each of the depressive episodes described above had been preceded by a phase of 5-6 months of elevation. According to family: "He was a bit high, even more outgoing, would go and visit so many relatives when he went out for an errand that he'd get distracted, would sleep little, and would read furiously about all different kinds of topics that have nothing to do with his

field. He had a lot of energy, would get up very early, and would be very active."

He had no past suicide attempts or psychiatric hospitalizations, had a medical history of hypertension and coronary artery disease, and a normal head MRI. He had no drug allergies and no substance abuse history. He had no history of trauma or abuse, had been married for 55 years, had four adult children, and worked as a lawyer.

Medication trials included multiple antidepressants (most of the serotonin reuptake inhibitors), multiple neuroleptics, but only one mood stabilizer (recent treatment with low-dose valproate).

In family history, his brother was diagnosed with "schizophrenia" 40 years ago: "He was quite lively, became obsessed with reading all medical books", and was treated with antipsychotics. This brother also had severe depressive episodes with marked loss of appetite and a catatonic state. Bipolar disorder was diagnosed in two second cousins, treated with lithium. A niece committed suicide.

The PL diagnosis and clinical impression

The PL diagnosis was bipolar disorder, type II, currently depressed. The diagnosis of bipolar illness, is clear, as previously noted by another consultant. Unfortunately, this diagnosis had not been taken seriously, and thus had not been treated with the appropriate treatment, namely, an adequate dose of a mood stabilizer *without antidepressants, which destabilize bipolar illness and counteract the benefits of mood stabilizers.* (For further explanation of this idea, see the PL website).

Prior evaluations missed the fact that each depressive episode is preceded by a clear hypomanic episode that lasts months. These hypomanic episodes are not questionable and are not brief. They exist, yet he has been treated as if

they didn't exist. Prior psychiatrists either didn't make the bipolar diagnosis, or saw it as therapeutically unimportant. The consultant who had diagnosed bipolar illness made no effort to stop antidepressants or recommend mood stabilizers. He even focused instead on psychosocial explanations, such as Erikson's stage of "generativity versus despair" in old age. (How this explanation would explain the patient's depressive episodes in his 20s, 30s, and 40s was left unexplained).

Prior treatment had focused on treating each acute depressive episode with antidepressant and antipsychotic combinations, rather than trying to prevent those depressive episodes with mood stabilizers. Divalproex had been used recently for his acute bipolar depression, but at a subtherapeutic dose of 500 mg/d, added to very high dose fluoxetine. If antidepressants counteract the benefits of mood stabilizers, that trial would not have been effective. This case is a good example of how antidepressants simply can be ineffective for acute bipolar depression, as found in the largest randomized clinical trials.

Hence the mistaken label of "treatment-refractory depression": *the depression isn't refractory when antidepressants have been proven ineffective for it.*

When the patient improved in the past, it likely was not because of antidepressant treatment, but rather as part of the natural course of bipolar illness, namely that each depressive episode tends to last a certain amount of time (usually about 3-6 months) and then resolves on its own.

When ineffective treatments are multiplied (such as combining olanzapine and risperidone) and

"Prior treatment had focused on treating each acute depressive episode with antidepressant and antipsychotic combinations, rather than trying to prevent those depressive episodes with mood stabilizers."

increased to maximal doses (such as 80 mg/d of fluoxetine), in an 80-year-old person, with coronary artery disease, then the likelihood of harm is magnified. These doses are meant for non-elderly adults. In elderly persons, it is a maxim that doses should be halved, because

decreased renal excretion over time leads to lengthening of drug half-lives. Thus 80 mg/d of fluoxetine in a nearly 80 year old gentleman is quite excessive, and

likely to be causing important physical harm. It is especially notable that fluoxetine is a very potent inhibitor of drug metabolism in the liver. Thus, this very high dose is also markedly increasing doses of almost all other medications, including olanzapine and risperidone, which would notably increase their side effects, including parkinsonian tremor and rigidity, akathisia, and - perhaps most importantly - diabetes and cardiovascular risks (hyperlipidemia and hypertension).

For all these reasons, the patient's medications were ineffective, and at the very high doses given, posed major medical risks to him, and were likely causing, or would soon cause, serious medical harm.

"The depression isn't refractory when antidepressants have been proven ineffective for it."

The PL treatment

Fluoxetine has the advantage of less serotonin withdrawal than other serotonin reuptake inhibitors (SRIs). It was tapered off over 2 weeks (40 mg/d for 1 week, then 20 mg/d for 1 week, then stop). The patient had no SRI withdrawal. Risperidone was discontinued immediately and olanzapine was

tapered off (10 mg/d for 1 week, then 5 mg/d for 1 week, then stop).

One week after the initial visit, a titration of lamotrigine was initiated, reaching a target dose of 100 mg/d over another month (25 mg/d for 1 week, then 50 mg/d for 1 week, then 75 mg/d for 1 week, then 100 mg/d.) Lorazepam 1 mg twice daily was given for anxiety and SRI withdrawal.

Two months later, the patient had improved moderately on lamotrigine 100 mg/d, and lorazepam 1 mg twice daily. Depressive and anxiety symptoms were still present, but somewhat less than previously.

The PL Bottom Line

- This apparent treatment-resistant depression is really mistreated bipolar depression - a common scenario.
- Very high dose fluoxetine with high dose olanzapine plus risperidone proved ineffective, and was no better than lamotrigine alone.
- At least we were able to get the patient off medically harmful drugs, like olanzapine, and drugs with major drug interactions (fluoxetine).
- Lamotrigine is now in place to help prevent future depressive episodes, with minimal long-term medical risks in this older gentleman with coronary artery disease.
- Erikson's stages are irrelevant if you get the diagnosis and/or treatment wrong.
- This type of case illustrates the adage: *Your treatment is only as good as your diagnosis.*

PL Reflection:

My treatment only fails in incurable cases. Galen

Curbside consults:

Questions and cases from you

Question: Today I saw a woman for a first follow up. She had seen a psychiatrist in my group a year ago who had diagnosed her with unipolar depression and treated her with sertraline (Zoloft) and clonazepam (Klonopin) as needed. She had moved out of the area a year ago and dropped out of treatment. She complained of insomnia and a lot of anxiety and depression recently after returning to the area, in relation to marital conflict and the psychiatric hospitalization of her adolescent son. Her sleep was poor, getting only about 4 hours or less. I realized today I didn't get the best psychiatric history on her; it turns out she had been diagnosed with bipolar disorder in the past and treated with divalproex (Depakote), later switched to topiramate (Topamax). I suggested Lithium and she reported she'd taken it 15 years ago, with the feeling she wasn't so much walking as floating, and her psychiatrist took her off it. When she returned today, after 3 weeks resuming sertraline 50mg daily, she reports her sleep has changed radically from not sleeping much to sleeping a lot, being tired and taking naps. Today I got pre-lithium labs drawn and started lithium 300mg twice daily. I didn't stop the sertraline or insist she stop it, but will see her in 2 weeks and likely will be more insistent that she stop the sertraline.

Having attended your seminar last summer I know that at least part of what I did today you will agree with, but I am a little worried about the side effect of feeling like she was floating. I assumed, as this report suggests, that she may have been feeling that way due to dehydration, but again it was years ago. Partly I think I should have been more insistent on stopping the sertraline, but also when SSRIs push people to

mania it isn't usually going from poor sleep to lots of sleep and is most often the opposite.

PL: Our colleague raises questions that we'd like to address on the following topics: (a) lithium titration, (b) overall lower dosing of lithium, (c) interpreting past side effects, (d) SRI-related apathy and mixed depression (e) antidepressant-induced mania and discontinuation of antidepressants. (For the purposes of this reply we aren't addressing the details of past bipolar diagnosis, i.e., whether hypomanic or manic episodes were present; we assume for our purposes that the bipolar diagnosis may be correct for this patient). (a) If you decide to prescribe lithium, we suggest you do it more slowly than in this case: we don't prescribe it 300 mg twice daily from the first visit. Rather we prescribe 300 mg at night for at least 4-5 days, and sometimes 300 mg at night for a week, before increasing to higher doses, like 600 mg at night. Note, as described in the Clinical Tip of the Month, we strongly urge that you only prescribe lithium once daily at night, not in twice daily dosing. (b) Not knowing the details of the patient's past manic symptoms, it is not entirely certain that she will need more than an overall dose of 600 mg/d. Only in type I bipolar illness are standard levels of 0.6-1.0 proven necessary. In type II illness or other parts of the spectrum, our experience and some clinical data suggest that lower levels (like 0.3-0.6) may be effective. She might not need more than 450-600 mg/d overall. We suggest waiting at least a few weeks on 450 or 600 mg/d; she might note improvement and not need higher doses. (c) Her past side effects with lithium may be completely irrelevant to current use: we don't know how fast she was titrated or the eventual dose. There is no special need to worry about those side effects as described. It's not clear that dehydration is relevant. In any case, the subjective description is so vague that it

doesn't correspond to any risk of medical importance. Again, using slow titration and low dosing, her risk of similar side effects should be lower than in the past. (d) The change from sleeping less to sleeping more can relate to the mood lability of mixed depression (see the PL website for more description of that mood state) or it can be SRI-related apathy, which can happen in some persons. That apathy is usually about interest, but it might in some cases lead to more sleep. (e) In this case, the main reason to stop sertraline (assuming the past bipolar diagnosis is correct) is not because it is causing current manic symptoms, but rather because it (like all antidepressants) has been proven ineffective for bipolar depression. Thus there is no reason to use it because we should not be prescribing ineffective drugs. (See the bipolar depression section of the PL website for more description on this topic). In her case, she may not be getting worse on sertraline currently, but the scientific clinical studies prove that she won't get better on it in the future either. That's the main reason to stop it, along with the potential for long-term worsening of mood episodes in about one-quarter of patients (as described on the PL website). Since she has only been on sertraline for 3 weeks, it is likely that it can be stopped without SRI discontinuation syndrome.

Note on terminology: PL uses the acronym "SRIs" rather than "SSRIs" because the first "S" stands for "selective", while these agents are not selective for serotonin effects only, but often have many other neurotransmitter effects, including norepinephrine and sometimes dopamine reuptake inhibition. For instance, sertraline is a moderately strong dopamine reuptake inhibitor, twice as potent in that respect as bupropion (E Richelson, Mayo Clin Proc, 2001, 76:511-527). The word "selective" was the product of a marketing effort by the pharmaceutical industry and doesn't

have a strong scientific basis. Hence "SRIs" is a more scientifically sound name.

Question: Which has less harmful effects on the kidney: lithium carbonate immediate release or lithium carbonate ER (extended release)?

PL: We recommend giving lithium in its generic slow release formulation (lithium carbonate ER) rather than the generic immediate release lithium. The initial peak of lithium in the immediate release is quite high and will affect kidney cells much more than in the slow release where that peak is cut off and lower initial levels occur in the blood. The slow release formulation of lithium does not appreciably increase its already long half-life of 24 hours, and the somewhat higher levels of lithium for a few extra hours in a day are still much below the high peak that initially happens with immediate release lithium, and thus should have less harmful effects on the kidneys in long-

term treatment. There are clinical studies which find a correlation between less long-term kidney effects with slow-release versus immediate-release lithium, and no studies which show the reverse, as long as both regimens were given once daily. (H Lokkegaard et al, Acta Psychiatrica Scandinavica, 71: 347-355). What is clear is that once daily dosing, no matter what type of lithium is used, clearly produces less long-term kidney impairment than multiple daily dosing (see Clinical Tip of the Month above).

PL Reflection:

All drugs are toxic.
Only their indication and dosage makes them therapeutic.

William Osler

Psychopharmacology course

Lesson 1: Think about drugs clinically, not biologically

Readers should know that PL will teach an approach to psychopharmacology that is quite different from, even opposite to, what you are usually taught. The most common approach, taught in the most popular psychopharmacology textbook and throughout training programs in the US, is the *biological* approach. This drug blocks this receptor; that drug blocks that receptor; this drug increases serotonin, the other increases norepinephrine. And this drug increases everything, so it's even more effective! This kind of biological teaching is not completely false; it is important to know biological mechanisms, which can sometimes correlate with clinical effects. But when used as the primary means to make judgments about how to use drugs, this biological speculation is just that: a *neuromythology* (as the

German psychiatrist/philosopher Karl Jaspers called similar tendencies a century ago). It has the trapping of science, and it makes clinicians feel like they know what they're doing: but it's pseudoscience - speculation that goes far beyond what we know.

The PL approach, in contrast, is *clinical*. We don't care about the biology of drugs (we do, but not as a matter of primary importance). Our primary interest isn't what drugs do to receptors or neurotransmitters in rats, test tubes, or PET scans. We care about what they do for clinical symptoms in human beings. In other words, in contrast to the psychiatric journals and NIMH grant funding, and opposed to the conventional wisdom of the psychiatric profession today, *we put clinical research above biological research*.

The primary scientific evidence about which drugs to use and how is based on randomized clinical trials in human beings, not biological speculations about clinical effects in psychiatric illnesses based on studies of receptors and neurotransmitter in rats (or even humans for that matter). A drug can enhance every neurotransmitter in the world, but if it isn't better than placebo in a RCT, it doesn't work, and you shouldn't prescribe it.

A drug can block every receptor that you'd like to block theoretically, but if it has never been tested in a RCT for a psychiatric condition, then you don't know if it really works or not, and you shouldn't pretend otherwise.

So we will approach clinical psychopharmacology, based on randomized trials and clinical studies as the primary source of evidence, with biological mechanisms as a secondary consideration. *This is the reverse of the approach of the most prominent psychopharmacology textbook and current conventional wisdom.* The latter approach leads to many speculative judgments about drugs, and their overuse and polypharmacy, causing, in our opinion, more harm than good. The PL approach will lead to use of fewer medications, but more effectively and on more solid scientific ground.

Thus, we will privilege and focus on clinical trials rather than biological theories. You'll need to

learn about how to interpret RCTs, and statistical knowledge will be necessary, and PL will help you understand that knowledge. It is more work than speculating about the benefits of having more of some neurotransmitter. But it is scientifically more sound, and clinically more effective.

We hope you'll find that this philosophy of psychopharmacology is fruitful, and you'll join PL in following the old teaching of Hippocrates, who focused on clinical evidence and opposed

biological speculations about too much or too little of four humors (similar to theories about "chemical imbalance" with neurotransmitters). In sum: *Don't privilege theories (including biological ones) over clinical evidence.*

The PL Bottom Line

- Clinical evidence is more valid than biological theory, even in psychopharmacology.
- Focus on clinical research studies, especially RCTs, instead of speculation about clinical effects based on biological mechanisms.
- Neuromythology leads to polypharmacy.

Stay tuned next month for lesson 2: Basic neuroanatomy for clinical psychopharmacology

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THE PSYCHIATRY LETTER

"Depression" that isn't just depression

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Welcome to the second issue of the Psychiatry Letter.

This issue has a main theme: use of antipsychotic agents in mood conditions. The case of antipsychotics in bipolar depression is an excellent case example of the PL approach to psychiatry. In the extensive special article on this topic, we examine the scientific evidence, and think outside of the boxes set by the pharmaceutical industry and the Food and Drug Administration (FDA). Good clinical practice isn't as simple as just following FDA indications, which doesn't mean FDA indications don't matter. We need to interpret FDA indications in the context of looking at the scientific literature ourselves, and drawing our own conclusions. That's what PL is here to help you to do.

The treatment of bipolar depression with agents that aren't standard "antidepressants" also raises the question of the meaning of "depression." In this issue, we discuss the concept of "mixed depression", or depression with psychomotor excitation and sometimes frank manic symptoms. This kind of depression doesn't improve, and may worsen, with antidepressants, while it improves with antipsychotics and mood stabilizers. Understanding mixed states of depression is key to knowing when to use antidepressants versus antipsychotics; and it's not all about whether bipolar illness is present or not.

We end with a case where not making these distinctions can have tragic consequences.

If you are one of our inaugural subscribers, thank you for continuing this journey with us into a new psychiatry of the future. If you are newly joining us, we hope you find new ideas that can help you improve your practice.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Antipsychotics (dopamine blockers) in bipolar depression*

FDA indications don't tell the whole story

FDA-indicated medications for acute bipolar depression are quetiapine (Seroquel), olanzapine-fluoxetine combination (Symbyax, also called OFC), and most recently lurasidone (Latuda). PL holds the view that two medications which do not have FDA indications, ziprasidone (Geodon) and aripiprazole (Abilify), also have a scientific rationale for efficacy in bipolar depression.

Of these agents, quetiapine and OFC have, by far, the worst risks, especially if used long-term (given that they worsen metabolic syndrome and cardiovascular risks). Thus, *PL recommends lurasidone, aripiprazole, and ziprasidone - not quetiapine or OFC - as the primary dopamine blocker treatments for bipolar depression.* The rest of this article will explain this recommendation.

Dopamine blockers, not “antipsychotics”: It's illogical to speak of “antipsychotics” for bipolar depression. Most cases of bipolar depression don't involve psychotic symptoms (delusions or hallucinations). So why do we speak of “antipsychotics” for non-psychotic bipolar depression? Drug companies will tell you: Well, there are “antidepressant effects” to antipsychotics; or, worse: antipsychotics are also antidepressants.

Readers of George Orwell will recognize here his dystopic vision of a “Newspeak” that abuses language for other purposes. This is not just PL's opinion. The European College of Neuropsychopharmacology (ECNP) and the American College of Neuropsychopharmacology (ACNP) recently convened a task force on

psychiatric drug nomenclature where they draw the conclusion that the names we use for our drugs are scientifically incorrect and clinically misleading (Zohar et al 2014). Orwell said it long ago: Thought is constrained by language. *If we use false terms, we'll have false thoughts.*

So let's stop using the phrase “antipsychotic” (or “antidepressant”, for that matter; PL will address that topic in a future issue). “Antipsychotics” are not just effective for psychotic symptoms; they have many other non-psychotic uses: for depressive symptoms, anxiety, sleep, agitation in dementia or delirium, even physical states like emesis. The ECNP/ACNP task force recommends using clinically neutral terms based on biological mechanisms. PL

recommends the general term “dopamine blocker” for this class of agent. (Biological definitions have their own limitations, we realize: drugs have more than one mechanism, and they differ on potencies for any mechanism; see PL website).

By changing our language, we'll immediately realize that these agents aren't limited to “psychotic” conditions. Hence their utility in (non-psychotic) bipolar depression.

Acute bipolar depression:

Studies using dopamine blockers exist mainly for *acute* bipolar depression, meaning a current severe clinical depressive episode that usually lasts 1-6 months untreated. The usual duration of treatment, in standard FDA studies, is 6-8 weeks.

Thus, to the extent there is scientific evidence of efficacy of dopamine blockers in bipolar depression, that evidence exists for about 2 months of treatment. That's it. Not 2 years. And certainly not 20 years.

In other words, this research evidence, if valid, would instruct you to treat bipolar depression with dopamine blockers for two months, and *then stop those agents*. To say that dopamine blockers should be continued, we would need evidence of maintenance efficacy of these agents. It is worth pointing out that there are no data on OFC for maintenance treatment (olanzapine is not the same), and that the aripiprazole maintenance study found that it was *not* effective in prevention of bipolar depressive episodes (efficacy was present only in prevention of manic episodes). Thus, *long-term preventive efficacy cannot be assumed from acute efficacy data*.

Olanzapine-fluoxetine combination (Symbax): The Study of the Month dissects the data behind OFC. As described there, that study proved that olanzapine did *not* work for treating bipolar depression, and the amount of data supportive of OFC is rather small in size and less definitive than you might believe.

Quetiapine (Seroquel): Acute bipolar depression studies with quetiapine are, superficially, more straightforward than with OFC. Astra Zeneca planned two large 8 week trials of quetiapine alone versus placebo, and the drug worked in both cases, with large effect sizes of benefit that included core mood symptoms (like anhedonia, low energy, and sad mood). The FDA provided the bipolar depression indication.

As clinicians and patients know, quetiapine is an extremely sedating drug. It has potent antihistaminic, antiadrenergic, and anticholinergic effects. One would tend to notice taking it. Some academic leaders involved in the quetiapine studies acknowledge that it's likely that those RCTs weren't truly blinded: Patients could tell when they took quetiapine, and when they didn't (received placebo). Unblinded studies tend to increase treatment effect sizes, hence the quetiapine studies likely overestimate its benefits.

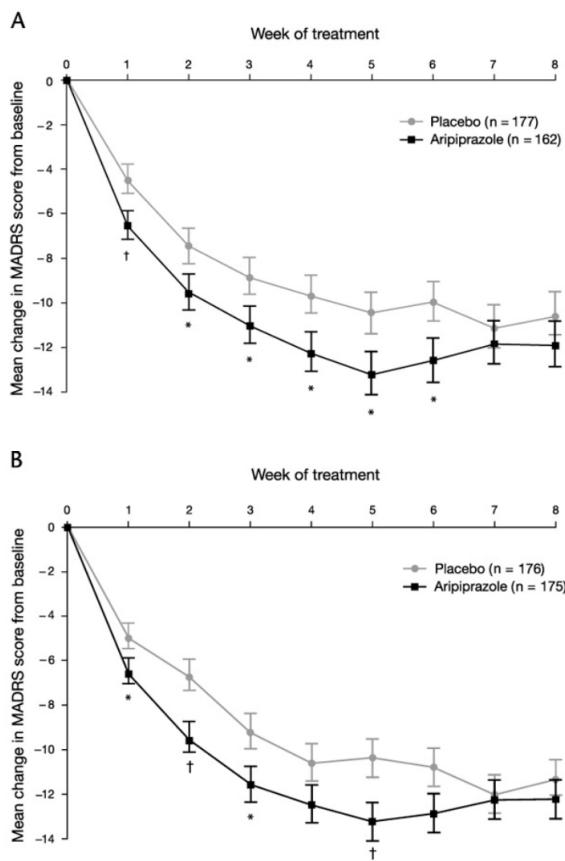
This doesn't mean quetiapine isn't effective in bipolar depression at all. It means that the claim that it is *especially* effective, more so than other agents, may be inflated based on sedating non-mood effects.

In sum, quetiapine showed benefit; but *is it as big of a clinical benefit as it seems, or an inflated effect of a highly sedating drug?*

Lurasidone (Latuda): The newest FDA-indicated agent, was shown effective in two 6-week RCTs of bipolar depression. It isn't sedating, and other aspects of study design seem valid. Of the three agents with FDA indications, this one seems to have the most valid scientific proof.

Aripiprazole (Abilify): Now we come to agents without FDA approval for bipolar depression. Let's begin with aripiprazole. Bristol Myers Squibb did two 8 week trials of this agent for bipolar depression. In both cases, repeatedly, the drug was better than placebo from weeks 1 through 6, but at week 8, placebo showed a benefit which reduced the overall effect size and led to a p-value above 0.05 (not statistically significant). (See figures: MADRS= Montgomery Asberg Depression Rating Scale). FDA indication

wasn't given since the study was designed with the a priori outcome of improvement at 8 weeks.



The PL viewpoint is that aripiprazole was effective in bipolar depression, because the benefits seen at 4 and 6 weeks are more meaningful scientifically than the final 8 week endpoint. This is why: *The duration of a study should be adjusted to the duration of an illness.* There is no general rule that a study should be long, or that the longer the study, the better it is. Mania RCTs are only 3 weeks in duration, because manic episodes are short, lasting 2-4 months untreated according to some studies. Unipolar depression studies are 8 weeks long because unipolar depressive episodes are long, lasting 6-12 months untreated. But bipolar depressive episodes, though longer than mania, are shorter than unipolar depressive episodes. According to a

century of natural history data dating back to Kraepelin, bipolar depressive episodes tend to last 2-6 months, less in those with rapid-cycling course (about one-quarter of bipolar subjects). So, if you conduct a trial that is 8 weeks long, in a condition where a substantial minority of patients is improved by 1-3 months, you will have a "placebo" rate of improvement, due to natural remission, that is high. This makes it difficult to show drug benefit. Thus 6 weeks is more scientifically valid than 8 weeks for the duration of a bipolar depression trial. The PL editor made this point to Bristol Myers Squibb when it planned the original bipolar depression study. That mistake has confused some clinicians into thinking the drug has no benefit for a condition in which it showed benefit. This is why the lurasidone studies were 6 weeks long. And this is why the aripiprazole study's effect at 4 and 6 weeks shouldn't be ignored.

If aripiprazole improves depressive symptoms, it isn't surprising that other studies found it to be effective in unipolar depression, leading to FDA indication as augmentation of antidepressants.

Lastly, although PL strongly believes that biological rationale should not be the primary factor in treatment decisions, biological mechanisms are relevant for interpreting clinical trial data. Aripiprazole is a moderate dopamine agonist. Dopamine agonists (like amphetamines and bupropion) improve depressive symptoms. In contrast, olanzapine and quetiapine have little monoamine agonist effects (minor effects were shown retrospectively in some animal studies later conducted by their companies), and certainly not as much as aripiprazole (or ziprasidone).

Ziprasidone (Geodon): Based on biological mechanism, if any dopamine blocker is going to be effective for depressive symptoms, it should be ziprasidone. It's the only modern dopamine

blocker that also is a serotonin reuptake inhibitor (SRI) and a norepinephrine reuptake inhibitor (NRI). Its effects are about equally as potent as standard SRI and tricyclic antidepressants. The trouble is that Pfizer conducted two RCTs of ziprasidone versus placebo in acute bipolar depression, and it didn't work. Unlike aripiprazole, there wasn't benefit at some weeks but not others. There just wasn't benefit.

This should seem odd: Drugs without strong monoamine agonism, like quetiapine, are supposedly "antidepressant" in their effects, while drugs with strong classic antidepressant mechanisms, like ziprasidone, are not. How can this be?

Perhaps it serves to come back to clinical concepts.

"Bipolar depression" just means a current "major" depressive episode in someone with past mania/hypomania. As with "major" depressive episodes in unipolar depression, it may represent multiple different depressive subtypes, as discussed in the PL website. One relevant subtype is "mixed depression", i.e., depression mixed with manic symptoms. It could be that the apparent "antidepressant" effect of dopamine blockers has to do partly with dopamine blockade itself, which is effective for mixed manic/depressive states, rather than with mood elevating monoamine agonism effects of classic SRIs/ NRIs. In other words, dopamine blockade provides benefit for mixed states - this is well known. *Most "bipolar depression" is, in fact, a mixed state*, as described in the Psychopathology article. Hence almost any dopamine blocker should help, not just quetiapine or OFC.

This hypothesis could be tested directly by studying ziprasidone (or any antipsychotic) in patients selected for "mixed depression". The PL

editor designed and conducted this project and indeed ziprasidone was effective, better than placebo, in an overall sample of 73 subjects.

This result is similar in size to the OFC study arm (n=86). In other words, the widespread use of OFC is based on an amount of scientific evidence that is similar to what exists with ziprasidone for mixed depression. Pfizer never sought FDA indication for mixed depression efficacy because ziprasidone was about to become a generic medication when this study was completed (hence there were no profit to be gained by marketing this use). If clinicians only went by FDA indications, they would ignore ziprasidone, not because efficacy data don't exist, but because there weren't economic motivations to obtain FDA indication for them.

The case of ziprasidone and OFC shows why clinicians should focus on science, not primarily presence or absence of FDA indications.

Low doses: William Osler's axiom was that all drugs are toxic; it's only the dose and indication which makes them therapeutic. In the aripiprazole studies of bipolar depression, secondary analyses found that in those treated with *lower* doses (5-10 mg/d), aripiprazole was *more* effective than placebo; it was in the higher dose group (>10 mg/d) that placebo seemed similar to aripiprazole. In the lurasidone monotherapy studies, the low dose arm (20-60 mg/d; mean dose 32 mg/d) was equivalent in efficacy to the high dose arm (80-120 mg/d; mean dose 82 mg/d). It is the PL clinical experience that a similar principle may apply with ziprasidone. At low doses (<80 mg/d), we've seen patients show good improvement for bipolar depression; it could be that *higher* doses are *less* effective. This observation seems to contradict common clinical intuitions: *we tend to believe that more is better*. But

this isn't always the case. A biological explanation may be as follows: At lower doses of all dopamine blockers, there is less dopamine blockade. It's commonly believed that about 80-90% dopamine blockade is needed for full antipsychotic effect. That's great, but we're not treating psychosis here; we're treating mostly non-psychotic bipolar depression. It could be that only about 50% or so of dopamine blockade is sufficient to get benefit for the mixed depressive state in bipolar depression. Thus, higher doses of dopamine blockers may confer no further mood benefit. Turning to the dopamine agonism of aripiprazole and the serotonin/norepinephrine reuptake blockade of ziprasidone, *these effects are present to the same extent at any dose, including low doses.*

So it could be that low doses provide a good amount of "antidepressant"-like monoamine agonism, with sufficient dopamine blockade for manic symptoms. While higher doses might just produce more and more dopamine blockade, which might just produce more antimanic effect, moving the mood down, rather than elevating it.

These biological explanations may or may not be correct, but as we said in issue 1, the PL approach is to emphasize the clinical research evidence, which indicates *more* benefit in bipolar depression with *lower* doses of dopamine blockers. *We encourage clinicians to avoid using the high doses shown effective for schizophrenia and mania as their standard for treating bipolar depression.*

Weighing risks and benefits: Osler's dictum that the art of medicine is the art of balancing probabilities also comes into play. Clinicians shouldn't just use those drugs which are FDA-indicated, and hence marketed to them. They should compare the scientific evidence of all

drugs, take into account comparisons of side effects among drugs with scientific evidence of efficacy, and then weigh probabilities of benefits versus harms. As discussed on the PL website, quetiapine has notable and long-term metabolic syndrome and harmful cardiovascular effects. So does olanzapine. When these known common harms are taken into account, the benefit/harm calculation tilts in the direction of lurasidone, aripiprazole, and ziprasidone.

These three agents are left mainly with the risk of akathisia (discussed in detail on the PL website), which can present as worsened agitation and/or suicidality. (Note: We are aware that other side effects exist with these agents, such as QT prolongation with ziprasidone, but those risks are less frequent than akathisia, which is the most common reason for dropout and serious adverse events in practice. See the PL website for further

discussion of why QT prolongation is not the major problem with ziprasidone.) Akathisia is clinically

dangerous and immediate intervention is needed, either by stopping the dopamine blocker, or by lowering its dose and/or adding a counteracting agent. Among counteracting agents, PL experience and a limited scientific literature suggest that beta-blockers are the most effective, especially propranolol, which best crosses the blood-brain barrier. In the US, a generic slow-release formulation, propranolol ER, is now available without insurance restrictions. We recommend it to be given at night, since its benefits extend throughout the day. Doses begin at 60 mg/d. Pulse should be followed so it doesn't fall below 60 beats/minute. In healthy middle-aged persons, the propranolol ER dose range for akathisia tends to be 60-120 mg/d.

How to dose:

- Lurasidone: Give 20 mg at night for 2-3 weeks. Increase to 40 mg at night if there's no benefit at all. In a minority of cases, consider going to 60 mg/d. Remember: higher doses above 60 mg/d were *not* more effective in the monotherapy RCTs of bipolar depression, where the mean effective dose was around 30 mg/d. A common mistake is to use higher doses, like 60-120 mg/d, based on FDA labeling for schizophrenia, not bipolar depression.
- Aripiprazole: Begin with 2 mg at night for 2-3 weeks. If there's no effect, increase to 5 mg at night for 2-3 weeks. If there's no effect, increase to 7.5 mg at night for 2-3 weeks. If there's no effect, increase to 10 mg at night. Higher doses than 10 mg/d are proven less effective for bipolar depression than lower than 10 mg/d. Thus there is no reason to use more than 10 mg/d. Again, a common mistake is to go up to 20-30 mg/d based on FDA labeling for schizophrenia or mania, not bipolar depression.
- Ziprasidone: Begin with 20 mg at night for 2-3 weeks. If there's no effect, increase to 40 mg at night for 2-3 weeks. If there's no effect, increase to 20 mg in the morning and 40 mg at night for 2-3 weeks, then if needed increase to 40 mg twice daily. In the PL experience, higher than 80 mg/d doesn't tend to produce more efficacy for bipolar depression. Instead, akathisia increases with higher doses.

If patients develop akathisia despite having some benefit, PL recommends propranolol ER 60 mg at night, increasing as needed to 80-120 mg at night. If there's no or little benefit with one of these agents, and akathisia occurs, we recommend stopping the current drug and using another. If akathisia occurs with multiple dopamine blockers, we recommend *pre-treatment* with propranolol ER 80-120 mg at night *before* starting a different dopamine blocker trial.

The PL Bottom Line

- PL recommended agents for bipolar depression are lurasidone, aripiprazole, and ziprasidone.
- Low doses should be used. Akathisia is the main problem with these agents. Propranolol ER can be used to manage that problem in some cases.
- The benefit of quetiapine is probably overestimated in its studies.
- Olanzapine alone is proven ineffective.
- Dopamine blockers may mostly help "bipolar" depression when it represents "mixed depression", the combination of severe depression with some manic symptoms.

Selected References: J Zohar et al, European Neuropsychopharmacology, 2014, 24: 1005-1014. ME Thase et al, Aripiprazole monotherapy in nonpsychotic bipolar I depression, Journal of Clinical Psychopharmacology, 2008, 28: 13-20. A Patkar et al, A 6 week randomized double-blind placebo-controlled trial of Ziprasidone for the acute depressive mixed state. PLoS One. 2012;7(4):e34757. A more complete reference list and links are available in this article on the PL website.

PL Reflection

We will develop better new drugs but it will be a continual challenge for doctors to learn how to properly use them. Otherwise it would be like giving a driver's license to someone who can't drive.

Frank J. Ayd, Jr MD 2005

Study of the month: Symbyax dissected

Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression.

M Tohen et al, Arch Gen Psychiatry 2003; 60: 1079-1088

When side effects masquerade as efficacy

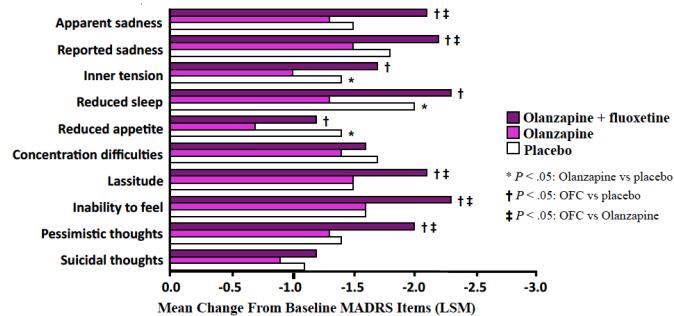
The PL editor was once invited by Eli Lilly to present the main results of this OFC study at the annual meeting of the American Psychiatric Association. Speaking to a large audience, the PL editor noted that the “OFC” (olanzapine/fluoxetine combination) study was designed originally to prove efficacy of olanzapine alone, not OFC. The study was powered statistically for that purpose: 370 subjects were randomized to olanzapine and 377 to placebo. Luckily for the manufacturer, a small sample of 86 subjects also was randomized to OFC. Olanzapine alone showed benefit over placebo using p-values, but the “effect size” was tiny: a very small improvement in the Montgomery Asberg Depression Rating Scale (MADRS) of about two points: one for sleeping more and another for eating more (see figure). Sedation and increased appetite are side effects of olanzapine, not proof of efficacy for bipolar depression. The PL editor made these points; he was never invited by that company to give a lecture again.

In the published paper, the company and its 7 academic coauthors begin the conclusion section of the abstract with a first sentence that is technically true but clinically false: “Olanzapine is more effective than placebo....” Later in the paper, they have to admit absence of effect on core mood symptoms, but that admission was buried in the text. Clinicians continue to have the false impression, a decade later, that olanzapine alone is effective in bipolar depression.

It isn’t.

The FDA reached the same conclusion. Olanzapine was shown *not* to be effective in acute bipolar depression, despite its “statistically significant” benefit over placebo. In contrast, OFC showed efficacy, including for standard mood symptoms of sad mood and low interest and low energy, albeit in a small sample of 86 subjects.

Bipolar Depression – OFC MADRS Item Analyses



Tohen et al 2003

Should a drug get an FDA indication when its only data involve less than 100 subjects treated in the effective arm in one randomized clinical trial? Usually, the general FDA rule is that companies need to show efficacy in two randomized clinical trials before an indication will be given. Exceptions are made, though, especially for clinical conditions in which few or no treatments already are approved. This was the case for acute bipolar depression in 2003. No FDA indications existed at that time for any drug. (Keep in mind that “antidepressants” are not FDA-indicated as having efficacy for bipolar depression).

So the FDA gave approval for OFC based on one RCT, with a small sample, even though the study was never designed for that purpose! Now that two other agents are approved for bipolar depression, if the same OFC data were presented to the FDA today, the FDA probably would reject it as insufficient to be given an indication for bipolar depression. But OFC is now grandfathered into its FDA indication. And, going by the mere fact of FDA indication, many clinicians will assume that the scientific evidence for efficacy of OFC in bipolar depression is as good as quetiapine or lurasidone. It isn't.

The PL Bottom Line

- Olanzapine alone is proven ineffective for acute bipolar depression.
- OFC's efficacy is based on a small sample.
- OFC has the same problems with long-term metabolic and cardiovascular harm as exist with olanzapine.
- There is no evidence of long-term efficacy or safety with OFC in prevention of depressive episodes in bipolar illness.

Drug of the Month: Quetiapine (*Seroquel*)

Sedating, but not much of a dopamine blocker

Clinicians of a certain age will remember thioridazine (Mellaril). At low doses, it helped sleep and reduced anxiety; at higher doses where it helped psychosis or mania, it knocked people out. But at least it wasn't a benzodiazepine, and it didn't have as much extrapyramidal side effects as other neuroleptic agents, especially at low doses. So clinicians loved it. And so did many patients.

Quetiapine is the Mellaril of the 21st century. Unlike thioridazine, it has very minimal risk of

tardive dyskinesia, so it has proved a natural replacement for a drug which clinicians can give to patients for that inevitable request: Doctor, please give me something to help me sleep (or in another variant, to help me be less anxious). Benzodiazepines are the class of medication for those uses, of course, but their potential dependence limits their use in some people. Hence the never-ending search for the holy grail of the benzodiazepine-like drug which doesn't cause addiction. Hence quetiapine.

Fast Facts: Quetiapine

Typical effective dose: 50-150 mg/d for anxiety or insomnia, 200-300 mg/d for bipolar depression, 300-400 mg/d for mania, 300-800 mg/d for psychosis/schizophrenia

Biological mechanism: Mild dopamine blockade

Typical side effects: Sedation, weight gain, metabolic syndrome/cardiovascular harms, diabetes, akathisia

Less common but important side effects: orthostatic hypotension

Clinically proven efficacy: acute bipolar depression, acute mania, schizophrenia,

Questionable efficacy: unipolar depression, anxiety, maintenance prevention of bipolar mood episodes

Clinical efficacy and inefficacy

The popularity of quetiapine isn't about schizophrenia, although this medication is listed among "antipsychotics", as described above. PL will focus on the many other uses of this drug, besides schizophrenia. The special article above discusses bipolar depression. Quetiapine also was studied for generalized anxiety disorder and major depressive disorder, and some benefit reportedly

was seen at low doses (< 200 mg/d), but FDA reviewers were reluctant to give FDA indication for those uses given concerns about medical harms from widespread use in the primary care setting. Efficacy in acute mania has been shown in standard studies. Efficacy in maintenance prevention of bipolar illness has been shown using randomized discontinuation trial designs, which may have questionable validity (see PL website).

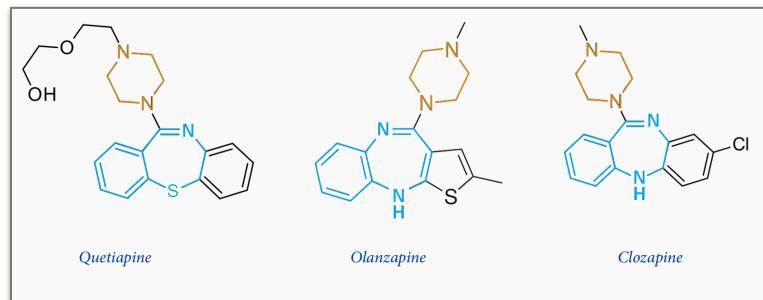
Biological mechanism

Although it's called an "antipsychotic", quetiapine is different from other treatments for psychosis in that it never reaches, at any dose, more than mild amounts of dopamine blockade. From about 400 mg/d to 800 mg/d, there is a plateau of about 30-40% D₂ receptor blockade, nowhere near the 80-90% D₂ blockade obtained with all other antipsychotics except clozapine (see PL website).

Side Effects

Sometimes, similarity of chemical structure entails similar side effects. Quetiapine's basic chemical structure is similar to clozapine and olanzapine (see Figure). All three have notable antihistamine, anticholinergic and antiadrenergic effects, all of which add up to marked sedation. Importantly, all share the major harm of metabolic syndrome: increasing susceptibility to hypertension, diabetes, and hyperlipidemia. All these are major cardiovascular risk factors. Separate from these direct physiological effects

(decreasing insulin sensitivity), quetiapine *also* causes weight gain, which further worsens these cardiovascular risk factors. Regarding neuroleptic effects, quetiapine can cause akathisia, although apparently less frequently than other dopamine blockers (based on the CATIE study); it doesn't cause much parkinsonism because its inherent anticholinergic effects reduce parkinsonian symptoms; tardive dyskinesia is rare.



Note the structure similarity between quetiapine, olanzapine and clozapine. All of them share the piperazine ring in orange and also the benzotriazepine or the benzodiazepine structure, respectively, in blue. These structures and their spatial conformation are responsible for the shared pharmacodynamic drug-receptor properties. The antagonism at the central H₁, 5-HT_{2C}, M₁, and 1-noradrenergic receptors have been suggested as possible molecular mechanisms for the metabolic dysregulation.

The PL Bottom Line

- Quetiapine is a mild dopamine blocker.
- It is effective in bipolar depression, mania, and schizophrenia; sedation effects may be interpreted as mood and psychosis benefits
- Long-term efficacy in bipolar illness can be questioned based on study design questions.
- Benefits for anxiety/insomnia/agitation likely relate to antihistamine/antiadrenergic/anticholinergic effects.
- It causes metabolic syndrome, worsens cardiovascular risks, & has notable weight gain.

Selected reference on biological mechanism: E Richelson, Receptor pharmacology of neuroleptics: Relation to clinical effects. J Clin Psychiatry. 1999;60 Suppl 10:5-14.

PL Reflection

Treatment is pruning a rose of its thorn.

Jeffrey Gilbert MD

Psychopathology: Mixed depression

Depression with psychomotor excitation is not just a major depressive episode

Clinicians use the word "depression" loosely. The DSM concept of a "major depressive episode" combines very different kinds of depressive states: Take melancholia: there is no reactivity of mood, which means that the patient is just plain sad all the time - not angry or anxious or anything else. There is marked anhedonia, meaning the patient has basically no interests at all, and is often unable to get out of bed or function at all. Now take its opposite: "mixed depression", where the patient has highly reactive mood, ranging from very sad to very angry to very anxious to very agitated; there is decreased interest but patients can still function somewhat.

"Major" depression isn't really one thing: it includes many things, including types of depression that can be completely opposite in their symptoms.

Does this matter, practically? It may. If agitated, labile, angry "mixed depression" is different than the slowed down, sad, anhedonic "melancholia", they may have different treatments. European researchers, often less influenced by DSM, have been studying the concept of mixed depression a great deal in recent decades. They've shown that it occurs more commonly in bipolar than unipolar depression, that it

seems to respond especially well to dopamine blockers (neuroleptics), and that it worsens with antidepressants.

In one study of over 5000 depressed patients, Angst and colleagues reported that 47% of DSM-defined "major depressive" episodes included 3 or more DSM manic symptoms. This was the case even with DSM-defined "major depressive disorder", not just bipolar disorder. In other words, *about half of depressive episodes in major depressive disorder involve multiple manic symptoms, i.e., are mixed depressive states.*

"There is a kind of depression where...patients also have psychomotor excitation: they are angry, revved up at times, sometimes high in libido, and very agitated."

This may seem odd: how can you have "major depression" with three manic symptoms? It happens because DSM doesn't allow you to diagnose mania or hypomania unless those manic symptoms occur for 4 or more days. But these "mixed depressed" states often involve consistent depression, with bursts of manic symptoms for a few hours or a day or two. DSM says: Ignore those manic symptoms; they didn't happen. Just diagnose a major depressive episode. Yet those are exactly the kind of agitated, labile depressive states that seem to respond to dopamine blockers.

Koukopoulos' mixed depression criteria

- A DSM-defined major depressive episode
- At least 3 of 8 items:
 - Psychic agitation or inner tension
 - Racing or crowded thoughts
 - Irritability or unprovoked rage
 - Absence of retardation
 - Talkativeness
 - Dramatic description of suffering or frequent spells of weeping
 - Mood lability or marked reactivity
 - Early insomnia

As importantly, if we give antidepressants to those agitated, labile, angry depressed patients, they seem to

get *more* agitated, labile, and angry. This sometimes ends in suicide, which may explain why some depressed patients get *more* suicidal on antidepressants (see the Case of the Month below and the PL website on this controversial topic).

In short, there is a kind of depression where, despite being sad and low in interest and energy and sometimes suicidal, patients also have psychomotor excitation: they are angry, revved up at times, sometimes high in libido, and very agitated. In other words, *some manic-like symptoms are mixed into the depressive state.*

This concept of mixed depression was organized into diagnostic criteria by the late Athanasios Koukopoulos, the leading thinker, clinician, and researcher in this field (see Table).

The PL Bottom Line

- About one-half of all depressive episodes, irrespective of whether the overall mood diagnosis is bipolar or unipolar, involve "mixed depression".
- These psychomotor excited mixed depressive states worsen with antidepressants and improve with dopamine blockers.

Further reading: A. Koukopoulos. *Melancholia agitate and mixed depression.* Acta Psychiatr Scand Suppl. 2007;(433): 50-7. J. Angst et al, *Prevalence of undiagnosed bipolar disorder in patients with a major depressive episode: the BRIDGE study.* Arch Gen Psychiatry. 2011 Aug;68(8): 791-8.A. Koukopoulos and Angst articles A Koukopoulos and SN Ghaemi. *The primacy of mania.* Eur Psychiatry. 2009 Mar;24(2):125-34.

Case of the month:

A mixed depressive suicide

A 69 year-old male seeks treatment for severe depression. He had experienced one depressive episode 30 years earlier, leading to psychiatric

hospitalization and improvement after one month of treatment with imipramine. He remained well for three decades without any psychotropic medication treatment. He was a successful journalist, writing a number of books; he was passionate, liberal, and opinionated, often having some interpersonal conflicts with those who had different political views. He possessed a wide circle of friends, and an equally wide circle of enemies. He raised three adult children, was divorced, remarried, and happy in his current relationship. He had partially retired five years earlier, but was still writing, traveling, and enjoying his activities. He was normally high in energy, slept about 6 hours nightly, had many activities, high libido, and was very creative.

In March, he began to feel inexplicably sad, with low energy and decreased interest in his usual activities. His libido remained high and active, though, and when he would have a good day, he would describe pleasurable sexual activity with his wife. He was also agitated and anxious and worried about being depressed again after decades of wellness. He was more angry than usual.

Family history was positive for severe depression in some relatives but no one sought help and no official diagnoses or treatments existed. The patient had no drug allergies and no drug/alcohol abuse. His medical history was normal except for mild hyperlipidemia.

He visited his primary care doctor who prescribed sertraline 25 mg/d. He immediately felt better for a few days, but then became more depressed again. Sertraline was increased to 50 mg/d. He improved for a few days, then felt worse again. Sertraline was increased to 100 mg/d. He then felt high in his mood, with markedly increased energy, very high libido, and a complete inability to sleep. He called a friend and complained about this mood state: it was uncomfortably energetic and

he was worried about not sleeping at all. After two days, these symptoms went away and he went back into his depressive state. His primary care doctor consulted DSM-5 and concluded that since those symptoms had lasted two, not four, days, they didn't represent a hypomanic episode. Since they had gone away and the patient remained very depressed, his doctor increased sertraline to 150 mg/d and consulted a psychiatrist.

The patient had investigated the topic on the internet, had read about antidepressant-induced mania/hypomania as representing possible bipolar illness, and told

the psychiatrist that he was willing to take lithium for his current depression. The

psychiatrist told the patient that the diagnosis was major depressive disorder and that lithium wasn't necessary.

Over the next three months, the psychiatrist increased sertraline to 200 mg/d, added bupropion plus lorazepam, and gave brief trials of quetiapine 25 mg for sleep, venlafaxine in place of sertraline (added to bupropion), and trazodone for sleep. The patient had no further brief hypomanic-like episodes, but his depression didn't improve, and he became more and more agitated and angry. He was taken to the emergency room a few times by his wife due to concerns about some expression of suicidal ideation, but he would always deny imminent intent or plan, and would refuse voluntary hospitalization. He wasn't hospitalized. One morning he hung himself.

"Using DSM definitions, the patient can't be diagnosed with bipolar illness...yet he clearly had multiple manic symptoms. Thus he meets the definition of 'mixed depression.'"

The PL diagnosis and clinical impression

The PL diagnosis is a mixed depressive episode. Using DSM definitions, the patient can't be diagnosed with bipolar illness because the hypomanic episode lasted two days, not four. Yet *he clearly had multiple manic symptoms. Thus he meets the definition of "mixed depression".*

He was never offered lithium or dopamine blockers (except low dose quetiapine for sleep) so we can't know if those agents would have helped him. But PL would have recommended at least low dose lithium for his suicidality (see PL website) and some dopamine blocker (like aripiprazole) for his overall mixed depression.

It's clear that antidepressants didn't improve his mixed depression, and they may have worsened it, hastening its suicidal conclusion.

The PL Bottom Line

- Manic symptoms during depression, lasting less than four days, were ignored.
- "Mixed depression" was present and didn't improve with multiple antidepressants.
- Lithium or dopamine blockers weren't offered for mixed depression because of over-reliance on identifying a DSM-defined bipolar diagnosis.
- Suicide was the result either of lack of efficacy of antidepressants for mixed depression, or antidepressant-related worsening of the mixed depressive state.

PL Reflection

Our first reaction after a suicide is surprise. Our second reaction is: Well, *of course* it happened.... The gap between the two reactions is the paradox of suicide.

Leston Havens MD

Curbside consults:

Questions and cases from you

Question: In the first issue of PL, you discussed bupropion but you didn't mention its use in ADHD. What is your perspective on that topic?

PL: We emphasized that bupropion is a mild amphetamine, so it isn't surprising that it works for ADHD. We used to recommend bupropion for ADHD as a presumably non-amphetamine agent. Since this isn't the case, PL has no special preference for bupropion in ADHD.

Question: I have an 80 year old attorney patient, treated with lorazepam 1 mg BID. Is that acceptable? Should I be concerned about anything in particular, like falls or hip fracture?

PL: For every year of life, renal function declines by about 1%. By age 80, people have 50% less renal function than at age 30. So 2 mg/d at age 80 is like 4 mg/d at age 30. That's why doses should

be cut in half in the elderly. Generally, PL suggests not exceeding 2 mg/d lorazepam long-term in younger adults, or 1 mg/d in the elderly. Not only are there risks of poor coordination and falls, but also delirium and possibly dementia, since cognition also is impaired. It's best, in sum, to minimize benzodiazepines in the elderly.

Question: What should we tell patients about taking ziprasidone with food?

PL: Its manufacturer recommends that ziprasidone be taken with about 500 calories of food to maximize absorption. Otherwise, it's about half less absorbed. Some patients find this onerous, especially if they worry about weight gain. The clinical relevance is that you may need to prescribe a higher dose for the same effect if patients don't take it with food. PL recommends that ziprasidone be taken with some food, but we don't insist upon it, since PL recommends titrating dose to clinical effect in any case.

Clinical tip of the month: Give lithium for suicidal symptoms, even at low dose.

In the case of the month, lithium was avoided in a suicidally depressed individual because DSM-defined bipolar illness couldn't be diagnosed. Lithium is the only psychotropic drug shown to prevent completed suicide based on randomized studies. Blood levels and doses are based on mania efficacy, not suicide prevention. Multiple studies of lithium in drinking water indicate anti-suicide benefits at doses that would be considered trace in clinical practice, equivalent to about 1 mg/d. In the experience of PL editors, and based on these studies, *any dose of lithium may help prevent suicide*. Consider giving suicidal patients 150-300 mg/d of lithium carbonate, or even less with lithium citrate, for suicide prevention. These doses are unlikely to cause major medical problems or blood level toxicity. But they may save a life. (Sources: S. Mauer et al, Australian and New Zealand Journal of Psychiatry, 2014, 48: 809-818. A. Cipriani et al, BMJ. 2013; 346:f364)

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THE PSYCHIATRY LETTER

The fever of psychiatry

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In the second issue of PL, we discussed how "depression" doesn't just mean depression. Now we turn to the second major presentation of unhappiness in the clinic: anxiety.

Anxiety is the fever of psychiatry. It's the most common, and most nonspecific, symptom of psychiatric clinical presentations. Just as fever is very uncomfortable, but not the cause or main focus of medical treatment of infections, anxiety is a major complaint, but it's not usually caused by an anxiety disease, nor should it be the main focus of treatment. Fever can be a sign of a healthy immune system, so too can anxiety itself be a sign of health, not needing treatment at all.

This issue describes five basic kinds of anxiety, not just the DSM definitions. The history and science behind some DSM definitions, like generalized anxiety disorder (GAD), are examined and found to be questionable in scientific validity.

The concept of neurotic depression is discussed in detail in the psychopathology article, and we review an important historical debate in England and the US about whether all depression is the same (as in major depressive disorder, MDD) or different (as in the neurotic depression subtype).

In keeping with the anxiety theme, benzodiazepines are the drug class of the month and the case of the month is about the treatment of anxiety in post-traumatic stress disorder.

The current study of the month examines a recent analysis that shows that placebo effects, so commonly hailed as beneficial in practice, also bring with them nocebo (pain-producing) effects.

I hope you enjoy this issue of PL, as we continue to systematically examine and discuss the major fields of psychiatric practice.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Understanding anxiety*

It's usually a personality trait or part of another illness, not "GAD"

Anxiety is the fever of psychiatry. It's common, bothersome, and nonspecific. It happens with depression, psychosis, mania, and is a personality trait. In short, anxiety is all over the place. In fact, the philosopher Soren Kierkegaard saw anxiety as *the* central human emotion, part of mere existence. If you exist, you're anxious.

Types of anxiety

So how are we to make sense of anxiety in psychiatric conditions. If anxiety is present, does it immediately mean that a person has an anxiety "disorder"? If so, then if Kierkegaard was right, all of humanity has an anxiety disorder.

Half a century of extensive personality research has proven Kierkegaard right. Perhaps the most replicated normal human personality trait - present in most studies in some

way - is a trait of anxiety. Long ago the British psychologist Hans Eysenck labeled this trait "neuroticism", and that term remains used in personality research. We'll see that the term "neurotic" has become contentious and confused in psychiatric work, mostly due to the influence of Freudian ideas, and so most mental health clinicians don't refer to the concept of the personality trait of neuroticism. But perhaps they should.

Anxiety is a personality trait. We all have it; or, more properly put, we all have some of it. So it isn't valid to identify anxiety as anxiety "disorder" automatically. The questions should be: How much anxiety? And in what context?

PL suggests that you consider anxiety in five different categories:

1. A personality trait
2. Part of mood illness (unipolar or bipolar)
3. Part of psychotic illness (schizophrenia)
4. Part of specific anxiety illnesses (OCD and PTSD) or specific phobias (especially in children)
5. Existential anxiety (part of life)

Anxiety as personality trait

In the mid 1950s, a transplanted German psychologist in post-war London had a strange idea. Hans Eysenck was coming of age at the peak of Freudian influence. The Freudian view was that personality, if nothing else, was all about

c h i l d h o o d
e x p e r i e n c e s ,
conscious or
unconscious, about

one's parents and in one's social world. In other words, personality was all about environment - the family and the larger world. There might be other conditions - like schizophrenia - that could be seen as biological. But personality was quintessentially environmental.

Eysenck had an odd idea: What if personality also was biological, at least in part? Eysenck began to use new statistical methods to answer this question. "Factor analysis" was a quantitative method that allowed researchers to look for basic qualities that could be pulled together from a mass of data. Using that approach to personality questionnaires, Eysenck identified three basic personality traits that could be seen repeatedly in many studies of the normal population. People didn't seem so unique as Freudian ideas suggested:

coming from different family backgrounds and different cultural settings, they still had the same basic traits in factor analysis of personality questionnaires. No Oedipus Complex showed up in those factor analyses, no unconscious sexual traumatic experiences. This is not to say that such possibilities didn't exist; they obviously can't be captured in personality questionnaires. But whether or not we all suffer from Oedipus Complexes and unconscious sexual conflicts related to our parents, we *also*, at least, have identifiable personality traits that are replicated across large populations.

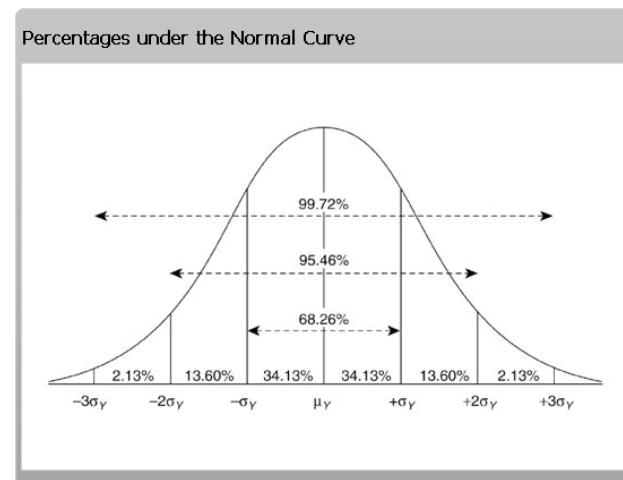
There were three traits: a trait for anxiety - which Eysenck called "neuroticism"; a trait for sociability, which he called "extraversion"; and a trait for abnormal thinking, which he called "psychoticism." Later researchers reinterpreted psychoticism as a trait that is not so much about thinking patterns, but rather about openness to experience, or willingness to be curious about new experiences, or to take risks. Stated positively, this third trait is about "openness to experience"; stated negatively, it's about risk-taking behavior.

In the past half century, Eysenck's basic work has been confirmed in literally hundreds of studies in dozens of cultures in many thousands of persons in the normal population. These three personality traits, defined one way or the other, have stood up. The most common terminology is "NEO" standing for Neuroticism, Extraversion, and Openness to Experience.

This background is useful to understand how the idea of anxiety as a personality trait, or neuroticism, is among the most well established scientific concepts in psychology.

We all have anxiety, these studies show, in a normal curve, just like height or weight and other biological traits of the normal population. Most

of us have anxiety to a middling degree, near the median of the normal curve, at or around the 50th percentile. The figure will remind you how this works in a normal curve. By definition, a small percentage of 2.5% have a lot of anxiety (two standard deviations) and 2.5% have very little anxiety. A much larger group 16% is one standard deviation to each side; this group, on the high side, is still quite anxious compared to most people. The very high anxiety persons are high in neuroticism; we call them "neurotic" colloquially, or "worry warts". The very low anxiety persons are low in neuroticism; we call them Buddha-like, super-calm persons.



The first step to understanding anxiety is to comprehend the fact that by far the largest portion of the population, about 16%, has high anxiety as part of a "normal" personality trait. This is not an illness, not a "mental disorder": it is a normal variation in a normal personality trait in the normal population.

Part of a mood illness

After this large group of one-fifth of the general population which has high anxiety as a normal personality trait, the next largest group would be persons with mood illnesses, namely unipolar and bipolar illness, which is thought to represent

about 10% of the general population in the US and in most Western nations. Anxiety is a frequent symptom of both depressive and manic/hypomanic episodes. When persons have those episodes, they have marked anxiety.

It's commonly said that if anxiety persists at one's baseline personality, in between mood episodes, then it's independent of the mood illness. This can be the case; those persons with mood illnesses may also have, independently, high neuroticism as a personality trait. But there's another possibility: they could have mood temperaments. About one-half of persons with mood illnesses also have mood temperaments (see PL website for further clarification):

namely, dysthymia (constant mild depressive symptoms), cyclothymia (constant mild manic and depressive symptoms), and hyperthymia (constant mild manic symptoms). So, even in between mood episodes, many people have mood symptoms as part of their usual temperaments, as part of their personalities. In these cases, anxiety can be present, still secondary to the mood symptoms. The PL experience is that many persons with cyclothymic temperament, for instance, often have anxiety symptoms as well. When cyclothymia improves with low-dose mood stabilizing agents, anxiety also improves. In other words, the anxiety isn't independent of mood temperament.

Part of a psychotic illness

Perhaps the least common kind of anxiety occurs in schizophrenia and schizoaffective conditions. In the Freudian era, the term "psychotic anxiety" was used, and it is observed that many persons with schizophrenia, especially early in the course of the illness, will be notably anxious and agitated.

A subgroup develops frank obsessive-compulsive disease later in the course of the schizophrenia disease process. This illness occurs, as is well known, in only about 1% of the population. But it is relevant to realize that despite flat affect, anxiety can be part of the illness of schizophrenia.

An independent anxiety illness or disease

If a person has a lot of anxiety, but doesn't have a mood illness or mood temperaments or schizophrenia - after assessing all these other causes of anxiety - it is possible that a person has a specific anxiety condition. PL suggests dividing anxiety conditions into three categories that PL considers to be well-validated scientifically:

- Specific phobias:
These are the most common kinds of specific anxiety conditions, typically about public speaking, height, airplanes, animals or snakes, and such. Specific phobias are common in childhood, but some types - especially speaking - persist in adults also. Behavioral therapy methods are effective.
- Post-traumatic stress: After the experience of a major trauma, anxiety symptoms follow, both acutely and long-term, related to flashbacks and nightmares. This is not a disease, in the biological sense where a genetic or biological cause has a natural course unrelated to life experiences, but rather a psychological response to extremely stressful experiences. PTSD occurs in about 10-20% of persons who experience major traumatic events, like childhood sexual abuse or war. Overall, PTSD in the US in recent years is diagnosable in about 5% in men and 10% in women.

- Obsessive-compulsive disease: This condition is a genetic disease, or the result of streptococcal infection, occurring mainly in childhood, and persisting in some persons into adulthood. One might say it is the only pure anxiety disease. A common error is to diagnose the disease of OCD when anxiety symptoms of OCD occur as part of mood or psychotic illnesses. In those cases, once again, when the underlying illness is treated, and mood or psychotic symptoms completely resolve, OCD symptoms also resolve. **One review** suggests that about one-half of cases of apparent comorbidity of OCD with bipolar illness in fact represents OCD symptoms as part of mood episodes of bipolar illness, which resolves without specific anti-OCD treatments when the mood episodes resolve. Like schizophrenia, the independent disease of OCD is uncommon, happening in about 1% of the general population.
- "Anxiety in the face of unavoidable life crises...is no disorder."*

Existential anxiety

Kierkegaard was on to something. Not all anxiety is normal; certainly there are four major kinds of abnormal anxiety, as described above. But some anxiety is normal, which could be conceived in the concept of the normal curve. Another way of thinking about how anxiety can be normal is in terms of psychological development: The Freudian notion that we go through life stages has a rationale. There is childhood, then adulthood, then late life. And in each phase there are transitions that can be difficult: adolescence, mid-life, late-life illness. Losses occur, and death is present in the end. This is what Kierkegaard and others, like the psychiatrist Karl Jaspers, meant by the normal anxiety of existence. The existential psychiatrist Viktor Frankl, who was imprisoned in

Auschwitz, noted that the healthiest prisoners were the anxious ones; they survived. It was the calm apathetic ones who perished.

The pale DSM term is “adjustment disorder” which is both weak and false. Anxiety in the face of unavoidable life crises - in someone who isn’t high on neuroticism as a personality trait and who doesn’t have manic-depression or schizophrenia or OCD or PTSD - is no disorder; it’s human existence. And it’s healthy.

A little history on GAD

Readers will note, after all this discussion on anxiety, that PL has not mentioned “generalized anxiety disorder” (GAD) or “panic disorder” or “social anxiety disorder”. There is a reason for this fact, which a little history can explain.

These three terms, which are the most common DSM diagnoses made in persons with anxiety symptoms, were created with DSM revisions, beginning in 1980 with DSM-III. As described below in the psychopathology article, none of these terms were used for a century in favor of another concept: “neurotic depression”.

As reviewed well in **new historical writings** using the minutes of the DSM-III task force, and interviews with participants in that process, we now know that the creation of GAD in particular involved finding a political compromise to allow for the removal of the term “neurotic depression.” As described below, the DSM-III leadership, headed by Dr Robert Spitzer, wanted to remove neurotic depression, but many of the psychoanalysts who were rank and file members of the American Psychiatric Association (APA) resisted this radical change. Neurotic depression

had a Freudian basis in unconscious conflicts, and it was their main insurance code. The term “major depressive disorder” (MDD) was created broadly to include those with neurotic depression, but some psychoanalytic psychiatrists still felt that the importance of anxiety was not captured by the MDD category. Spitzer then invented the term “generalized anxiety disorder” for those same patients; the criteria were created to capture the neurotic depressive presentation, and hence they overlap in most symptoms with MDD. But a little more emphasis is placed on anxiety. Look, said Spitzer: You can replace neurotic depression with not one, but two, codes: you can say those patients have MDD comorbid with GAD. There was still opposition. Literally about a week before the final vote the APA assembly on passing DSM-III, Spitzer went to a psychiatric dictionary, and found the term “dysthymia”, which had meant a mood

temperament of mild chronic depression occurring in persons with manic-depressive illness. The term was hardly known in American psychiatry in 1980. Spitzer resuscitated it and redefined it to reflect chronic mild depression in general, unrelated to bipolar disorder. He argued to the APA assembly that now three codes could be given in the old neurotic depression patients: MDD and comorbid dysthymia (“double depression” some now call it) and comorbid GAD. Three diagnoses in place of one.

Still the APA general assembly hesitated. In the final hours of the vote on DSM-III, still another final compromise was brokered. The new category of dysthymia would be included with a parenthesis next to it as follows: “Dysthymia (neurotic depression)”. The term for neurotic depression, was, after all these controversies,

“Someone joked: DSM-III passed the APA assembly vote because of a parenthesis.”

included in DSM-III in the end. But only as if it was a synonym for dysthymia (which it isn’t).

Someone joked: DSM-III passed the APA assembly vote because of a parenthesis. Seven years later, DSM-III quietly removed the parenthesis of neurotic depression from the dysthymia category.

“GAD” or personality?

This brief history can highlight for readers that the origin of GAD is based on professional/social considerations, not on scientific studies. As reviewed earlier, the scientific evidence base is extremely strong for mild constant anxiety as being part of an extreme of a personality trait. The scientific evidence base for GAD in the past

30 years is, in the estimation of PL, weak. When thinking of diagnostic validators

that demonstrate that a condition is a different valid diagnosis compared to other conditions, as reviewed in the first issue of PL, the scientific consensus is to examine symptoms, genetics, course, and biological markers. GAD does not differ from MDD on most of its symptoms; **some genetic data** indicate that GAD has low genetic heritability (about 30%) and cannot be differentiated genetically in twin studies from MDD; its course is constant which is similar to personality traits; and its biological markers are nonspecific markers of stress, such as elevated adrenal activity; there are no specific definable biological markers that differ from mood illnesses or other conditions. In short, the evidence for the validity of GAD as an independent valid clinical construct is weak both historically and scientifically.

This is why PL recommends that anxiety be seen in the above five constructs, with the chronic mild anxiety that DSM-5 continues to label as GAD being seen by PL as usually part of the personality trait of high neuroticism.

A brief comment on panic disorder and social anxiety disorder: These terms were also created for DSM-III in 1980 or in later revisions. Panic attacks and social anxiety usually happen in persons also diagnosed with GAD, or often as part of mood or psychotic illnesses. The PL view is the same regarding these anxiety states as with any anxiety symptom: they often represent other conditions, like mood illnesses, or they are simply part of the high anxiety state of persons who have a high score on the baseline personality trait of

neuroticism. As with GAD, if the scientific literature is examined in the four diagnostic validators, the PL viewpoint is that there is very weak scientific ground to claim that panic “disorder” or social anxiety “disorder” are valid independent clinical constructs. (In other words, these conditions do not differentiate well from other diagnoses or from personality traits on symptoms, course, genetics, and biological markers). PL thus recommends seeing panic attacks and anxiety in social settings as anxiety symptoms that occur as part of other anxiety states (like OCD or PTSD), or as part of other illnesses (like mood conditions), or as simply expressions of the heightened tendency to anxiety of some persons with the personality trait of high neuroticism.

*Selected References: For DSM history, Hannah Decker, *The Making of DSM-III*, New York: Oxford, 2014; Hans Eysenck: *The scientific study of personality*, 1952; PT Costa, RR McCrae, *The NEO Personality Inventory, Psychological Assessment*, 1992, 4:5-13; Viktor Frankl, *Man's search for meaning*; 1946. A more complete reference list and links are available in this article on the PL website.*

Current study of the month: Placebo and nocebo effects for anxiety and depression

The role of patient expectancy in placebo and nocebo effects in antidepressant trials.
BR Rutherford et al, *J Clin Psychiatry* 2014 Oct;75(10):1040-6

Placebo effects aren't all good

Some people worship the placebo effect. They think it's all good. They don't realize that the same person who has good benefits from a drug, based on psychological expectancy, will also have bad effects from drugs, based on psychological expectancy. In other words, the placebo effect is not always positive; there's also a negative placebo effect - called the “nocebo” effect (Latin for pain-producing). This study suggests that *wherever there is a placebo effect, there is also a nocebo effect*. We can use older terms to understand this process: it may be that placebo/nocebo effects happen in suggestible persons, people who used to benefit from hypnosis, people who used to develop

hysterical paralysis of limbs. These persons are psychologically sensitive: they expect to get better, so they feel better; but they also worry about getting worse, so they get worse.

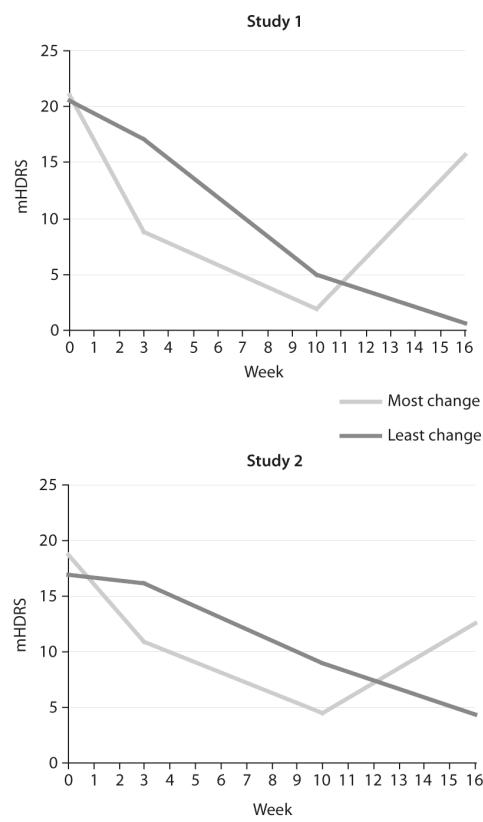
This is a major problem in the treatment of anxiety conditions. Randomized clinical trials (RCTs) of generalized anxiety disorder (GAD) and panic disorder all suffer from the major problem that placebo responses are always quite high (usually 50% or subjects or more). But as all clinicians who treat anxious patients know, those same patients worry so much - about side effects, about loss of response, about not getting better - that any placebo-related benefits are transient.

Sooner or later, the mind, which happily feels better for a while, worries itself back sickness.

This analysis of two RCTs of fluoxetine in major depressive disorder (MDD) provides data to prove this point. (Recall that “MDD” includes many patients with anxiety who used to be diagnosed with “neurotic depression”, as discussed below). The study examines patients who responded to fluoxetine in 8 weeks of open treatment (meaning they knew they received the medication). Then they were blindly randomized to continue fluoxetine or switch to placebo. This analysis is not about how fluoxetine did in the randomized trial. It's about how the fluoxetine responders did once they realized that they might *not* continue to receive it. The figure shows the main finding: The best responders to fluoxetine (the top 10%) had a major improvement in Hamilton Depression Rating Scale (HDRS) scores; the lesser responders to fluoxetine (the lowest 10% in the open phase) also improved in the HDRS but with a smaller slope. Keep in mind that they all responded to fluoxetine: it's just a comparison of those who responded strongly versus those who responded moderately.

In the figure, the data shown are for those who were randomized to stay on fluoxetine, even though they didn't know it. Note that the very strong responders to fluoxetine in the open phase suddenly worsened, with rising HDRS scores, despite staying on fluoxetine. In other words, their worry about coming off the drug made them get more depressed, *despite staying on the drug*. This is the nocebo effect. Conversely, their major benefit with fluoxetine in the open phase (when they knew they received it) was likely a partial placebo effect. In contrast, the group that had a moderate open phase benefit continued to improve in the double-blind randomized phase.

Figure 4. Mean Trajectories for Individuals Remaining on Fluoxetine Who Had the Highest 10% and Lowest 10% Amount of mHDRS Change Postrandomization^a



^aCurves are based on mean mHDRS trajectories across 29 (most change) and 30 (least change) individuals in study 1 and 14 (most change) and 13 (least change) individuals in study 2.

Abbreviation: mHDRS = modified 17-item Hamilton Depression Rating Scale.

Their benefits were probably more physiological than psychological.

In short, be careful about praising and relying on psychological expectations. Placebo effects may occur, but so can nocebo effects. If a person's mind controls their body for the better, it can also control it for the worse.

The PL Bottom Line

- Placebo and nocebo effects go together.
- The same patients who get better based on psychological expectations also get worse based on psychological expectations.

Drugs of the Month: *Benzodiazepines*

More addictive than caffeine, less than cocaine

Benzodiazepines were the source of major controversy, and major drug company profits, in the 1980s. Now they are all generic, and as past controversies have subsided, clinicians seem to have settled into two basic camps: one group thinks these drugs are very addictive, and rarely prescribes them; another group thinks addiction concerns are way overblown, and prescribes them commonly. The PL approach is a third way: they are addictive, but not in most people.

It's useful to numbers to addiction concerns. In **available data**,

about 15% of persons with severe mental illness (schizophrenia or severe bipolar illness) who are prescribed benzodiazepines eventually become addicted to them. This isn't a small number, but it is a minority. Rates

should be even lower in milder anxiety/depressive conditions.

So the PL perspective is simple: These agents can be given to persons with mild anxiety/depressive conditions, but should be avoided in those with more severe psychiatric conditions with past substance abuse. Addiction is highly unlikely in the former, and possible in the latter.

Clinical efficacy and inefficacy

Once the addiction question is settled, the main issue is efficacy. These are basically symptomatic drugs that reduce anxiety symptoms immediately, in all persons, normal and sick; that is why they can be addictive. Like amphetamines and other addictive medications, everyone who takes them "gets better"; this doesn't mean that any disease has been treated.

As discussed above on the different kinds of anxiety, the main question is when and how much of these agents should be used for anxiety symptoms. When

severe anxiety is caused by another disease, which is the most common case, then the mood disease, for instance, should be the focus, not reducing anxiety symptoms with benzodiazepines. Of course, like Tylenol for fever, these agents can

be used temporarily to make patients more comfortable. But the focus should remain on treating the mood disease that is causing the anxiety symptoms. In other types of anxiety, like personality traits or existential anxiety or neurotic depression, benzodiazepines can have a symptomatic role, but again as with opiates or NSAIDs for pain, clinicians should be aware that the treatment is purely symptomatic, and not a long-term solution. The benzodiazepines should be used short-term and at low doses at

Fast Facts: Three typical agents

Typical agents: Short onset (<30 minutes)/short half-life (2-3 hours) - alprazolam; Medium onset (30 minutes)/medium half-life (8 hours) - lorazepam; Long onset (>30 minutes)/long half-life (12-24 hours) - clonazepam

Typical agents' effective dose: 0.5-2 mg/d for all three agents. Note that clonazepam is more potent per mg dose than other agents. Maximum recommended dose is 4 mg/d of any agent.

Biological mechanism: GABA agonism

Typical side effects: Sedation, incoordination, poor memory

Less common but important side effects: withdrawal seizures

Clinically proven efficacy: acute panic attacks

Questionable efficacy: long-term prevention of anxiety symptoms

possible, and preferably as needed rather than standing dose.

This doesn't mean that some persons may not need standing dose and long-term treatment, but the clinical concepts of anxiety described above, and the scientific literature on benzodiazepine efficacy, do not support such constant and long-term use for these agents.

The **longest outcome study** in a randomized clinical trial for any benzodiazepine (which was with clonazepam) is about 6 months. FDA language is clear about benzodiazepines: they should be used mainly short-term. In this case, the scientific evidence seems to support the FDA language. Yet it is commonplace for benzodiazepines to be used long-term with little question. PL recommends that many, if not most patients, be treated short-term and then benzodiazepines should be stopped and retained for later short-term use if needed. Of course, tolerance, with reduced response over time, also occurs (to be discussed in future PL issues, along with more detail on withdrawal and tapering protocols).

Biological mechanism

These agents are GABA agonists by directly opening chloride channels. This effect is immediate, as is the clinical effect.

Specific agents

There are over a dozen agents in this class, mostly differing in pharmacokinetics: speed of onset and

half-life. PL has selected three representative agents that differ in pharmacokinetics: clonazepam (slow onset, long half-life), lorazepam (medium onset, medium half-life), alprazolam (fast onset, short half-life). In general, PL prefers lorazepam for most uses, especially intermittent as needed use. Alprazolam is somewhat more addictive due to its very rapid onset and offset, and clonazepam is usually too slow for as needed use. Clonazepam can be used long-term standing use, but as noted, PL prefers to limit long-term benzodiazepine treatment.

Side Effects

Sedation is the most common side effect of the class, along with cognitive impairment (clonazepam being worst for both). Incoordination can be risky (e.g., automobile driving), and ataxia can occur. Withdrawal symptoms include risk of seizures.

The PL Bottom Line

- Since most anxiety treatment is symptomatic, and not reflective of an anxiety disease, these agents are best used short-term as needed.
- Long-term efficacy of benzodiazepines is not established in randomized clinical trials and is questionable.
- Of the three prototypic agents, lorazepam is most preferable, followed by clonazepam. Alprazolam is more addictive than the others and should be avoided generally.
- Side effects include sedation & incoordination. Seizures can occur in withdrawal.

MF Brunette et al, Psychiatric Services, 2003, 54:1395-1401. See website article for more links.

Clinical tip of the month: Divalproex is anxiolytic, lamotrigine is anxiogenic.

If using anticonvulsants in someone prone to anxiety, all other things being equal, keep in mind that valproate may have an advantage over lamotrigine for anxiety. Valproate has moderate gabaergic properties, so it can have some direct anti-anxiety effects. The glutamate blocker lamotrigine has no effects on GABA and is not anxiolytic directly; at higher doses, especially above 200 mg/d, it causes increased anxiety as a side effect.

Psychopathology: Neurotic depression

There are two (or more) depressions, not one

In the 1970s, there was a major debate in London between two different ways of understanding depression. To simplify: one group believed that all depression was of one kind, the other group believed that there were two different kinds of depression. The consequence of this great battle – won by the “one depression” group – has produced the nosology of the last 40 years, of the one great big depressive category we call “major depressive disorder” (MDD).

The British debate

The main proponent of the single depression theory was Sir Aubrey Lewis, leader of the Maudsley Hospital, England’s most prominent psychiatric institution. Lewis’ professional power in that position likely helped him win the day. His main opponent was Sir Martin Roth, who held positions in less

prestigious universities, like Birmingham, although he would end his career

at Cambridge University. Both men were immigrants, Lewis from Australia and Roth from Austria. Their origins had some impact on their views: Lewis was the classic example of the British Commonwealth empiricist; he was pragmatic, hard-nosed, fact-oriented, and experiential. Roth was more of a Germanic thinker, who had trained under the influence of Karl Jaspers, the great founder of the psychopathology school. Roth was empirical also, and conducted many more clinical research studies than Lewis, who was mostly an administrator. But Roth was more attuned to psychopathology, to paying attention to differences in symptoms or course and seeing

This great battle – won by the “one depression” group – has produced the nosology of the last 40 years.

them as important, as opposed to Lewis’ tendency to see a mass of facts that were hard to organize. Where Lewis saw the biases of theories used to manhandle facts, Roth saw unorganized facts that could be shown to have an inherent structure.

Lewis won, Roth lost. British psychiatry – and, more importantly, their American colleagues – was convinced that depression was one big, complex mass. And you couldn’t make much more sense of it. In the US, at the same time, intense work was being conducted on the beginnings of DSM-III, which would be formalized at the end of the decade in 1980. A major change was the creation of the category of MDD, a very large depressive group that would become the most commonly diagnosed psychiatric illness in succeeding decades, and which would lead, with

the introduction of Prozac, into an explosion of antidepressant use, reaching about 10% of the population in many Western countries.

The claims

What did they say? What were the claims made for and against the one depression theory?

Roth claimed that there were two kinds of depression. They can be labeled with different, similar but not entirely synonymous terms: endogenous versus exogenous, biological versus situational, organic versus functional. Those terms had been used for decades, but, by the mid 1970s, the psychiatric profession had grown tired of them. Lewis systematically showed their illogic: The “endogenous” depressions could be shown to be triggered by environmental events;

and the “exogenous” depressions could be shown to have bodily changes in neurotransmitter function. The biological depressions were said to have genetic sources, but familial transmission could be shown in the situational ones too. The organic depressions supposedly involved changes in the brain, but imaging studies until then had failed to demonstrate such changes.

In sum, no clear distinction could be drawn among the mass of depressive presentations based on the biological versus non-biological distinctions proposed.

There was another way of putting these distinctions which Roth described, but which Lewis and the rest of the psychiatric profession appears to have failed

to understand. Roth said the real distinction to be made was not any of the

dichotomies above, but the distinction between *neurotic depression* and manic-depression. 40 years later, using not just Roth's studies but future ones, PL thinks that this distinction made by Roth is supported scientifically much better than the claim that all MDD is one condition that cannot be differentiated further.

Neurotic depression: American versus European definitions

What is this neurotic depression? It's important to appreciate that it meant something different to Roth in the German psychopathology tradition, as opposed to what it meant in the US in studies from the 1970s, based on the Freudian tradition. For Roth and his followers, neurotic depression simply meant the presence of anxiety mixed with depression. This anxiety tended to be mild to moderate in intensity, and it was chronic and constant. It could have brief exacerbations, to

being more severe in intensity, triggered by environmental events. But it always returned to its mild to moderate baseline of a mixture of anxiety and depressive symptoms. The “neurotic” component was simply a synonym for what we would call “anxious”. No inference was made as to the causes of the anxiety component, beyond the general implication that it was part of a person's “constitution”, i.e., part of their personality or temperament.

In the US, the phrase “neurotic” was interpreted in a Freudian manner: neurosis and psychosis were the two basic categories used to organize symptoms. Their definitions had to do with presumed psychological causes, not the symptoms primarily. So, all symptoms were due to

unconscious emotions
or drives, derived from
childhood, which were
repressed or
transformed in some
way by defense mechanisms. If the unconscious emotional conflicts were mild to moderate, neurotic symptoms of anxiety and/o depression and/or mania and/or obsessions were produced; if the unconscious emotional conflicts were severe, psychotic symptoms of delusions and/or hallucinations were produced. That's it.

The politics of DSM-III

The DSM-III advocates in the US wanted to get rid of Freudian interpretations as the basis for psychiatric diagnoses, so the term “neurosis” had to go. (It's interesting to note that the term “psychosis” wasn't rejected, and still remains in all future DSM revisions in the general category of “psychotic disorders”.) “Neurotic depression” had been the most commonly used diagnosis by psychoanalysts in the US into the 1970s; by the use of that term, American psychiatry inferred that everyone had some unconscious emotional

conflicts, hence everyone was treatable, in principle and often in practice, with psychoanalysis. If we worry about overpathologization today, that same concern was magnified exponentially with the psychoanalytic approach to diagnosis. So American DSM-III advocates were adamant on this issue: “neurotic depression” had to go.

The American inclination to reject this diagnosis for professional reasons merged with the British clinical debate, but no one noted that the two groups were discussing *two completely different definitions* of the same phrase. This error looms large now and calls for an explicit clarification: By neurotic depression, PL refers to *the psychopathological observation of anxiety symptoms mixed with depression, not the Freudian idea of unconscious emotional conflicts*.

As noted above, GAD also evolved in the process of DSM-III as another way to compromise with clinicians about neurotic depression.

Neurotic depression today

The table describes Roth's definition of neurotic depression (ND), as modified by the PL editor. To examine the validity of ND, we'll use the four diagnostic research validators, as described in the PL January issue: symptoms, genetics, course of illness, biological markers, and treatment response. A contrast with manic-depression (by which

we mean bipolar disorder and unipolar depression, see PL website) is made.

Symptoms: In ND, anxiety symptoms are prominent and mixed with depressive symptoms. In manic-depression, depressive symptoms are prominent and occur with little to no anxiety.

Course: In ND, anxiety and depressive symptoms are constant and chronic; they are the baseline state. In manic-depression, mood symptoms occur as severe episodes, which differ markedly from the baseline state.

Genetics: ND has little to no genetic loading, unlike manic-depression.

Biological markers: In ND, there is no strong definable consistent biological abnormality in the brain. In manic-depression, there are strong definable consistent biological abnormalities in the brain (e.g., hippocampal atrophy in depression, amygdala enlargement in mania).

Treatment response: In ND, antidepressant medications are modestly effective, and can be shown to reflect placebo response mostly. In manic-depression, mood-stabilizing and/or antidepressant medications are notably effective.

Roth had data to support some of the distinctions above (symptoms, genetics, course), and future research has added material in support of his view (in genetics, biology, & treatment).

Roth's criteria for neurotic depression (modified)

- 2-4 major depressive episode criteria (i.e., does not meet full MDE criteria)
- Chronic psychological worry or multiple somatic symptoms every day most of the day
- Duration > 6 months
- Mood is reactive to environment stresses (unlike melancholia)
- Absence of severe rage or marked psychomotor agitation (unlike mixed depression)
- Full major depressive episode exacerbations occur but are brief (< 2 months in duration)

It is relevant to mention here, as is explained further on the PL website, that the term manic-depression is meant to reflect what today we call bipolar illness, as well as what was termed “unipolar depression” in the 1970s. (Unipolar depression is now folded into MDD; see the PL website for further clarification).

The red herring of life events

How did Roth lose this debate? He lost because neither he nor Lewis appreciated the life events, and the influence of social stressors, was a red herring in the diagnostic question.

The “neurotic” aspect of this condition can be understood, as Roth and the Germanic tradition long hypothesized, as part of the personality trait of neuroticism, as described previously. Those who are naturally high on neuroticism are likely to respond to their environment more sensitively, and become more anxious and even depressed temporarily in reaction to negative environmental experiences. The rest of us, more middling in anxiety, may be transiently unhappy or anxious with those same life experiences, but for hours or days, not for weeks and not as severely as in the more neurotic person. Twin studies show that personality traits are about 50% genetically heritable, which is about equivalent to the physical trait of weight. In other words, about half (which is a good portion) of neuroticism is genetic, i.e., biological.

So life events are relevant to neurotic depression for acute exacerbations, but they aren’t relevant for baseline symptoms. And neurotic depression is partly biological, not completely environmental.

Similarly, in manic-depression, life events often trigger the timing of acute mood episodes, but twin studies show that bipolar illness is about 80% genetically heritable, which is about equivalent to the genetic heritability of physical

height. In other words, life events have very little role in baseline predisposition to having severe mood episodes in manic-depressive illness. But environment influences the timing and frequency with which a person with that predisposition will have mood episodes; with more negative life events, more mood episodes occur.

So, just as with neurotic depression, life events are relevant to manic-depression for acute mood episodes, but they are not very relevant for etiology or baseline predisposition to mood episode. And manic-depression is partly environmental in its episode frequency, not completely biological. These were the overlaps that Lewis noticed, and used to beat Roth into submission. But these overlaps can be understood easily, as representing different contributions of biology and environment, in different ways, for two different conditions. Genetics and course and biological markers still distinguish these two clinical conditions, and life events/environment can be understood in that context. In other words, similarities in the role of life events/environment don’t invalidate a diagnostic distinction between these two conditions.

Treatment implications

Since neurotic depression has been legislated away by DSM for 4 decades, few studies examine its treatment. Until that vicious circle is opened by research on this condition, the PL experience is that antidepressants may be less effective, and long-term psychotherapy more effective, in neurotic depression as opposed to other depressive states. The evidence of antidepressants includes two likely relevant analyses (with more detail on the PL website and in future PL issues): In the large STAR*D study, where GAD was “comorbid” with MDD, antidepressants were less effective than in MDD without GAD. In a large meta-analysis of randomized trials in the FDA

database, antidepressants were equal to placebo in MDD of mild symptom severity. Those analyses may be proxies for the clinical population defined here as neurotic depression. Patients got better, but they got better with placebo equally to antidepressants; there was nothing physiologically important about taking antidepressants. This reflects, in the PL viewpoint, the natural fluctuations in mood symptoms in neurotic depression, but it also raises the question whether psychotherapies might be sufficiently effective so as to render antidepressants unnecessary, or infrequently needed. Since neurotic depression is a personality-based condition that doesn't go away, that psychotherapy would be long-term and would have modest goals, such as better coping skills, rather than complete removal of symptoms. Little research has been done along these lines.

The PL Bottom Line

- Neurotic depression - a mild to moderate chronic anxiety/depression condition - is a valid clinical diagnosis
- In neurotic depression, anxiolytics and antidepressants are less effective, and should be used mainly short-term for exacerbations.
- Long-term psychotherapy may be most useful.

Further reading: Edward Shorter, *The doctrine of the two depressions in historical perspective*. Martin Roth, *Unitary or binary nature of classification of depressive illness*. *Journal of Affective Disorders* 64 (2001) 1–18. SN Ghaemi, *Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression*. *Bipolar Disord.* 2008, 10:957–68.

PL Reflection

Some neuroses you have to bore to death.

Elvin Semrad

Case of the month:

Treating anxiety symptoms in PTSD

A 25 year-old female seeks treatment for anxiety and depression. She experienced repeated childhood sexual abuse by her father at ages 8-10. In the last few years, she has had constant depression, with periods of worsening related to life stresses. She is also constantly anxious, with panic attacks at times, and flashbacks and nightmares that occur in waves (i.e., a week or two of multiple flashbacks/nightmares, followed by 2-3 weeks without them). She doesn't abuse substances, is a single mother with two children, and lives on disability. She reports anxiety and depression in family members but they mostly avoid psychiatrists, so most are not diagnosed.

Five years ago, she received fluoxetine, later sertraline and duloxetine, each with mild benefit. In the past year, she took venlafaxine, which helped her anxiety moderately at 150 mg/d, but then she began to worsen again in the past few months. Her psychiatrist tried to switch venlafaxine to citalopram, but she experienced marked serotonin withdrawal. Current medications are Effexor 75 mg/d, clonazepam 1 mg twice daily, and quetiapine 50 mg for sleep.

The PL diagnosis and clinical impression

The PL diagnosis is PTSD, based on available information. As reviewed on the PL website, PTSD improves only moderately, at best, with medications. Her history with SRIs is consistent with this scientific evidence. Thus, the PL approach is to realize that there is not much benefit to be gained by medications. Modest symptoms benefits on one hand are weighed against some side effects, the most important now being serotonin withdrawal syndrome. The patient becomes connected to SRIs in a way that is very difficult to stop, and can lead to years and

years of treatment, despite only modest symptomatic improvement.

The PL recommendation is to cross-taper venlafaxine with fluoxetine (add 20 mg of fluoxetine, reduce venlafaxine to 37.5 mg/d for 2 weeks, then stop venlafaxine. Then reduce fluoxetine one month later to 10 mg/d for one month, then stop it), since the latter has the least serotonin withdrawal. Clonazepam is changed to lorazepam 1 mg twice daily as need for more immediate symptom benefits. In weeks where the patients' flashbacks and nightmares are worse, she is instructed to take lorazepam on a standing dose twice daily. When the PTSD symptoms naturally remit, lorazepam is reduced again to as needed.

In the year following these changes, the patient does not do better than she had in prior years with SRIs, but she does not feel worse either. She continues to engage in weekly psychotherapy, very gradual but persistent improvement in severity and frequency of PTSD exacerbations.

The PL Bottom Line

- Benefit for PTSD with long-term SRIs is limited.
- As needed benzodiazepine use provided similar benefit to more extensive SRI use, with less medication usage and thus less overall harms.
- Psychotherapy, not medication, is the main effective long-term treatment in this case.

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Curbside consults:

Questions and cases from you

Question: Back in the day, we used a descriptive category "agitated depression." People were depressed, pacing, wringing their hands, crying. Do you think this was what you are now calling "mixed depression" in the February PL issue?

PL: Yes, agitated depression is subsumed in the mixed depression concept, but the latter is a bit broader. Koukopoulos explained it this way: the mixed depressive patients are generally agitated, but that's not the whole picture. They also are rageful and have a lot of mood lability; those latter concepts aren't appreciated with just the concept of agitation. Agitation and rage and mood lability all combine to give the whole picture. Add in bipolar genetics (frequently) and worsening with antidepressants, and then note that it happens in both bipolar and unipolar illness, and you get the overall concept. By challenging the bipolar/unipolar distinction and introducing poor antidepressant effects, the mixed depression concept is not purely descriptive, but a new subtype of depressive illness that challenges the MDD dogma.

PL Reflection

Irrationally held truths are more harmful than reasoned

THE PSYCHIATRY LETTER

Suicide special issue

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Springtime has the highest rate of suicide, with April the peak in the Northern hemisphere, so this April issue of PL will focus on suicide. Most people with psychiatric symptoms present with depression or anxiety; a smaller group has delusions or hallucinations; many also abuse alcohol or drugs. Many suffer. Some die. Suicide is the ultimate psychiatric suffering - a major way these illnesses directly lead to death.

The job of the clinician is to relieve suffering and, if possible, to stave off death. In psychiatry, this means preventing suicide. There is, in the end, no more important task for the mental health clinician.

Those of us who have been in practice long enough, and have seen enough patients, have experienced this unfortunate outcome. I've experienced it about half a dozen times in two decades, with patients or ex-patients, and even more in consultation with families of those who killed themselves.

In this issue, the special article provides an overview of how to understand suicide, with the conclusion that mood diseases are central. Two studies of the month examine major meta-analyses of medications and suicide, showing some harm with antidepressants and major benefit with lithium. We introduce a "Statistical Concepts" column to help us understand the clinical research literature; there the most important statistical concept of confounding bias is explained. The case of the month examines a young adult whose suicidality improves by stopping antidepressants, consistent with the FDA meta-analysis described earlier. The issue ends with a lesson from the psychopharmacology course on the neuroanatomy of monoamines, explaining why serotonin reuptake inhibitors aren't selective.

Thank you for your continuing to read and follow PL.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Explaining suicide*

Complex, but not unpredictable

Fill up a small baseball stadium, like Fenway Park in Boston, with people. About 41,000 persons. Those are the number of people who kill themselves every year in the US. That comes out to over 100 persons daily, about 5 persons per hour. The World Health Organization estimates that about 1 million people in the world commit suicide yearly.

Suicide is to psychiatry what mortality is to medicine: our ultimate goal and responsibility in treating psychiatric illnesses. We may or may not succeed in making people happier, or more functional, or more satisfied with their lives. But we ought to at least help them stay alive. We can't be satisfied with the old morbid surgical joke: The operation was a success, but the patient died.

The only philosophical problem

Suicide is not solely a psychiatric matter. Albert Camus wrote that suicide is "the only really serious philosophical problem. Deciding whether or not life is worth living is to answer the

fundamental question in philosophy. All other questions follow from that." Death, more broadly, is a basic human dilemma. We are born all of a sudden; we are alive. We don't choose to live. But suicide raises the fact that we do have to choose to keep living. For most people, this is not a problem. We want to live, so we just keep living.

But there is a good deal of biological, and clinical, and sociological evidence that human beings are very aggressive creatures. In other words, as Freud put it, besides our Life instinct, we have an aggressive or destructive instinct. We not only

want to live, we want to harm, to hurt, even to kill. Sometimes we even want to kill ourselves.

It is a basic fact, hard to deny, that most human beings throughout history have demonstrated a willingness, under the right circumstances, to kill others. We kill animals routinely, to eat them. And there has never been a period of human history without wars, where we kill each other.

So, at one level, it can be considered that Camus may have been right: there is a basic human instinct to aggression, to violence, usually directed to others, but sometimes to oneself.

The question then becomes: Bad as it is to kill others, to commit homicide, why do some people kill themselves?

"Secular" factors

Before we go on to psychiatric explanations, it is worth pointing out that there are other perspectives. A prominent one is the social explanation, the view that suicide has to do with problems in

society. The French sociologist Emile Durkheim first described this view in the 19th century in his classic book, *Suicide*. Durkheim was the first person to describe population-based statistics on suicide. His impression was that suicide had increased in frequency in the 19th century compared to what was presumed to be the case in earlier centuries. He drew a simple conclusion: Suicide is the result of modern life. The big difference between modernity and the middle ages is industrialization; we work in factories and offices in cities where we avoid each other and where we are separated from families of origin.

“Anomie” was the phrase Durkheim coined: our modern sense of isolation and alienation from each other and from the verities of the past - religion, God, the King.

Many have debated Durkheim’s claim, but it’s clear that some related claims are wrong: they mistake correlation with cause. Some thought that living in cities caused suicide, since suicide rates are much higher in cities than in the countryside. Of course, there are more people in cities too, and those with psychiatric illnesses are often brought to cities, or decide to go there, to seek treatment at medical centers.

This latter point is important - a common mistake people make about suicide. Antidepressants were introduced decades ago; suicide rates went down. But you can’t draw a causal relation. Republicans took over the White House for most of three decades; suicide rates went down. The connection isn’t necessarily causal.

These are called “secular” factors in suicide: social and cultural changes that can affect the entire population, and possibly affect those more prone to suicide negatively.

Four relevant secular factors are poverty, political crisis, war, and sunlight.

Poverty, tyranny, and war

John Kennedy identified, in his 1961 inaugural address as president, four major scourges of mankind: “poverty, tyranny, disease, and war itself.” We can think of each of these scourges as causes of suicide. We’ll discuss disease at length. Here let’s put together the other three major social factors: poverty, tyranny, and war.

One way of addressing these complex social factors is to examine national rates of suicide:

Greenland has by far the highest rate of suicide in the world, followed by Lithuania, South Korea, Guyana, Kazakhstan, Slovenia, Japan, and then a number of other East European countries. The lowest rates in the world are in Nepal, preceded by Haiti, Grenada, other Caribbean islands, and then Egypt and multiple Middle Eastern states.

Examining this list, poverty doesn’t stand out as a risk factor: Japan is wealthy but has a high suicide rate; Haiti is quite poor but has low suicide rates. The presence of multiple East European nations suggests that tyranny, or something related like political instability, could be a risk factor; but the very low rates in Middle Eastern states suggests otherwise. The countries with very high rates don’t tend to have had recent wars, but there is no clear correlation. Bosnia suffered a major recent war but ranks similar to the US in

suicide rates (28th in the world for Bosnia, 30th for US, out of 111 countries examined).

In short, these secular factors, which you might think would increase suicidality, don’t have strong correlations with suicide. Of course moderating factors, like religion perhaps, could be relevant, and deserve more study.

Sunlight

The last secular risk factor of sunlight turns out to have a much stronger effect, compared to poverty and war, on risk of suicide.

As described in the first issue of PL, there is a direct correlation, though small, between more sunlight and more suicide. There is a much larger correlation between season of the year and

suicide, with springtime being the highest risk, followed by fall. In the spring, there is rapid increase in sunlight as winter transitions to summer; in the fall there is steep decline in light, as summer transitions in winter. In both cases, it seems that the *slope* matters: when there is a change in light, people become more suicidal. Specially, people with mood illnesses appear to be most sensitive to these seasonal changes in light. The slope upwards, from less to more light in April and May, seems to be the most harmful change: one can infer that winter depression is shifting to summer mania, with many people developing mixed mood states, which are the most likely mood states to produce suicide.

Psychological autopsies

One way of identifying what causes suicide is to do “psychological autopsies.”

This involves taking cases

of suicide and trying to identify common correlates. In this research the following correlations have been found at the time of suicide: clinical depression; the use of antidepressants; anxiety; past suicide attempts; financial or marital/romantic problems; alcohol and substance abuse; male gender; access to firearms; social isolation; older age; white race; German or northern European ethnicity.

When you look at this list of risk factors, you might create the ultimate suicidal profile: an older white male of German ancestry who drinks alcohol excessively, owns a gun, lives alone, just got divorced, tried to kill himself previously, is anxious and depressed, and just got started on an antidepressant. This isn't a serious claim of course. The idea is that the more of these types of features we see, the more we should be concerned about suicide. In studies where many suicidal risk factors are identified in at-risk

persons, though, most such persons still don't commit suicide. So these risk factors are about relative risk, not any predication that all or even most such persons would commit suicide.

It's easy to overestimate or underestimate these risk factors. Take past suicide attempts: It's rational to view them as a risk factor for suicide. But about one-half of persons who kill themselves do so with the first attempt. For half of all suicides, the first time is the only time. You can't predict their cases by past attempts.

Take anxiety: As discussed in the last PL issue, anxiety is a basic personality trait, with a normal distribution. About one-fifth of the general population has “high” anxiety based on being in the top 2 standard deviations of the normal curve.

But much less than 1% of the general population commits suicide.

Anxiety itself is a poor suicide predictor.

Psychiatric diseases

Of all the risk factors from the psychological autopsies, the most common and predictive appears to be clinical depression. Not only is it present in the vast majority of completed suicides, it works the other way around: A good chunk of persons with severe clinical depression eventually commit suicide (in contrast to anxiety and being white or being northern European in ethnicity).

It turns out that up to 20% of persons with severe clinical depression eventually commit suicide. This is a very large number, in contrast to anxiety. It is more if people have bipolar illness, as opposed to unipolar depression, and more if they've ever been psychiatrically hospitalized as opposed to solely needing outpatient treatment. If only outpatient with less severe depressive

episodes, and no manic periods, the suicide rate can go down to a 2% lifetime prevalence.

So a major risk factor for suicide is the presence of the bipolar or severe unipolar depressive diagnosis. Now we can start adding other important risk factors.

We mentioned that suicide attempts aren't present in half of patients, but when present, suicide attempts are important predictors: almost 10% of persons who make a suicide attempt will kill themselves within the following decade (Tidemalm et al 2008).

The whole picture

All these risk factors have to come together in a specific time and place. That's the final, least predictable, but most definitive description of suicide. Leston Havens

gave it a classic formulation: "Suicide is the final common pathway of diverse circumstances, of an interdependent network rather than an isolated cause, a knot of circumstances tightening around a single time and place, with the result, sign, symptom, trait, or act."

Now we can take the major risk factors, and place them in the mix as usually necessary for suicide. As philosophers put it, they are *necessary but not sufficient* conditions for suicide. Other factors - like access to a handgun, a recent relationship break-up, the failure of a clinician to return a phone call - are also needed. They provide the exact constellation that leads to the event: they are *sufficient but not necessary* conditions for suicide.

Havens always emphasized the importance of doing something about the sufficient but not

necessary conditions: those are somewhat in our control. So, return all patients' phone calls, ban handguns, help patients with their relationships. This is true, but it can be difficult to achieve these goals. Banning handguns in the US, for instance, is difficult politically.

PL suggests focusing on the necessary conditions for suicide: pay attention to past suicide attempts, be on high alert in all persons with severe depression or bipolar illness. Treat those conditions appropriately for suicide prevention, which, as we'll see, doesn't involve most of the medications we use, like antidepressants, but rather a drug most clinicians avoid: lithium.

Military suicide

A special subgroup of persons who commit suicide are current or former members of the military. This problem has been in the news recently, as a result of suicide in those who return to the US from wars in Iraq or Afghanistan. More US soldiers have

committed suicide than were killed in action in those wars. There has been some debate about what is causing these suicides. Deployment itself doesn't seem to be causal; but combat experience may be a key factor.

The experience of extensive research on PTSD in Vietnam veterans and in World War II is relevant. In that work, a major causal factor for PTSD, and resulting suicide in some veterans, was the premorbid presence of depression or high neuroticism as a personality trait. As with the civilian PTSD literature, it appears that one's psychological make-up before experiencing trauma is a key predictor of harmful outcomes,

whether it be PTSD or suicide. (See PL website on PTSD)

These observations bring us back to the importance of biology: a predisposition to depressive disease and/or anxiety as a personality trait seems to determine who responds to combat trauma with severe PTSD and even suicide, and who doesn't.

Parasuicide and borderline personality

Another at-risk clinical group involves those who engage in self-cutting or other self-harm (burning themselves with cigarettes, head-banging). Called "parasuicide", this kind of self-harm doesn't have intent to end one's life.

It's most common in borderline personality, happening in about 60% of persons with that condition. It tends to be associated with a history of past sexual abuse, but not invariably so. It's unclear whether these persons are at high risk of completed suicide, if they don't make more typical suicide attempts like overdose. As noted previously, if they do also make standard suicide attempts, like overdose, they do have a notable risk of future suicide.

Antidepressants: Causes or cures?

We come to the great debate about whether antidepressants cause or prevent suicide. In the classic article in this issue, we provide the evidence from the FDA database showing that SRIs increase the risk of suicide in young adults and children (although not in middle age or older persons).

The profession of psychiatry has worked hard to minimize the implications of this FDA analysis and its follow-up black box warning. It's claimed that suicide rates went down when antidepressants were introduced widely in the

1970s through the 1990s. It's claimed that suicide rates went up after the black box warning when antidepressant use declined in adolescents and children. It's claimed in some analyses of insurance records that suicide rates don't go up after antidepressants are given, but rather decline.

All these claims are scientifically invalid, because they use non-randomized, observational data to try to contradict the FDA-based randomized data. This way of thinking ignores the concept of "confounding bias", which is the central reason why clinicians need to pay more attention to randomized studies than to anything else, including their own clinical experience. (This

concept is described further in the Statistical Concepts section of this issue).

As noted above, social factors can affect suicide, and thus population-based rises or declines cannot be directly linked to antidepressant use.

In fact, randomized data with antidepressants repeatedly demonstrate little to no appreciable suicide prevention, although the harm of causing actual suicide also seems to be very low in frequency, as described in the Classic Article.

In sum, the PL view is that SRIs aren't major benefits in prevention of suicide. In some people, they can be part of the mix that can be harmful.

A neglected drug

If we are looking for drugs with a robust benefit shown to prevent completed suicide, there are only two agents shown to do so, lithium and clozapine. If focusing on randomized trials, clozapine has only one study and it showed reduction in suicide attempts but not in completed suicide. Lithium has four placebo-controlled randomized trials, which, taken

together (as described in the Current Article of the Month), demonstrate almost 90% reduction in completed suicide.

In short, we have something like a cure, if we're willing to use it.

The PL Bottom Line

- There is a social component to suicide, but the most important cause appears to be psychiatric disease, especially manic-depressive illness.
- The most important predictors are severe depression and suicide attempts.

- Parasuicidal self-harm may not predict suicide without other risk factors.
- Military suicide is mainly predicted by premorbid depressive disease or neuroticism as a personality trait.
- Antidepressants don't prevent suicide, and hasten it in some persons.
- Lithium and clozapine have anti-suicide effects, with lithium being the only drug proven to prevent suicide definitively in randomized clinical trials.

Selected References: *Albert Camus, The Myth of Sisyphus, 1942; Emile Durkheim, Suicide, 1897; FK Goodwin and KR Jamison, Manic Depressive Illness, 2nd Edition, 2007; LL Havens, Anatomy of a Suicide, NEJM, 1965, 272:401-406; B Shepherd, A war of nerves, 2003, Harvard Univ Press. D Tidemalm et al, BMJ, 2008;337:a2205*

Classic study of the month: The FDA analysis of antidepressants and suicide

Suicidality in pediatric patients treated with antidepressant drugs

TA Hammad et al, Archives of General Psychiatry 2006, 63(3):332-339.

It's not as bad or as good as you think

As discussed in the statistics article this month, randomized data are more valid scientifically than non-randomized data. This collection of randomized studies is the largest and most definitive evidence regarding risk of suicidality caused by antidepressants in children and adults.

The background is as follows: Pharmaceutical companies were encouraged by the FDA to conduct randomized clinical trials (RCTs) on antidepressants in children and adolescents. The wish was to make these agents, believed to be so effective for major depressive disorder (MDD) in adults, available to children too.

Unfortunately for the pharmaceutical companies, who conducted over a dozen trials in search of this lucrative market, the agents were only somewhat effective. To make things worse, as the FDA examined side effects in these trials, it identified some evidence of suicidality, defined as worsened suicidal ideation or suicide attempts. This is when the FDA decided to meta-analyze the data from all the studies which the companies had done (which they were legally obligated to provide to the FDA, although they have no legal obligation to make those data available to the public or the scientific community). When the FDA statisticians conducted those analyses, they found the results which they later published in

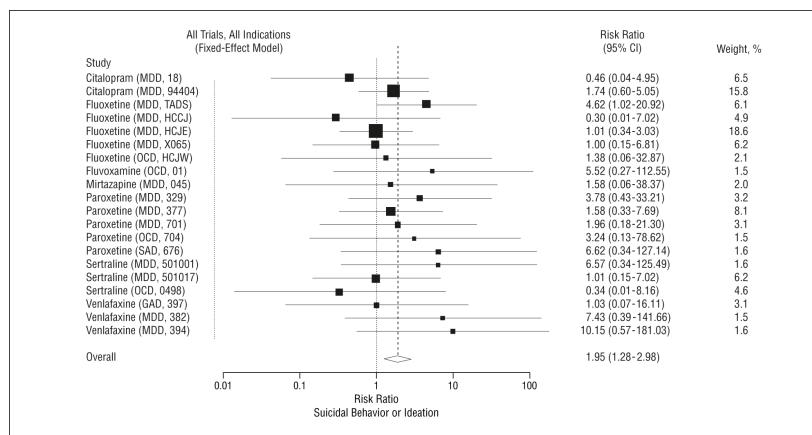
this paper. The FDA and its advisors then voted to institute a black box warning in the serotonin reuptake inhibitor (SRI) package inserts saying these agents may cause or worsen suicidality.

All this occurred in 2004, and led to a major backlash from the psychiatric community, especially from child psychiatry clinicians. Nonetheless, the FDA had an impact, and antidepressant use has declined in the last decade in children. Various epidemiological studies have been published since that date, looking at insurance databases or clinical samples, arguing that suicide rates did not decrease, or even increased, after the FDA black box. But, as described in the article above, population based suicide rates,

observed in a completely uncontrolled fashion, cannot be causally attributed to any single purported cause. As explained in the statistics article, only RCTs can justify claims of causality that are likely valid.

In this meta-analysis, a few points are important:

1. All the studies were conducted quite similarly for FDA approval, being of similar duration, with the same rating scales, and similar inclusion and exclusion criteria. Hence, they are comparable and the meta-analysis has limited “heterogeneity” (confounding bias, as described in the statistics article). In other words, this review is about as valid as a meta-analysis can get.



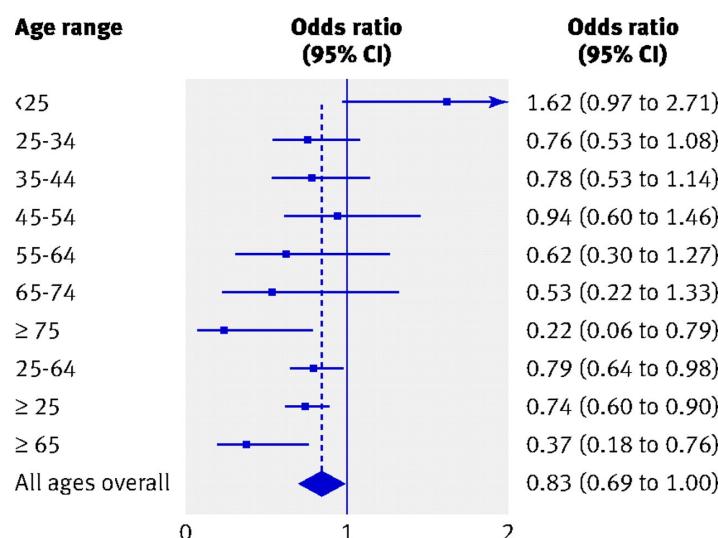
2. There were no suicides, as many of the opponents of the FDA black box always point out. But these RCTs were conducted for FDA approval of drugs for kids. The last things drug companies could afford would be a suicide in a RCT. The media backlash that would ensue would cost a lot of money. Suicidal ideation is a major exclusion criterion for these studies. In short, the patients were selected carefully to be highly *non-suicidal*. And yet some of them got suicidal as shown in these data. This argues for these data being even more, not less, concerning.

3. The absolute rates matter. The meta-analysis shows about a 67% increase in suicidality with SRIs over placebo. But the absolute rates were about 2% with SRIs versus 1% with placebo. In other words, about 1% of children will get more suicidal with SRIs, as opposed to placebo (mainly a stand-in for natural history). Put otherwise:

99% of children will not get more suicidal. This absolute rate provides clinical context for decision-making. This doesn't mean one should completely ignore these data. There is an increased risk of suicidality here, but it doesn't apply to most patients. Nonetheless, the 1% matter, especially when death is the end-result.

4. But will any child die? Many assume not, since no one died in these 8 week trials. That assumption ignores the research literature that about 10% of persons who make suicide attempts will eventually kill themselves. Elsewhere

(Ghaemi 2009) the PL editor has calculated the “number need to harm” using these figures, which is a way of combining the high relative risk of suicidality (almost two-fold increased risk) with the low absolute rate of 1% increased suicidality, and then estimating that about 10% of that number will eventually commit suicide. The calculation made using these numbers produces about a 1 in 500 risk of completed suicide. In other words, about 1 in 500 children treated with SRIs over time will commit suicide, attributable to the SRI (based on RCTs versus placebo, which infers causality). 1 in 500 isn’t a high rate for a side effect, but if it’s fatal, it’s worth at least getting informed consent from patients.



It will be argued that

SRIs also improve depression, which is true, and prevent suicide indirectly by improving depression. The PL editor has conducted a similar “number needed to treat” analysis of suicide prevention rates, combining improvement with depression with actual suicide rates in depression in adolescents. The overall result was again prevention of suicide in 1 in 500 persons. So 1 in 500 commit suicide and 1 in 500 are prevented from committing suicide. In this risk-benefit analysis, antidepressants come out neutral.

5. In another FDA analysis of all their antidepressant studies in adults (M Stone et al BMJ, 2009;339:b2880), seen above, increased

suicidal risk is only present for young adults below the age of 25 and for children. There is a notable increased risk there, but a decreased risk in all older adult groups, such that there is an overall decreased risk of suicidality with antidepressants of 17% (odds ratio of 0.83 which is 17% decreased risk compared to the null value of one).

What does this mean? As readers of the PL website will know, early onset of depression (below 25 years) was said to reflect a higher probability of bipolar illness, as opposed to unipolar depression. This raises the question that perhaps antidepressants are causing suicidality in young adults and

children because “depression” in those ages is not “MDD” but rather bipolar illness. The PL website elaborates on how antidepressants could lead to suicidality, such as in mixed states.

The PL Bottom Line

- SRIs increase suicide risk in 1% of children, and lead to completed suicide in about 1 in 500, which is the same as their prevention rate.
- Their overall effect is probably neutral when benefits are weighed against harms.
- SRIs shouldn’t be viewed as completely safe.
- SRIs shouldn’t be used routinely in children and young adults below age 25.

PL Reflection

The first principle [of science] is not to fool yourself. And you are the easiest person to fool.

Richard Feynman

Current study of the month: A cure for suicide?

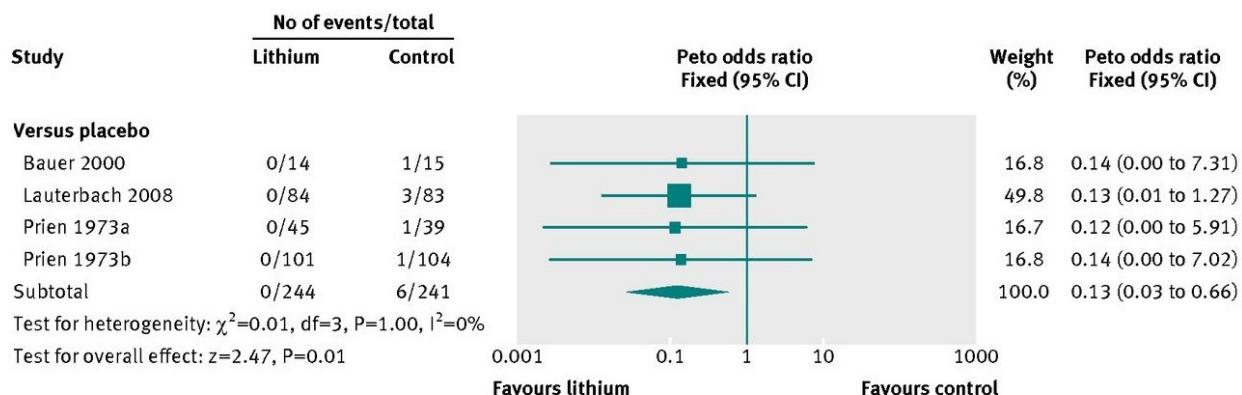
Lithium in the prevention of suicide in mood disorders:

A Cipriani et al, British Medical Journal 2013; 346:f3646

Unlike antidepressants, lithium has a large preventive effect

In this meta-analysis, 48 RCTs were included with 6674 participants. Let's focus on the placebo comparisons, which are four RCTs (see figure). Overall there was a 87% decreased risk of suicide (odds ratio 0.13), which means that only about one in ten persons committed suicide who would have committed suicide without lithium. (There were zero suicides in the lithium arm versus six suicides in the placebo arm). Contrast this large effect size with the modest 17% decrease in suicidality (not completed suicide) with antidepressants in the second figure of the prior article. Since only about

Other aspects of this meta-analysis are interesting: Parasuicidal self-harm, was not affected by lithium (odds ratio 0.60, confidence intervals 0.27 - 1.32). The benefit seen with lithium was present also in unipolar depression (odds ratio 0.36), with a 64% decreased suicide rate. Lithium also generally had less suicide rates than most active comparators, including other agents known to be effective in bipolar illness, like carbamazepine. Other studies have compared lithium and valproate, and again lithium seems to have a preferential anti-suicide effect in bipolar



5-10% of persons who make suicide attempts eventually commit suicide, the antidepressant benefit for completed suicide is not more than about 1% at best. This contrasts with 87% with lithium. In other words, lithium is about 90 times more powerful in prevention of suicide than antidepressants. Or, put another way, for every one person whose suicide is prevented with antidepressants, lithium would prevent suicide in 90 persons.

illness, while suicide rates are not decreased by valproate.

The importance of this meta-analysis is that it combines different RCTs to demonstrate statistical efficacy for prevention of completed suicide. In all RCTs, researchers tend to design inclusion and exclusion criteria such as to avoid suicide or other major harms. Since there is careful scrutiny of research by many groups, at least in the West, a suicide in a double-blind trial

would receive attention that would be negative, by institutional review boards (IRBs; ethics committees), university administrators, and possibly the media. Studies also tend to be short, usually a few months, and a year or two at the longest. Suicide is uncommon enough that in such short time frames, which such attempts to exclude those who might be at risk, it is even more uncommon to have any suicides in RCTs.

There has never been a RCT specifically designed to prevent suicide. It probably would be seen as unethical to design such a study. So if we ever obtain RCT data about suicide prevention, it would have to occur in studies in which suicide just happened, unfortunately. These suicides are needed as outcomes, otherwise one could never know whether a drug could prevent them, compared to other comparators (such as other drugs or placebo).

This is why this meta-analysis is important. Lithium has been around for decades and there have been 48 RCTs of it, and there have been some suicides. So it is only in this setting that one could possibly even try to answer the question of whether lithium prevents suicide.

All this description is meant to explain how hard it is to answer this kind of research question with randomized data. When we have them, we should appreciate how important and rare they are.

It's also relevant that there are hundreds of studies with antidepressants, also over decades, like lithium. Yet the meta-analysis in the previous Classic Study in this issue shows the reverse of the lithium data: There was not 90% reduction in completed suicide, but about 70% increase in suicidal thinking or behavior in those below age 25. Yet antidepressants are used widely, while lithium is avoided widely.

For suicide prevention, these randomized studies of lithium and of antidepressants demonstrate that the reverse - using lithium more widely and using antidepressants less - would be more consistent with our best scientific evidence.

A final point is that these studies tended to use standard doses of lithium. There is an extensive literature on examining the effects of lithium in areas of the world where there is a "high" amount of lithium in the drinking water. "High" means about 1-2 mg/d of lithium (compared to standard doses of around 900 mg/d). Even at these very low doses (1-2 mg/d), the lithium in the water studies showed notable evidence of decreased suicide rates associated with "high" lithium in the water, compared to other regions with low or no lithium. Those studies were observational, and thus could be affected by confounding factors, but some did control for some predictors, like urban versus rural location and socioeconomic status.

If randomized studies didn't exist, one couldn't be certain that this lithium effect was causal, as discussed previously. But since we have randomized data that lithium prevents suicide, it's likely these epidemiological data are also valid.

In short, lithium may prevent suicide even at very low doses, down to a few mg/d. Concerns about side effects and toxicity, discussed below, relate to much higher doses (usually about 900 mg/d).

The PL Bottom Line

- Lithium is the only drug proven to prevent suicide in RCTs versus placebo.
- It has a large effect size of almost 90% reduction in suicide risk.
- Lithium may prevent suicide in many persons even at very low doses.

Drug of the Month: *Lithium*

More effective, and less harmful, than you may think

Lithium is one of the first modern psychotropic drugs, discovered for mania in 1949 by John Cade in Australia. It was the first psychotropic drug proven effective in a randomized clinical trial (RCT), in 1952. Yet it's been consistently undervalued by clinicians and patients.

Clinical efficacy and inefficacy

In the 1980s, drug makers for anticonvulsants (like valproate) claimed that most patients with bipolar illness didn't respond to lithium. These predictors of negative response were factors like rapid-cycling, substance abuse, mixed states, and psychosis. Now we know that these features predict poor response to all mood stabilizers, including anticonvulsants, not just lithium. Further studies in the last two decades often used lithium as a comparator arm, in studies designed to show benefit for agents like lamotrigine or antipsychotics. Those studies generally found that lithium was as, or more, effective than new putative mood stabilizers. This conclusion isn't appreciated based on some claims made by drug companies. For instance, it's claimed that lamotrigine was more effective than lithium in dementia prevention. But (as reviewed on the PL website), those studies were designed to preselect only lamotrigine

responders to enter them; hence it wasn't a fair comparison to lithium.

In short, after half a century, lithium remains the best proven, and overall most effective, mood stabilizer, both for prevention of depressive and manic episodes.

Biological mechanism

For decades, the profession had no clue how lithium worked, because it had little synaptic effects on neurotransmitters. In the last few decades, it's become clear lithium has multiple effects inside neurons, on G-proteins and second messengers. Those effects are extensive, and include many neuroplastic effects that keep neurons alive longer. They likely produce many of lithium's long-term benefits, in prevention of mood episodes and perhaps in anti-suicide and anti-dementia effects.

Side effects and dosing

Polyuria is its most common side effect. Cognitive side effects can occur short-term, even though it produces cognitive benefits long-term throughout its neuroprotective effects.

Its medical side effects are known, but the risk of chronic renal insufficiency is about 1% at 20 years (H Bendz et al, Kidney Int. 2010;77:219-24). This risk can be decreased by once daily dosing, as opposed to multiple daily dosing, and by avoiding acute lithium toxicity (which kills kidney cells).

Fast Facts: Lithium

Typical effective dose: 600-900 mg/d. Levels 0.6-1.0

Biological mechanism: G protein and second messenger effects

Typical side effects: Polyuria, thirst, diarrhea, tremor

Less common but important side effects: Acne, psoriasis, cognitive effects, weight gain

Medically important side effects: Hypothyroidism, renal impairment

Clinically proven efficacy: Acute mania and depression, prevention of mania and depression

Questionable efficacy: Acute mixed episodes

Other proven uses: Suicide prevention

This is why PL strongly recommends not giving levels higher than 1.0, so as to avoid borderline toxicity either by error or dehydration. Further, levels of 0.6-0.8 are shown equivalent in efficacy to 0.8-1.0 in type I bipolar illness. Thus, there is no need for “high therapeutic” levels. Thyroid effects occur more quickly but are reversible with thyroid hormone supplementation. Weight gain is a common concern, but it's less with lithium than with valproate or other commonly used antipsychotics like olanzapine or quetiapine.

The PL Bottom Line

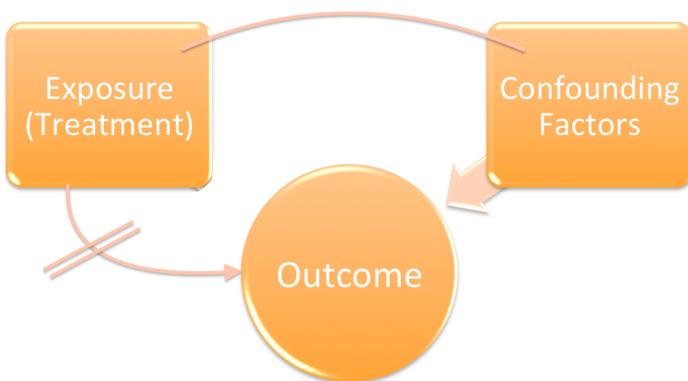
- Lithium is the most effective mood stabilizer, including for depression and mania prevention.
- Lithium affects second messengers, a unique mechanism providing long-term benefits.
- Levels above 1.0 aren't needed for efficacy.
- Long-term kidney effects are 1% at 20 years.
- Lithium should be prescribed only once daily to reduce long-term renal effects further.

PL Reflection

Human life begins on the far side of despair.

Rollo May, citing Jean-Paul Sartre

As seen in the figure, the confounding factor is associated with the exposure (the apparent cause) and leads to the result. The real cause is the confounding factor; the apparent cause, which we observe, is just along for the ride. Coffee is associated with cancer, but it doesn't cause cancer, because coffee drinkers are more likely to smoke cigarettes, the actual cause of cancer.



Randomization is the best solution to confounding bias. By randomly assigning people to getting a drug or not, we equalize confounding factors in both groups; the confounding factors then cancel each other out. That's why you can interpret the results straightforwardly: whatever happens can be attributed to the drug. That's also why you can never interpret any non-randomized data straightforwardly: Whatever happens could have happened because of many factors, often unmeasured or even unknown.

Statistical concepts: Confounding Bias Why clinical experience isn't the final word

The most important idea in understanding clinical research is the concept of *bias*. This means systematic error (as opposed to chance, which reflects random error). With systematic error, we make the same mistake repeatedly because of some inherent problem with our observations. “Confounding” is a kind of bias that has to do with factors, of which we are often unaware, that can influence our observed results.

This bias is why the basic concept of evidence-based medicine is that randomized data are more valid, more accurate and true, than non-randomized data. This includes your own clinical experiences, the ultimate non-randomized data. *This bias of clinical experience is called confounding by indication:* As a clinician, you are trained to be a non-randomized treater. What this means is that you are taught, through years of supervision and more years of clinical experience, to tailor your

treatment decisions to each individual patient. You don't treat patients randomly. You don't say to patient A, take drug X; and to patient B, take drug Y. You don't do this without thinking any further about the matter, about why each patient should receive one drug and not the other. You don't practice randomly; if you did, you'd be a poor clinician. But by practicing non-randomly, you automatically bias all your experience. You think your patients are doing well because of your treatments, whereas they should be doing well because you are tailoring your treatments to those who would do well with them. In other words, it's not always the treatment effects that you're observing, but other factors you may not even know about. Even with huge epidemiological studies, such as reports where there are claims of increased suicide rates after reduction in antidepressant use, the same problem applies. Many potential factors, usually not controlled in epidemiological analyses, influence suicide.

The PL Bottom Line

- Clinical experience is biased by confounding factors, so you can't believe your eyes: You can't be sure when you're right or wrong.
- Well-conducted randomized trials are more valid than our clinical experience.

Case of the month:

Suicidality and antidepressants in borderline personality

A 25 year old adopted Asian female is treated with bupropion 300 mg/d and atomoxetine 60 mg/d. She reports chronic and constant suicidal ideation for the past 10 years. She has abused alcohol and marijuana regularly for years, and cocaine as well more recently. She was hospitalized once at age 14, has had many overdoses and some cutting behavior. She also has bulimia at times. She was

adopted, so biological family information is not available. She grew up in a wealthy, white, upper-class suburb. Her mother accompanied her and the family appears very supportive of her. She went to excellent schools and never experienced any trauma of any kind. She was never married, has no children, graduated from college, and lives alone while working for a retail store.

She describes past manic symptoms as follows: "I'm always rushing around, racing thoughts, pretty hyper, I can get so much shit done." This is associated with talkativeness and distractibility: "I'm always confident." She has impulsive behavior of all kinds: sexual, spending, reckless driving. "I've always been nocturnal, I like to stay up at night." Normally, she sleeps at 4 AM and wakes up at 8 AM, without being tired. When she's depressed, she has very low energy and sleeps over 13 hours nightly. There are no definable episodes of mania above this baseline.

She was diagnosed with borderline personality disorder plus MDD at age 15 and has received weekly psychotherapy for 10 years; she also has taken antidepressants for the past 5 years. She briefly received lithium at age 15, added to citalopram, without benefit.

Her course of illness was rapid-cycling: 3 months earlier, she had a depressive episode for one month; followed by her hyperthymic baseline.

The PL diagnosis and clinical impression

The PL diagnosis is hyperthymic temperament. As reviewed on the PL website, mood temperaments exist, but DSM only recognizes dysthymia and cyclothymia. Hyperthymia was also described a century ago by Kretschmer, who formalized the definitions of dysthymia and cyclothymia as well. As a state of constant mild manic symptoms as part of one's personality, hyperthymic temperament can produce unstable

interpersonal relationships and constant irritability, which may be mistaken for borderline personality. In the absence of sexual trauma and self-cutting, the PL approach is that borderline personality shouldn't be diagnosed mainly based on less specific features such as unstable interpersonal relationships, anger, and suicidality.

The PL recommendation was to discontinue antidepressants. Her chronic suicidal ideation, persistent for ten years, completely resolved immediately. In six month follow up, she refused mood stabilizer treatment but was much better off antidepressants without psychotherapy than she had been previously.

The PL Bottom Line

- Antidepressants caused long-term suicidality in a young adult with hyperthymic temperament misdiagnosed as borderline personality.
- Even without lithium, suicidality resolved once antidepressants were stopped.

Curbside consults:

Questions and cases from you

Question: A patient felt depersonalized most of his life, alienated from himself, spaced out. Years of psychotherapy had no impact. A consultant said that he had "depersonalization disorder" and that marijuana could help. It did for a few hours after each use. Should he request medical marijuana?

PL: The most common cause of depersonalization is anxiety, such as panic attacks. If this person's anxiety is life-long, and doesn't solely relate to depressive episodes or panic attacks, for instance, then the anxiety can be conceived as a personality trait, like a high amount of neuroticism (as discussed in the March PL issue). In that case, a low-dose of a benzodiazepine (like 0.5-1 mg/d of lorazepam) can move the person's neuroticism up

on the normal curve somewhat closer to the middle range. This reduced anxiety would then be accompanied by reduced feelings of depersonalization. Marijuana has strong anxiolytic effects, so the benefit this person had with that agent is probably a reflection of anxiety as the cause of the depersonalization symptoms.

The DSM approach of adding "disorder" to every symptom is not scientifically correct or clinically helpful. Rather, the question should be: what is causing the symptoms? In this case, anxiety as a personality trait seems most likely. Keep in mind that any intervention for personality will have modest symptomatic benefit at best: personality traits aren't completely removed, like diseases; they are increased or decreased. So the patient should have modest symptom benefit expectations. Further, long-term treatment will be needed, and benzodiazepines are most useful short-term. Low-dose SRIs could be used if the patient doesn't have any variety of bipolar illness.

Psychopharmacology course

Lesson 2: Neuroanatomy for clinical practice

In the inaugural issue, in Lesson 1 of the Psychopharmacology Course, PL suggested we think about drugs clinically, more than biologically. An example is shown in the articles this month on suicide prevention based on clinical randomized trials. Nonetheless, biology is relevant, when seen as secondary to the clinical research evidence. In that sense, there is some basic neuroanatomy that can be helpful in the practice of clinical psychopharmacology.

One basic observation has to do with the distribution of two major groupings of neurotransmitters. The monoamines - serotonin,

dopamine, and norepinephrine – are *specifically* distributed, mostly in the midbrain. In contrast, the inhibitory agent GABA and the excitatory agent glutamate – which are not monoamines – are *nonspecifically* distributed throughout the neocortex. So the monoamine system has just a few tracts of connections, which involve the limbic system, the main area of the brain that regulates emotion. In contrast, GABA and glutamate are present in the entire surface of the neocortex and affect higher cognitive functions, as well as motor and sensory activity.

A key point is that the median forebrain bundle (MFB) mediates all three major monoamine neurotransmitter projections to limbic and frontal regions. Since those projections are closely intermingled in the MFB, they interdigitate and have multiple interaxonal connections. In other words, they communicate with each other in the MFB, before they reach their ultimate limbic destinations.

Hence it's impossible to affect one of the monoamines without affecting others. Noradrenergic neurons will communicate with serotonergic neurons in the MFB, and cause changes in serotonergic activity. And vice versa. This is a major reason why there is no truly "selective" serotonin reuptake inhibitor, and hence the acronym "SSRI" is a marketing tool which has no valid scientific meaning. These drugs are "SRIs", but they are not selective, because they produce changes in noradrenergic and dopaminergic function, indirectly, through

the MFB. (Further, as explained on the PL website, most "SSRIs" aren't selective because they directly affect other neurotransmitter systems, besides serotonin, in the synapse).

In contrast, the glutamate and gabaergic systems are distributed throughout the neocortex, not just in the deep midbrain nuclei, as with dopamine and serotonin and norepinephrine. That's why if you prescribe a benzodiazepine (which is gabaergic) or topiramate (which is anti-glutamtergic), you can get widespread cognitive or sedating effects: the whole brain is being affected. For the same reason, at least with gabaergic agents, you can get widespread anxiolytic effects: again, the whole brain is being affected.

PL Reflection

To know that we know what we know, and to know that we don't know what we don't know – that is true knowledge.

Henry David Thoreau, citing Confucius

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THE PSYCHIATRY LETTER

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Personality examined

This month, PL examines the topic of personality in a special article that contrasts the concept of personality "disorders" with personality traits. This was a major issue of some debate in the DSM-5 process.

The concepts of borderline and narcissistic personality also are examined in the classic study and case of the month. The classic study demonstrates how acute depression can be mistaken for borderline personality, and the case shows how manic symptoms can be mistaken for narcissistic personality. The importance of distinguishing personality from mood illnesses is highlighted in these discussions.

The drug of the month examines a commonly used anticonvulsant, oxcarbazepine. Clinicians seem attracted to it because of limited side effects, and it is commonly used for nonspecific mood swing symptoms, either as part of personality disorder diagnoses or as a putative mood stabilizer for bipolar illness. The article emphasizes and examines the evidence that this drug is either proven ineffective, or insufficiently proven effective, for mood states. The notion that its clinical efficacy is analogous to carbamazepine, due to chemical structure similarity, is challenged.

We appreciate your continued interest in the Psychiatry Letter and we encourage questions, comments, and cases directed to the email address provided on the left sidebar of this page.

We also invite you to join us for a week-long summer course in Cape Cod this July where we'll be able to interact about many of the topics and approaches discussed in PL.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: Personality - Traits or disorders?

The concept of personality traits is more scientifically valid, and can be more clinically useful, than personality “disorders”

Personality always has been an important aspect of psychiatric diagnosis and practice. In the DSM era, personality has been conceptualized, like everything else, through the prism of “disorders,” an explicitly vague term. One feature of personality “disorders” is its commitment to a categorical concept. Your personality is either normal or disordered. Besides this approach, there is another approach, long established in the experimental psychology (not psychiatry) literature: the concept of personality traits, or dimensions. On this view, personality traits are present in everyone, occurring on a normal curve, with all of us having more or less of a trait. At the extremes, personality traits can be seen as “abnormal”, but not in a categorical sense, not as being *qualitatively* different than normality.

“Temperament...is...the biological part of personality.”

These three basic traits - Neuroticism, Extraversion, and Openness to Experience - have been called the NEO scale. Twin studies demonstrate that these three traits are about half genetic and half environmental. This is similar to other partly genetic traits or conditions like physical weight or hyperlipidemia. Since these conditions have a genetic aspect, they can be seen as the biological aspect of personality. The term “temperament” often is used for the biological part of personality.

Another important model besides NEO is C. Robert Cloninger’s Temperament and Character Inventory (TCI), which has four basic temperament traits: harm avoidance, novelty-seeking (similar to openness to experience), reward dependence, and persistence. He also

identifies three basic character traits: self-directedness, cooperativeness, and self-transcendence. One importance to Cloninger’s work is that he is a psychiatrist, not a psychologist, unlike most personality trait researchers, and thus he has directed much of his work at trying to study “abnormal” personality, i.e. persons who psychiatrists treat as having personality “disorders”. Hence the TCI has been studied a great deal in clinical samples, while many NEO studies have been done in normal populations (often college students).

As noted, while NEO is about biological temperament, TCI adds an aspect of environment-based “character.” Other scales have also tried to capture non-biological factors: one’s family environment, culture, religion, society. For

Personality traits

Over the past century, many experimental psychology studies have established that human personality can be identified in the general population as having a few basic traits. These studies name these traits somewhat differently, but they cover similar features. For instance, there is a general personality trait of anxiety. In the prior March 2015 PL issue, we discussed how it was labeled as “neuroticism” by the psychologist Hans Eysenck. There is another general personality trait of interpersonal skills, which Eysenck called “extraversion”, contrasting with introversion. A third general trait has to do with curiosity or risk-taking, as opposed to being routinized; it has been called “openness to experience”.

instance, using the NEO scale for the initial three traits, personality researchers have added two other character traits of “agreeableness” (being friendly and trusting) and “conscientiousness” (being dutiful and achievement-oriented). These latter character traits have little to no genetic component, and are almost completely environmental.

In sum, whichever specific trait names one uses, personality researchers agree that temperament (mainly biological) plus character (mainly cultural/familial) produces personality.

Personality “disorders”

There is a completely different way to look at personality, the one that is more familiar in psychiatry, since it’s enshrined in DSM. Personality “disorders” were first introduced in 1980 with the third revision of DSM (DSM-III), and were based mostly on psychoanalytic theory.

It's important to note that of the ten DSM personality disorders, 7 do not have good scientific evidence of empirical validation, as defined by nosological validators demonstrating that they can be distinctly identified from each other and from other diagnoses. These include paranoid, schizoid, avoidant, narcissistic, histrionic, obsessive-compulsive, and dependent.

Three personality disorders had, and have, some empirical basis outside of pure psychoanalytic theory: antisocial, borderline, and schizotypal.

Antisocial personality has the longest history: it always was described in psychiatry dating to at least the 19th century, often termed “psychopathy” or “sociopathy.” The basic idea was that there might be some psychiatric

condition that relates to being a criminal, or having criminal tendencies. These persons tend to lack “conscience”, are unethical towards others, and use others purely for their own wishes. This general attitude frequently can lead to violence and crime. Whether or not there is a biological cause to this type of personality has been a topic of long debate. The general consensus tends to be that early childhood neglect is a major factor.

Borderline personality as a concept was more complex. The term “borderline” stems from the notion that these patients are at the “border” between neurosis and psychosis. The psychoanalytic tradition didn't care much for diagnosis. It only conceived of two major diagnostic groupings, depending on reality testing: psychosis and neurosis. The neurotic patient mostly was in touch with reality but had some unconscious emotional conflicts that aroused anxiety and depressive symptoms. The psychotic patient was less in touch with reality and had

unconscious emotional conflicts that aroused delusional or hallucinatory symptoms. The difference was in degree, not kind. There was a single continuum for neurosis to psychosis, and at the borderline from one to the other, there were patients who were usually neurotic, but who could become, under the right circumstances, somewhat psychotic. The psychoanalysts had a practical test for this type of patient: she (usually she was female) would enter psychoanalysis as a somewhat normal neurotic person; but after some time on the couch, she would become psychotic. In other words, psychoanalysis would diagnose the borderline patient by making her worse.

Psychoanalysts used the phrase “psychotic” loosely: it simply meant being out of touch with

reality to a greater degree than whatever would be termed neurotic. And the phrase “psychosis” was more or less identified with the older concept of the diagnosis of schizophrenia. So, an early term from the 1950s for what would later be called borderline personality was “pseudoneurotic schizophrenia”: these patients seem neurotic in daily life, but they’re really schizophrenic (psychotic) underneath it all. In the 1960s, the psychoanalyst Otto Kernberg coined the term “borderline personality organization”, which was taken up in the 1970s by John Gunderson, who, with others, convinced the DSM-III leadership to introduce the new diagnosis of “borderline personality disorder.”

It requires a great deal of allegiance to the DSM insistence on the word “disorder” to categorize schizotypal personality as a “personality disorder”, but the concept has empirical validation as a mild version of schizophrenia, which occurs in families with the genetics of that disease. It has no origin in psychoanalytic theory.

DSM-5: No change

An odd thing happened in 2014; over three decades after these 10 personality disorders were introduced based mostly on psychoanalytic theory in 1980, DSM-5 changed nothing.

It’s odd because DSM leaders tend to pay homage to science, and the scientific evidence for personality traits is huge and for most personality disorders is slight. Indeed the DSM-5 personality disorders task force recognized this fact, and over about 5 years of preparation, it recommended that the 10 original personality disorders be reduced to 6 and that personality traits be added to DSM-5. There was some question about which traits and

“These ten personality disorders were introduced mostly base on psychoanalytic theory in 1980”

how to define them, but the DSM-5 personality disorders experts admitted that it was time to introduce personality traits into psychiatry. Half a century of replicated research should be sufficient to make this change in psychiatric diagnosis.

In the final weeks of the DSM-5 approval process, this recommendation was rejected by the American Psychiatric Association Board of Trustees (leading academics and APA activists, most of whom were not personality research experts). The reasons are unclear, since the DSM-5 leadership has not described publicly all its reasoning for its decisions. It is reported that some DSM-5 leaders thought that personality traits would be too complicated for psychiatric clinicians to understand.

This failure to accept well-proven science occurred despite the fact that the DSM-5 field trials showed

that even after three decades of usage, psychiatrists mostly disagreed about how to use personality disorder criteria. In other words, they have poor reliability (consistency of agreement among clinicians when applied to the same patient). The only exception was borderline personality.

So DSM-5 didn’t change the basic structure of DSM-IV, which was basically the same as DSM-III. The ten personality disorders live on. Personality traits remain unknown in DSM-based psychiatry.

A potential solution

DSM-5 had a golden opportunity to make the approach of clinical psychiatry to personality more scientific. Its personality disorders task

force wanted to do so, but the APA leadership apparently wouldn't allow it.

So clinicians are left with a dilemma: Should they follow the science of personality traits, or should they continue to repeat three decades of psychoanalytic theory-based definitions of personality disorders?

PL thinks that the concept of personality traits is more clinically helpful because it is more scientific than the concept of personality "disorders." Of the latter, the three empirically proven ones may be clinically worthwhile: antisocial, borderline, and schizotypal. But schizotypal personality isn't really a personality disorder, and antisocial personality is a complex phenomenon that ties into crime and legal aspects of psychiatric practice. Only borderline personality would seem to stand as a personality condition on its own, and in future issues, PL will examine it in more detail. The PL website provides a perspective

on how borderline personality can be viewed as a valid clinical picture, but not as broadly as in DSM criteria.

If we are willing to think about personality in terms of traits, and not just DSM-based disorders, then each patient can be examined for some of the basic personality traits. PL recommends using the three-item NEO as a basic screen. For each patient, after some period of clinical evaluation, you can determine whether they are high or low or in the middle on each trait for neuroticism (anxiety), extraversion/introversion, and openness to experience. This approach will open clinicians up to the many combinations of traits that patients can have, as opposed to the

unreliable attempt to push them into one DSM personality disorder category or another.

Further the concept of personality traits is less pejorative and stigmatizing than the DSM personality disorders concepts, and it allows for linking traits to variants of normality. This can allow for more free dialogue and discussion about a patient's personality, how it influences one's life and what might be done.

Treatment

The practical consequence of the DSM-based personality disorder concept was, from the beginning, that it would lead to psychotherapy treatments. In the last two decades, symptom-based medication treatment also has become the norm. The personality trait approach would be more realistic and more conservative.

Some psychotherapies, like cognitive behavioral therapy (CBT), are not very effective for changing

"Medications for personality traits...move patients from the extreme toward the middle...they don't remove symptoms completely."

personality, but are more helpful for acute symptoms, such as panic attacks or a current depressive

episode. High neuroticism as a personality trait (often labeled "generalized anxiety disorder" using DSM terms) is not responsive to CBT. Even long-term psychotherapies, such as psychoanalytically-oriented therapy, don't have much impact on making someone more or less extroverted, or more or less open to experience. Psychoanalytic psychotherapies can have many benefits, produce insights or awareness about oneself, but one's basic personality doesn't change much, whether with psychotherapies or with medications.

One could conceive the use of medications for personality traits in this manner: They move patients from the extremes of the normal

distribution curve toward the middle. But the effects are modest; they don't remove symptoms completely; rather, at best, they make symptoms somewhat less severe. This kind of thinking about medications would lead to more caution since the modest benefits might not outweigh even modest risks.

In all, personality traits can be a useful way to capture many of the problems presented by patients, without mistakenly labeling them as personality disorders that may not be valid, and without leading to excessive or likely ineffective psychotherapies and/or medication treatments.

The PL Bottom Line

- Personality traits are more scientifically valid than the concept of personality disorders.
- The three major personality traits of neuroticism, extroversion and openness to experience are the most clinically useful.
- Most DSM personality disorders are not valid based on standard research definitions, and they have poor reliability in clinical practice.
- Antisocial and borderline personality have the most validity of DSM personality disorders.
- Medications have limited use for personality traits or DSM-based personality disorders.

PL Reflection

Madness (Folie): A brain disease that keeps a man from thinking and acting as other men do.

Classic study of the month: *Borderline personality and depression*

Borderline personality disorder in major depression: Symptomatology, temperament, character, differential drug response, and 6-month outcome

PR Joyce et al, Comprehensive Psychiatry, Volume 44, Issue 1, January 2003, Pages 35-43

Borderline when depressed, not so borderline when not depressed

This paper provides the kind of scientific evidence behind a key clinical tip: Don't diagnose borderline personality in the midst of a clinical depressive episode.

In this study, researchers examined criteria and symptom severity for borderline personality in patients diagnosed with major depressive disorder (MDD), who were currently in the midst of an acute clinical depressive episode. They then were randomized to treatment with an antidepressant

or not, and were given mood and personality trait rating scales.

Personality traits were assessed by Cloninger's Temperament and Character Inventory (TCI). Cloninger had shown that patients who met DSM criteria for borderline personality also were identifiably different on some TCI personality traits: they were high on novelty-seeking and harm avoidance, and low on cooperativeness and

self-directedness. After 6 months, there was improvement in borderline-like personality traits.

Here are the details of the study:

195 patients were part of a larger study of MDD, where the acute major depressive episode was treated by unblinded randomization to nortriptyline or fluoxetine. Among many scales given, 183 patients were assessed for personality disorders using DSM-IIIR criteria with the Structured Clinical Interview for DSM-IIIR personality disorders (SCID-PQ).

Six weeks was the primary outcome for randomized treatment, but at that point, if they had not improved, patients were allowed to be switched non-randomly to a different antidepressant treatment, and outcomes were assessed up to 6 months afterwards.

Of the larger sample, 30 subjects met criteria for borderline personality disorder along with MDD when the study started. In these patients, there was more improvement with fluoxetine than nortriptyline for the clinical depressive episode (67% were fluoxetine treatment responders defined as more than half improvement in depression rating scale scores, vs only 27% for nortriptyline).

Most importantly, at 6 months, patients with borderline personality disorder had improved notably in their core personality traits, with more self-directedness, cooperativeness, and less novelty-seeking and harm avoidance.

In other words, what is supposed to be a pervasive life-long personality disorder turned out not to be so when clinical depression went away. Put otherwise, the patients only *seemed* borderline when they were depressed. When they weren't depressed, they weren't as borderline.

You might say: Well fluoxetine just "treated" the borderline personality disorder. This conclusion would require the assumption that SRIs are effective for pure borderline personality disorder. We already know they are effective for acute MDD, but are they effective for pure borderline personality disorder *without* MDD?

A typical study of this question was a randomized clinical trial (RCT) of fluvoxamine versus placebo for borderline personality disorder in persons without a current clinical depressive episode. Fluvoxamine was modestly effective at best, helping mood swings but not impulsivity or aggression (T Rinne et al, Am J Psychiatry 2002; 159:2048–2054). Other SRI RCTs are similar: little benefit is seen for borderline personality disorder itself (K Lieb et al, British Journal of Psychiatry 2009, 196:4–12).

The PL Bottom Line

- Acutely depressed patients may *seem* borderline, but when they're not depressed, they're often not so borderline.
- Don't diagnose borderline personality disorder routinely in patients who are actively clinically depressed.

PL Reflection

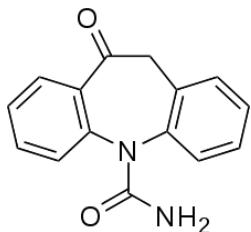
This higher knowledge amounts to...a novel and grand surprise on a sudden revelation of the insufficiency of all that we called Knowledge before.

Drug of the Month: *Oxcarbazepine (Trileptal)*

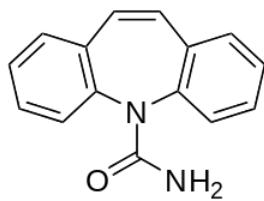
What doesn't work can hurt you

Oxcarbazepine is one of the most overrated drugs in psychiatry. It is used frequently, even though it has little to no scientific basis for being used at all. It's an anticonvulsant, but its use for psychiatric conditions is mostly for mood.

Why would carbamazepine "work" for mood illnesses, but not oxcarbazepine? For the same reason that chlorpromazine "works", but imipramine doesn't. Literally, the difference between carbamazepine and oxcarbazepine is one carbonyl bond (C=O).



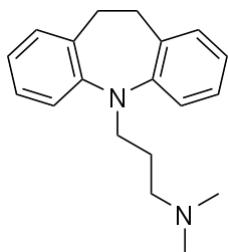
Oxcarbazepine



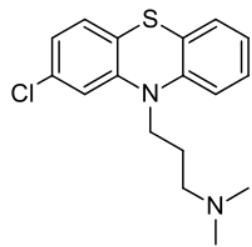
Carbamazepine

Similarly, the difference between imipramine (a tricyclic antidepressant) and chlorpromazine (Thorazine, an antipsychotic) is one chlorine bond and one sulfate bond.

Imipramine



Chlorpromazine



One is an antipsychotic that works for mania, but doesn't appear to work for depression (chlorpromazine); the other is an antidepressant that causes mania and doesn't work for schizophrenia (imipramine).

A chemical bond or two can make a huge difference.

This doesn't mean that similarity of chemical structure is irrelevant; sometimes it can imply similar clinical effects, whether for efficacy or for side effects. For instance, chlorpromazine and imipramine share many similar side effects (anticholinergic effects of dry mouth and constipation, and antihistamine effects of sedation and weight gain). But their clinical effects are quite different.

Similarly oxcarbazepine and carbamazepine share some side effects (like hyponatremia), but have important differences (e.g., no drug interactions with oxcarbazepine). So you can't assume their clinical effects are similar.

It would be like saying that since the same company makes Volkswagen and BMW, the two cars must be more or less the same.

In short, you shouldn't assume clinical efficacy based on chemical similarity. As emphasized in the inaugural January 2015 PL issue, clinical research, not biological speculation, is needed for clinical claims.

Clinical efficacy and inefficacy

What does the clinical research show about the efficacy of oxcarbazepine in psychiatric conditions? Most of the research is in mood illness. In acute mania randomized trials, some studies indicate similar efficacy to haloperidol, but without placebo controls, so we can't infer efficacy since mania resolves by itself spontaneously within weeks to months. There are no randomized trials in acute bipolar depression. Observational reports, including by the PL editor,

suggest some benefit, but they can't be assumed to be correct without randomized data, because of confounding bias (see April 2015 PL issue). Two maintenance RCTs found no benefit over placebo (A Vasudev et al, Cochrane Database Syst Rev. 2011 Dec 7;(12):CD004857).

More evidence that oxcarbazepine is ineffective overall involves studies of its active metabolite, licarbazepine, which was studied as a possible new agent by Novartis (oxcarbazepine is now generic, and no profits exist with it). Licarbazepine was found to be equivalent to placebo in multiple mania RCTs. These negative data were never published.

This inefficacy was proven again by another pharmaceutical company, Sunovion, which conducted two randomized clinical trials of an enantiomer of licarbazepine (eslicarbazepine), which found again that the agent was equivalent to placebo for acute mania (H Grunze et al, J Affect Disord. 2015;174:70-82).

In sum, oxcarbazepine and/or its active metabolite have been proven ineffective in acute mania and in maintenance prophylaxis of bipolar illness. It's never been proven effective in any randomized trial of an acute depressive episode. Hence oxcarbazepine and/or its active metabolite is proven ineffective for mood illness.

Biological mechanism

Like most anticonvulsants, oxcarbazepine raises the seizure threshold via sodium channel blockade. Any biological effects that are relevant to mood are unknown.

Side effects and dosing

The main reason mental health clinicians like this agent is because it doesn't have drug interactions, unlike carbamazepine, and thus it can be combined with other agents, such as dopamine blockers or monoamine agonists (antidepressants). It also has less risk of rash or leukopenia. It has more sedation than carbamazepine, however, and it has one potentially serious medical risk that can lead to seizures, namely a 2% risk of hyponatremia. Like carbamazepine, there's no weight gain.

PL cautions clinicians in the use of this agent in persons with eating disorders, who often wish to take medications

Fast Facts: Oxcarbazepine

Typical dose: 600-1200 mg/d.

Biological mechanism: Unknown

Typical side effects: Sedation

Less common but important side effects: Rash

Medically important side effects: Hyponatremia

Clinically proven efficacy: None (in psychiatry)

without weight gain. Frequently, such persons will drink water excessively, as a way of maintaining weight loss. This over-drinking of water, when combined with oxcarbazepine, can lead to dangerous hyponatremia. If sodium levels fall below 120, seizures can occur.

The PL Bottom Line

- Oxcarbazepine probably is ineffective in any psychiatric use.
- If you want carbamazepine-like effects, use carbamazepine.

PL Reflection

Windy errors have long been, and will long continue to be, swollen into transient consequence.

Oliver Wendell Holmes Sr

Case of the month:

"Narcissistic" personality that isn't

A 45-year-old male is diagnosed with narcissistic personality disorder (NPD) comorbid with generalized anxiety disorder (GAD) and major depressive disorder (MDD). He has been treated with long-term psychodynamic psychotherapy on multiple occasions for 6 months to two years at a time. He has taken escitalopram 20 mg/d for 10 years. Sometimes, he has brief periods of depression lasting a few weeks at a time.

He has occasional suicidal ideation for the past 10 years. He has abused alcohol in the past, but has been sober for 5 years. He has never been hospitalized, overdosed, nor engaged in cutting behavior. His first cousin was diagnosed with bipolar disorder and did well on lithium. He was raised by an intact supportive family, became a lawyer, divorced twice, now lives alone, and never had childhood trauma.

He was seen as narcissistic because he has very high self-confidence, generally thinks he is smarter than others, and devalues his ex-wives. When asked about his failed marriages, he says: "They didn't appreciate me enough." At work, colleagues see him as arrogant, and although he is productive, interpersonal tensions and disrespect for authority have limited his promotion in a corporate law firm.

On evaluation, when asked about his energy, sleep, mood, and activities, he reports constant mood swings, on an hourly basis, sometimes very happy for hours and sometimes irritable and down for

hours. He usually only needs 4 hours of sleep nightly, and has a high energy and activity level compared to peers, and a very high libido all the time. He reports feeling anxious and having "nervous energy" most of the time. He is an active rock climber, bikes 20 miles each morning before going to work, and sees himself as a "workaholic."

The PL diagnosis and clinical impression

The PL diagnosis is cyclothymic temperament. He also is high on the personality trait of neuroticism. The constant shifting of his moods, with frequent manic symptoms, was misinterpreted as "narcissism" because the grandiosity of manic symptoms was interpreted in the psychoanalytic paradigm of narcissism, within the DSM categorization of personality disorders.

The patient was treated with low dose Depakote, 250 mg/d for 1 month, then increased to 500 mg/d. Cyclothymic mood symptoms improved moderately, including inflated self-esteem as part of the manic component. His co-workers noticed that he seemed more responsive to interpersonal cues, interpreted as being less "arrogant." His libido and energy was lower, but still higher than most people. He remained productive, but had improved interpersonal relations.

The PL Bottom Line

- Manic symptoms of inflated self-esteem were misdiagnosed as narcissistic personality disorder.
- Low dose divalproex was more effective than long-term psychodynamic psychotherapy.

Clinical Tip of the Month

Don't diagnose borderline personality in the midst of a depressive episode. Don't diagnose narcissistic personality if someone has manic symptoms. In general, don't diagnose personality disorders routinely when depressive episodes or manic episodes/symptoms are present. Treat mood, and see what remains.

Curbside consults:
Questions and cases from you

Question: In the March issue's discussion of benzodiazepines, there was no discussion of possible risk for dementia. What does PL think?

PL: The potential association between benzodiazepine use and dementia was highlighted by a recent large epidemiological study (Billioti de Gage et al, BMJ, Sept 2014). That report was prominently published, and has had a good deal of attention. The problem with this kind of research, was highlighted in the April PL issue in the Statistics column on confounding bias. These non-randomized epidemiological studies always suffer from some confounding bias. This is why readers should never take the results of such epidemiological reports at face value.

The best way to reduce confounding bias in such non-randomized studies is to use "regression modeling." This means that some potential confounding factors - which could influence the results - are measured and "adjusted for" in the statistical model. In this case, the question was whether benzodiazepines increase the risk of dementia. Well, many things increase the risk of dementia, like age, diabetes, depression, anxiety, substance abuse, hypertension, and other factors.

The problem with large epidemiological studies is that people are impressed with largeness, rather than quality. But the larger the study, the more common it is that confounding factors aren't measured or adequately adjusted. When you have huge samples, you can't interview each person directly to know how much depression or anxiety they had in their lifetime, or to identify a host of other medical or psychiatric risk factors. In other words, huge samples have the advantage of hugeness, but the disadvantage of not characterizing clinical features in much detail.

All that being said, this epidemiological study was adjusted for some important confounding factors. Besides the usual easily measurable factors of age and gender, a regression model adjusted for some medical illnesses (like diabetes and hypertension) and for depression, defined as the diagnosis of "major depressive disorder" in medical charts.

This is better than nothing, but whether or not the study adequately adjusts for the presence and severity of depressive illness fully relies on whether the treating clinicians in this large sample had accurately and adequately identified and documented depressive symptoms.

Given that clinical charts aren't fully accurate for research purposes, there is some room for doubt as to whether the study adequately adjusted for depression, at least. Further, one might ask a question that has to do with "confounding by indication". Benzodiazepines are used frequently for anxiety. Anxiety increases adrenal hormone activity, which increases the risk for dementia. How do we know that the association between benzodiazepine use and dementia wasn't a classic case of confounding bias, where the third factor of anxiety, associated with benzodiazepine use, directly causes dementia?

One can't rule out this possibility from this analysis because anxiety diagnoses or symptoms weren't adjusted in the regression model, simply because the data weren't collected as part of the routine clinical practice which was the basis for the data used in the study.

The conclusion from this long discussion is that we simply can't accept the results at face value. Randomized studies would be much more definitive but they haven't been done. In the meantime, it's worthwhile noting that some animal studies show that benzodiazepines are neuroprotective, keep neurons alive, in human

and animal studies of stroke (WS Huang et al, *Psychiatry Clin Neurosci*. 2014;68:255-62). Thus, there are some biological data to counter this clinical hypothesis that benzodiazepines might increase dementia risk. There are other clinical studies which also don't find increased risk of dementia with benzodiazepines. As with many medical topics, the question remains to be answered with reasonable confidence. But we can say these data, as they stand, don't prove the claim that benzodiazepines hasten dementia.

Question: What do you think of Extended-Release formulations of drugs?

PL: There's no general answer to this question. Sometimes extended-release formulations are useful; sometimes they're not. Some examples: Lithium ER, which is now generic, probably is preferable to standard release generic lithium because the initial peak of a single dose is reduced, which may cause fewer renal effects or fewer cognitive or gastrointestinal effects. Carbamazepine ER, also generic, has much less nuisance side effects (dizziness, ataxia, diplopia) than standard carbamazepine. Divalproex delayed release (Depakote DR) has much less gastrointestinal side effects than generic valproic

acid. But Divalproex extended release (Depakote ER) produces no further appreciable reduction in side effects. Venlafaxine XR and Bupropion SR have less side effects than their immediate-release versions, but Bupropion XL produces no further reduction in side effects. Quetiapine XR has less sedation than immediate-release, but no other appreciable benefit.

An important point: Slow-release formulations don't necessarily extend the half-life of a drug. For instance, Depakote ER hardly increases the half life of Depakote DR (18 hours for ER versus 12-16 hours for DR); lithium and carbamazepine ER don't appreciably lengthen half-lives versus immediate release alternatives.

The most common benefit, when present, involves possible reduction in some specific side effects, but this isn't always the case.

PL Reflection

We perfect, we soften, we conceal what nature has put in us, but we do not put in ourselves anything at all.

Voltaire

Summer CME Course

Master Clinicians' Approach to Diagnosis, Drugs, and Psychotherapies

Nassir Ghaemi MD

32nd Annual Cape Cod Symposia, New England Educational Institute

July 20-24, 2015

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THE PSYCHIATRY LETTER

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Cape Cod, MA, July 20-24 2015
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Bipolar or not?

Is the patient bipolar or not? This question must be one of the most common dilemmas of clinical practice. This month, PL suggests way of trying to approach the question, including the idea that it might not matter at all, since the DSM structure may set us up for more confusion than we need for an already complex disease.

The special article this month examines different ways of thinking about manic-depressive illness, which isn't the same thing as bipolar disorder, but rather means both bipolar illness and "major depressive disorder."

The classic study of the month examines the ideas of Jules Angst, the great Swiss psychiatric researcher who in the 1960s published research that led to the bipolar/unipolar dichotomy. In the same long-term Zurich cohort, he now has four decades of further evidence that goes against his 1960s results. In short, his research study, after a lifetime of follow-up, now opposes a simple bipolar/unipolar dichotomy and provides more support for the concept of a bipolar spectrum (similar to the older notion of manic-depressive illness).

The drug of the month is lamotrigine. Emphasis is placed on the many ways it is ineffective, so as to better appreciate its efficacy as a preventive agent in bipolar illness. The case of the month addresses an example where carbamazepine, not lamotrigine, is the preferred choice in bipolar illness.

We again invite you to join us for a week-long summer course in Cape Cod this July where we'll be able to interact about many of the topics and approaches discussed in PL.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Understanding manic-depressive illness*

It isn't the same thing as "bipolar disorder"

Before 1980, there was no such thing as bipolar disorder. And there was no such thing as "major depressive disorder." There was depression, of course, and there was mania. And there was hypomania too. But clinicians and researchers saw all those mood states as parts of the same single illness. You could have just depression; you could have both mania or hypomania and depression. It didn't matter: it was all one illness.

Called manic-depressive illness (MDI), this single mood illness meant having *either* manic *or* depressive episodes, not having *both* manic *and* depressive episodes.

That's why manic-depressive illness is a very different condition than what came to be called bipolar disorder. Manic-depressive illness doesn't mean the same thing as "bipolar disorder." Manic-depressive illness means what today we call major depressive disorder *plus* bipolar illness.

What is bipolar? What is unipolar?

So this is the real question: Are mood conditions all variants on one illness (MDI)? Or do they represent two illnesses: bipolar and unipolar?

In 1980, the verdict of DSM-III came in favor of the latter view. MDI was split into two: Either/or was replaced by both/and. To say someone had "bipolar" disorder you had to have both mania and depression, not either one. If you only had depressive episodes, but not mania, then the term "unipolar" depression had been applied. By the time DSM-III definitions had gone through the sausage-making process of APA politics, the term "unipolar" was changed to "major depressive",

while the term "bipolar" was kept. There is a reason for this change that isn't minor.

"Unipolar" depression had been seen as part of what used to be called MDI. All MDI was seen as involving severe mood episodes, whether depressive or manic. The symptoms weren't mild; they were severe, at least some of the time. MDI was also seen as being mainly genetic and biological in origin, just as was the view on schizophrenia, at least among classic European thinkers like Kraepelin. Indeed, it was Kraepelin who had first identified MDI and schizophrenia (which he called dementia praecox) as two severe biological diseases that represented many of the patients who were hospitalized for years in German state hospitals.

So "unipolar" depression didn't mean just a little depression; it meant very severe, biological, recurrent depressive episodes.

In the DSM-III process, many of the APA leaders and activists, who were psychoanalytically-oriented, opposed biological disease assumptions for psychiatric diagnoses. They especially had this concern in relation to "unipolar" depression, since the most common diagnosis for their own patients who received psychoanalysis had been "neurotic depression" (see PL issue 3). This is where the word "major" comes in. The "unipolar" patients were mixed with the "neurotic" depressed patients, and the term "major" was applied to the combination. This would remove the assumption that these patients had biological diseases (as had been the case with unipolar depression), and thus non-biological treatments, like psychoanalysis, could be justified.

So we were left with a hybrid: “bipolar” patients and “major” depressive disorder (MDD) patients who were not “bipolar.”

Being “bipolar” today

So being “bipolar” today simply means not being “unipolar” and, in addition, not being “major” depressed in general. Mania has to slap you in the face to say someone has bipolar illness; otherwise they don’t. Perhaps you’re more sensitive to manic symptoms, and you’re willing to identify them when milder. Still, hypomania has to slap you in the face to say someone has bipolar illness. Even then, we sometimes qualify the hypomanic diagnosis by calling it “soft” bipolar illness, or by using the bipolar

“spectrum” phrase.

For two decades, the PL editor has been involved in some of these efforts of trying to make sense of how to identify and incorporate mild manic symptoms into the bipolar diagnosis.

All these efforts bring us back to the fact that the DSM system has forced the profession to obsess about manic symptoms in diagnosing mood. Everything rides on one question: Are manic symptoms present? If they are, the diagnosis is bipolar; if they’re not, the diagnosis is MDD.

But is this obsession justified? Is this the scientifically valid way to diagnose mood illnesses?

No “hypomanic” symptoms

Let’s make an initial point: there are no such things as “hypomanic” symptoms. This is the case for the same reason that there are no such things as “hypodepressive” symptoms.

One either has depressive symptoms or not; those symptoms might be mild, moderate, or severe; but

whether or not we want to say they represent a DSM-defined “major” depressive episode has nothing to do with each individual symptom, but rather with how many occur and for how long.

Similarly one either has manic symptoms or not; those symptoms might be mild, moderate, or severe; but whether or not we want to say they represent a DSM-defined “hypomanic” episode has nothing to do with each individual symptom, but rather with how many occur and for how long.

The fact that so many clinicians use the phrase “hypomanic symptoms”, which is meaningless, rather than “mild manic symptoms”, indicates the reluctance we possess to labeling manic symptoms at all, even if mild.

This reluctance, which is a big part of the stigma against the

“bipolar” diagnosis, can lead to even more obsession about whether manic symptoms are present or not. We obsess on manic symptoms because we’d prefer to diagnose MDD, not “bipolar” illness. Some of this preference has to do with the impression of fewer side effects with monoamine agonists (“antidepressants”) as opposed to “mood stabilizers.” But there also are deeper cultural factors at play, which strengthen the stigma against bipolar illness, a larger question for separate discussion.

Type II

One consequence of this resistance to the word “manic” is that if bipolar diagnoses are made, clinicians often prefer to use the term “hypomanic,” and then they make the diagnosis of “type II” bipolar illness. The type I vs type II differentiation is another story of DSM politics. Originally in DSM-III, there was no type I or type II. Bipolar disorder was diagnosed simply,

without any typology, because there was only one type: mania. There was no hypomania. The term “hypomania” had been used for a century to mean a mild manic episode. In the 1970s, some researchers suggested defining hypomania as a manic episode that wasn't severe enough to lead to hospitalization. So if you weren't hospitalized, you were hypomanic. If you were hospitalized, you were manic. (That was in the days when hospitalization was based on clinical judgments about severity, not financial factors, being as in later years of insurance management and government budget limitations).

Researchers had defined type II bipolar illness as never needing to be hospitalized, and type I as being hospitalized at least once.

Since DSM-III had not included hypomania as part of the bipolar definition, there was no need to include the type I vs type II definitions.

14 years later, in 1994, DSM-IV leaders reluctantly agreed to allow hypomania into the definition of bipolar illness (a decision the chairman of the DSM-IV task force, who opposes frequent use of the bipolar diagnosis, now says he regrets). By the 1990s, however, the insurance industry in the US had taken over much of the decision-making about hospitalization. So there was a need to define hypomania in a different way. It was decided to use the concept of “severe social or occupational functional impairment.” Hypomania would be diagnosed only if there was *no* severe social or occupational dysfunction.

But now the problem of the insurance industry had been replaced by the problem of cultural stigma. Who was to define whether or not there was severe functional impairment? Symptoms

could sometimes be subjectively interpreted or defined. Function was even more subjective.

Now defining hypomania is reliant completely on whether or not much functional impairment is present. If you have manic symptoms, and your boss gets mad at you, you're manic; if your boss doesn't get mad, you're hypomanic.

More importantly, clinicians often diagnose patients as “hypomanic” if they seem similar to clinicians: middle-class, employed, often white, solid-citizen types. If they're unemployed, or minorities, or legally-embroiled, or lower-class, they're more likely to get the full “manic” label.

If you have manic symptoms, and your boss gets mad at you, you're manic; if your boss doesn't get mad, you're hypomanic.”

Another common definitional error is that we may observe a bona fide hypomanic episode, and then we diagnose type II bipolar illness. But the type II concept meant that *all* manic symptoms occur as hypomanic episodes, *never* as manic episodes. If even one manic episode *ever* occurs, the diagnosis is type I, even if thousands of hypomanic episodes also occur.

In fact, most patients with bipolar illness have more hypomanic than manic episodes; i.e., their manic symptoms are more often mild than severe. This doesn't change the diagnosis from type I to type II. It's still type I, and not type II, if there is ever a single manic episode - ever.

Type II vs Type I: Any real difference?

This all comes down to a deeper question: Does any of this matter? Is there any major difference - in treatment response and biology - between type II and type I bipolar illness?

Most clinicians appear to assume that this is the case. Since we use different words - hypomania vs

mania, type II vs type I - then it is assumed that these are deeply different conditions. Many clinicians use the type II label with a certain skepticism, as if it is shorthand for saying: "Well, you could call it bipolar, but it's not the real thing." They then proceed to avoid mood stabilizers, or use antidepressants excessively, or add other labels, which they take more seriously in treatment (especially borderline personality).

In fact, these assumptions aren't well-founded scientifically. To answer the above question about type I and type II being different illnesses, researchers use the standard diagnostic validators described in the first issue of PL (January 2015), namely: symptoms, genetics, course of illness, biological markers, and treatment response. When these diagnostic validators are applied, there is a good deal of evidence that type I and type II definitions are similar, i.e., that they can't be distinguished from each other. They share similar genetics, course of illness, and biological markers. Their treatment response to mood stabilizers and dopamine blockers are also similar.

In short, these aren't different illnesses; rather they are misleading ways of saying "more severe" and "less severe." It's the same as saying that pneumonia can be mild or severe; those aren't two different illnesses, but two different severities of the same illness. Hypomania means less severe mania. Type II means less severe manic symptoms in bipolar illness. That's it.

Do manic symptoms matter at all?

The conclusion of the above discussion is that it may not matter whether or not manic symptoms are severe or mild, and whether or not they cause

functional impairment. From the perspective of diagnosis, it's all the same bipolar illness.

We can take this a step further, remembering the history of MDI and the fact that it wasn't the same thing as bipolar illness, and ask: Do manic symptoms matter at all? Even if manic symptoms are absent, and the patient only has depressive episodes, is it a different illness?

Again, DSM says so, but the science isn't clearly in agreement with DSM definitions.

We would again need to apply the standard diagnostic validators: symptoms, genetics, course of illness, and treatment response. How does MDD differ from bipolar illness there?

Take genetics: Have you ever seen patients with only depressive episodes (i.e., MDD) but family members who have bipolar disorder? If DSM is valid, this should never happen, or at least it should be rare."

(i.e., MDD) but family members who have bipolar disorder? If DSM is valid, this should never happen, or at least it should be rare. The claim from the 1970s that MDI should be split into bipolar and unipolar diagnoses was based partly on the claim that they separated genetically: bipolar illness predominantly happened in families of bipolar probands, and vice versa for unipolar depression. In the last four decades, the reverse has been shown: bipolar illness and unipolar depression do not separate well genetically. There are many persons with unipolar depression among family members of probands with bipolar illness.

Take course of illness: Have you seen patients with only depressive episodes whose illness began in childhood/adolescence or young adulthood? The 1970s studies claimed that MDI could be split into bipolar and unipolar groups because unipolar

depression began on average around age 30! It didn't start in young adulthood, much less childhood. Bipolar illness was found to begin in late adolescence (mean age 19). Research studies now show that many so-called unipolar depression cases begin in childhood/young adulthood.

Take treatment response: Have you seen so-called "unipolar" depression cases respond to antipsychotics? The DSM-III proponents in the 1970s believed that MDI could be split into bipolar and unipolar groups because the treatments seemed to be different: antipsychotics and lithium for mania, and antidepressants for depression. It turns out, as we now know well, that many "antipsychotics" work well for non-psychotic depression, and many "antidepressants" don't work so well for some kinds of depression (especially bipolar depression, see PL website).

Biological studies also haven't found clear and replicable differences in neurobiology between unipolar and bipolar groups.

In short, 40 more years of research puts into doubt the scientific bases for the radical decision in 1980 to claim that there are two separate mood illnesses - bipolar and MDD - as opposed to one -

MDI. We have been living for two generations, with the consequences of that radical claim.

In the setting of this scientific evidence, PL recommends that clinicians do not need to feel constrained to follow the DSM dictates on MDD and bipolar illness.

Instead, the scientific evidence is mostly supportive of the notion of being open to mild manic symptoms, through the notion of a bipolar spectrum, and even being open to the notion that manic symptoms might not matter at all, through the original notion of manic-depressive illness.

The PL Bottom Line

- Manic-depressive illness (MDI) means *both* bipolar and major depressive disorder.
- The bipolar spectrum concept implies that mild or brief manic symptoms matter.
- The MDI concept implies that manic symptoms don't matter at all, but that recurrence of any mood state is what matters, and it all represents the same illness.
- Type II is probably a milder variant of type I illness, not a completely different condition.

Sources: SN Ghaemi. The bipolar spectrum: Conceptions and misconceptions. *Aust N Z J Psychiatry*. 2014;48:314-24.
J Angst, A Marneros. Bipolarity from ancient times: Conception, birth, and rebirth. *J Affective Disorders*. 2001; 67:3-19.

PL Reflection

A long dispute signifies:
'Both parties are wrong.'

Voltaire

Clinical Tip of the Month

Hypomania originally meant mild mania, defined as not needing hospitalization. That's why DSM duration criteria for hypomania have an exclusion for hospitalization. If you're hospitalized, the diagnosis is mania by definition, since hospitalization implies severe dysfunction. In sum: *There is no such thing as a hospitalized hypomanic patient. If you're hospitalized, you're manic.*

Classic study of the month: *Bipolar or unipolar?*

The bipolar spectrum. J Angst, British Journal of Psychiatry, 2007, Volume 190, Pages 189-191

The modern founder of the bipolar/unipolar dichotomy revisits the idea

This paper is not a study itself, but rather a brief two-page summary of fifty years of wisdom. It bears careful reading.

The Zurich cohort study

Let's set the stage. Jules Angst is a Swiss psychiatrist who has been at the forefront of research in mood illnesses for half a century. In his youth, he studied at the home of Carl Jung, in addition to being trained by the most prominent mood researchers in Europe. In the late 1950s, he started a prospective outcome study that would be the largest and longest cohort study in mood research. The Zurich Cohort was collected in 1959-1963, consisting of all patients admitted to the psychiatric hospital in Zurich with diagnoses of manic-depressive illness (bipolar and unipolar). 406 patients were identified and followed prospectively at 5 year intervals for over 40 years; they have now been followed until the almost the entire cohort has died. In 1979, Angst added a normal general population comparison group from Zurich (n=4547), followed for 20-30 years.

In other words, Angst's Zurich cohort study is the Framingham heart study of psychiatry. It's a classic well-designed observational study where people are followed for a very very long time to see what happens to them. Contrast his efforts with almost all other studies in psychiatry. Most drug treatment studies are 8 weeks long. The "long" studies rarely last longer than one year.

One might say, without exaggeration, that 99% of all published psychiatric treatment or outcome studies are one year or less in duration. But you treat your patients for years, sometimes decades.

Where's your evidence for what happens to them over years and years? The Zurich study is the best such evidence: we are referring to 20 years, 30 years, even 40 years of outcome data here - not one year, and certainly not 8 weeks.

1966: For bipolar/unipolar

After getting his study started in 1959-1963, Angst had collected about 5 years worth of data, which he published in a classic paper in 1966. The same year, an independent researcher, Carlo Perris, published a similar study. Both men were looking at whether bipolar and unipolar mood illness could be distinguished based on the accepted diagnostic validators of genetics and course. Obviously patients differed in symptoms of mania versus depression, but did those differences matter? Kraepelin had said: No. And for 70 years, Kraepelin's view had held sway.

Angst and Perris independently found otherwise; they said: Yes. Their data showed that bipolar illness had more genetic loading of mania and than unipolar illness; they found that the course of the two conditions was different as well, with earlier age of onset and more frequent but briefer episodes in bipolar than unipolar illness.

Angst likes to tell the story that when he told senior figures in mood research about his findings, their initial reaction was: *This can't be right. It goes against what Kraepelin said.*

2014: Against bipolar/unipolar

Fast forward from 1966 to 2014 - about half a century. Angst's 1966 results of five years of follow-up were central to the radical changes of

DSM-III in 1980. Bipolar disorder and major depressive disorder (MDD) became official. Our definitions of those conditions have barely changed in the last 50 years.

Half a century later, Angst was invited as a consultant to the DSM-5 Mood Disorders Task Force. He presented, not five, but 40 years of research, with the exact same cohort. He presented the same research data, but much better. And he now found, with much longer follow-up, that he had been mistaken in his 1966 report: The 40 year follow-up finds that there is *not* a clear distinction between bipolar and unipolar illness on many diagnostic validators.

In this review paper, Angst summarizes his findings, and places them in the context of other research over the past decades.

He finds that manic symptoms do not radically separate from depressive symptoms in the diagnostic validators of course and genetics. Many people with mild manic symptoms have the same course and genetics as persons with more severe manic symptoms. For instance, the hypomania threshold of 4 days is disproven by the Zurich cohort, where 1-3 days of mild manic symptoms led to the same course and genetic findings as was the case for one week or longer of manic symptoms. Similarly, the presence of mild manic symptoms all the time, with no episodes at all, has been observed in the mood temperament of "hyperthymia." The same has been shown in the opposite polarity with dysthymia; and with both polarities with cyclothymia. And these mood temperaments are found in many normal

persons in the general population, who do not have full mood episodes of any kind, whether manic, hypomanic, or depressed. Such persons often have relatives with those mood episodes.

In sum, with the longest follow up over decades, Angst has concluded that there is a *spectrum* of mood symptoms, rather than a clear dichotomy of categories. We can still talk of categories as shorthand clinically, and at the extremes they may differ substantially: Severe elated mania is quite different than severe unipolar depression. But there are many variations in between; and the variations are the rule.

In 2014, Angst went to the DSM-5 committee with better, stronger, more valid results than he had in 1966, and the reaction was the same as half a century earlier: *This can't be right; it goes against what DSM-III/IV/5 says.*

Angst speaks now of two spectra: one of severity, and one of polarity. Some patients are a little bipolar but severely so; others are very bipolar but less severely so. Some are very unipolar but mildly so; and so on. There are many variations to mood, and the simple polarity distinction of DSM-III to 5, which was based on earlier analyses from the Zurich cohort, has been disproven by the same research study's longer and more valid database.

The PL Bottom Line

- The Zurich cohort initially supported the DSM dichotomy of bipolar/unipolar illness.
- The same cohort study now disproves that simplistic dichotomy, and supports a spectrum approach based on both severity and polarity.

PL Reflection

All interpretations are hypotheses, which must be forever tested and revised if unsatisfactory. That's why a change of mind in a scientist, particularly a great scientist, is not a sign of weakness, but of greatness.

Ernst Mayr (adapted)

Drug of the Month: *Lamotrigine (Lamictal)*

What doesn't get you well keeps you well

Lamotrigine is an anticonvulsant which has turned out to be the latest, newest, proven effective “mood stabilizer,” by which PL means an agent which prevents mood episodes in bipolar illness. The studies which proved lamotrigine’s efficacy were conducted over 15 years ago, and now the agent is available as a generic drug.

Clinical efficacy and inefficacy

In the late 1990s, when GlaxoSmithKline (GSK) was preparing its studies of lamotrigine, it had an ambitious agenda: Multiple randomized clinical trials (RCTs) were conducted for acute mania, acute bipolar depression, and even acute unipolar depression. Along with two studies in rapid-cycling bipolar illness, it added up to about a dozen randomized clinical trials.

In all cases, lamotrigine failed. It was completely ineffective. It was not better than placebo. Luckily for GSK, two RCTs were conducted in maintenance prevention of mood episodes in bipolar illness. In both cases, lamotrigine worked. It was effective.

In other words, the drug was proven *not* to work in any acute mood state, manic or depressive. *And*, it was proven to work in *prevention* of mood episodes, both manic and depressive.

Why would lamotrigine *prevent* future mood episodes, but not *improve* current ones? This seems like a major paradox for many clinicians

because they can’t get out of the mindset of treating acute symptoms. The thought always has been that if a drug works short-term, it’ll work long-term:

“What gets you well, keeps you well.”

This common clinical belief was disproven by lamotrigine. It doesn’t get you well, but it keeps you well. *Take lamotrigine when you’re well to stay well, not when you’re sick to get better.*

Since these ideas aren’t well known, there is a common clinical misconception that lamotrigine is effective for acute depression, whether in bipolar or unipolar illness. When patients have depressive symptoms, clinicians sometimes increase the dose of lamotrigine as if it will improve depressive symptoms within weeks or months. Multiple RCTs show that lamotrigine will not help current depressive (or manic) symptoms that way.

These misconceptions about lamotrigine’s acute efficacy were left uncorrected by GSK, which didn’t publish the many negative RCTs. After a legal verdict against GSK for a different medication (paroxetine), a court order required the company to publish all its negative data on a website. For a brief period, those data were publicly available on the Internet, from which the PL editor downloaded the results and published them separately (Ghaemi 2009). Without that legal intervention, the results never might have been known due to patent law protection.

Fast Facts: Lamotrigine

Typical dose: 50-200 mg/d.

Biological mechanism: glutamate antagonist

Typical side effects: Rash

Less common but important side effects: Anxiety

Medically important side effects: Stevens Johnson Syndrome

Clinically proven efficacy: Prevention of mood episodes in bipolar illness

Regarding the maintenance studies themselves, another misconception needs correction: It is sometimes thought that lamotrigine only prevents depression, not mania. In fact, in the combined two maintenance RCTs, lamotrigine was effective in preventing mania more than placebo; it did have mania prevention benefit. It just had *more* benefit in prevention of depression than mania.

Biological mechanism

Lamotrigine is a novel anticonvulsant, which raises the seizure threshold via glutamate antagonism. Glutamate is an excitatory neurotransmitter distributed throughout the brain. Whether this mechanism is relevant to this agent's mood effects is unknown.

Side effects and dosing

The main concern about lamotrigine is rash. Non-serious rash happens in about 5-10% of persons; serious rash usually involves Stevens Johnson Syndrome (SJS), which is potentially fatal. SJS occurs in about 1/5000 adults given lamotrigine, and in about 1/1000 children or adolescents. These rates assume the standard slow titration of lamotrigine. PL recommends a slower titration than the package insert, developed originally for epilepsy.

The PL recommendation is 25 mg/d increased every 2 weeks in 25 mg increments - no faster.

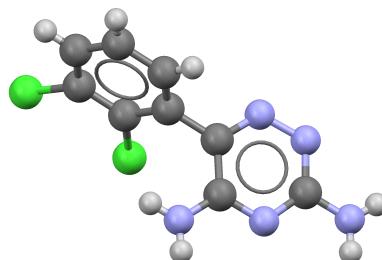
Risk factors for rash and SJS are rapid titration, other drug allergies (such as antibiotics), and autoimmune conditions (like lupus).

Of these risk factors, PL would emphasize drug allergies and autoimmune illnesses. Rash risk is higher with drug allergies, and in those cases

lamotrigine shouldn't be used as a first-line agent, and if used, the dosing titration should be even slower (such as 12.5 mg every 2 weeks).

If autoimmune illnesses are present, PL recommends that lamotrigine *not* be used at all. A number of cases exist of serious medical harm in autoimmune illness, with immunologic reactions such as SJS and aseptic meningitis.

The dose range proven effective in RCTs of bipolar illness was 50-200 mg/d. 400 mg/d was studied and was found to be no more effective than 200 mg/d. A common error is to increase lamotrigine dose to 300 mg/d or 400 mg/d, without realizing that these higher doses aren't more effective for bipolar illness. These higher doses only cause more side effects, particularly anxiety and cognitive impairment.



Lamotrigine structure seen on its triazine ring plane, unrelated to other anticonvulsants. Cambridge Structural Database. Cl N

The PL Bottom Line

- Lamotrigine is effective for prevention of mood episodes in bipolar illness, but not for acute depressive symptom benefit.
- There's no further mood efficacy above 200 mg/d, only more anxiety and cognitive side effects.

Source: SN Ghaemi. The failure to know what isn't known: Negative publication bias with lamotrigine and a glimpse inside peer review. Evidence Based Mental Health. 2009;12:65-68

PL Reflection

The key to longevity is to have a chronic incurable illness - and take good care of it.

Oliver Wendell Holmes Sr

Case of the month:*Carbamazepine to the rescue*

A 38-year-old female is diagnosed with anxiety and depression. She has had depressive episodes repeatedly, usually lasting a few months at a time. She also had manic and hypomanic episodes in the past; in college, she said, she “slept with way too many people.” These periods of sexual overactivity contrasted with months of decreased libido when she was depressed. During those hypomanic periods, she also had increased overall activity, talked rapidly, and had fast thoughts. Those periods lasted days to weeks. In recent years, her elevated moods were associated with overspending, which led to major financial problems. Depressive periods were characterized by low energy, decreased interest, sadness, insomnia, and high anxiety. Her mood swings were such that she was never able to maintain a long-term stable relationship. She’s never been married and has no children. She works in an insurance company. She had no childhood trauma and has never cut or harmed herself. She is pleasant and cooperative in the interview. She has no past substance abuse.

After failing to improve on paroxetine and sertraline and venlafaxine and bupropion, her doctor added divalproex to bupropion. She had a moderate improvement in anxiety and depressive symptoms, and fewer manic symptoms, though she still has some hypomanic episodes. She experienced marked hair loss with divalproex, however, with no benefit with mineral supplements. A trial of lithium also caused hair loss. Current medications are divalproex 500 mg twice daily and bupropion SR 300 mg daily.

She wants an alternative mood stabilizer that won’t cause hair loss.

The PL diagnosis and clinical impression

The diagnosis is bipolar illness type I. Some clinicians would diagnose borderline personality based on the broad DSM criteria of mood swings, unstable interpersonal relationships, and sexual impulsivity. The PL view (see website) is that the absence of childhood sexual trauma and parasuicidal self-harm argues strongly against the borderline label. In contrast, clear manic, hypomanic, and depressive episodes exist.

The two remaining standard mood stabilizers are carbamazepine and lamotrigine, neither of which cause hair loss (nor weight gain). Since she has had notable manic morbidity (financial impairment excludes hypomania), PL recommended carbamazepine rather than lamotrigine. Further, since bupropion is a mild amphetamine, which has been proven ineffective in bipolar depression (equivalent to placebo in the STEP-BD study; see PL website and January 2015 issue), the PL view is that it’s useless at best, harmful at worst. Since all monoamine agonists (antidepressants) can cause more mood cycling (see PL website), bupropion could be destabilizing her mood, worsening her continued depressive and hypomanic episodes.

The PL recommendation was to taper off bupropion (150 mg/d for 2 weeks, then stop) and to replace divalproex with carbamazepine ER 300 mg twice daily. Three months later, her mood had improved markedly, with resolution of hair loss, and no other side effects. Mild anxiety persisted which responded to lorazepam 1 mg daily.

The PL Bottom Line

- Use carbamazepine rather than lamotrigine when a patient’s history involves notable manic episodes with functional impairment.
- Remember to stop monoamine agonists long-term: there is no benefit, only possible harm.

Curbside consults:

Questions and cases from you

Question: I will be evaluating a 22 year-old female diagnosed with bipolar II who is presented as a rapid cycler. She also appears to have borderline traits. Her current medication list: Lamotrigine 300 mg at night; mirapex (pramipexole) 4mg twice daily and prozac (fluoxetine) 80mg daily. The current treating psychiatrist writes: "Although she is bipolar, because she does not hear voices and denies suicidal ideation, I will keep the current regime." Three weeks before, she was hospitalized with strong suicidal ideation. She describes herself as hypersexual, impulsive, racing. Her relationships are dysfunctional. Is my sense of surprise much to do about nothing or might we have someone who needs to be off prozac and mirapex? What are your thoughts on mirapex in bipolar depression? She also describes her depression as periods of anger and irritability. Makes me wonder if geodon (ziprasidone) or latuda (lurasidone) might be a wiser choice.

PL: Assuming the correct diagnosis of bipolar illness type II (future issues will address the differential diagnosis with borderline personality), the PL view is that monoamine agonists (antidepressants) are ineffective at best, and

harmful at worst (as reviewed in the PL website, also to be discussed in future issues). Fluoxetine (especially at this high dose) and pramipexole likely are contributing to the patient's mixed depressive state, which is itself causing her suicidality. Her anger and irritability are part of the mixed depressive state (see PL February 2015 issue). Pramipexole has been shown in small randomized trials to be more effective than placebo for acute bipolar depression, but it also has numerically higher mania switch rates than placebo. Hence, like any monoamine agonist, it likely can cause mania - including a mixed state.

PL agrees with tapering off fluoxetine and pramipexole, and replacing them with a dopamine blocker. The mere removal of the offending monoamine agonists should improve the mixed state and suicidality. But a little aripiprazole or ziprasidone or lurasidone would help too. Given the recent suicidality, PL would take the view that lithium would be the preferred choice, since it is the only drug proven to prevent completed suicide. It might help enough at low doses, 300-600 mg/d, in type II bipolar illness, especially when added to full doses of another mood stabilizer, like lamotrigine. These low doses also would limit side effects, like weight gain.

Summer CME Course
Master Clinicians' Approach to Diagnosis, Drugs, and Psychotherapies
 Nassir Ghaemi MD
 32nd Annual Cape Cod Symposia, New England Educational Institute
 July 20-24, 2015

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THE PSYCHIATRY LETTER

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Special Issue: Cape Cod summer symposium highlights

This month's issue presents highlights from the Cape Cod summer symposium, which was just completed in late July. Unlike other issues, there is no study or drug of the month. The usual columns will resume in the August issue.

The main goal of the week-long summer symposium was to identify how one could become a master clinician. What approaches to diagnosis, drugs, and psychotherapies would help us go beyond the average mainstream, and be better?

This special issue gives readers a view inside some of the content and discussion of this course about the PL approach to psychiatry. Besides a discussion of diagnosis and medications, the psychotherapy focus was on existential approaches, which are the least appreciated of the many schools of psychotherapy.

Some of the questions brought up by clinicians who participated in the course are described, and summaries of the discussions that followed are presented.

We hope you enjoy this peek inside this week-long interactive experience, and that this written description of the material discussed can help you as you continue to think about how we can best practice a new psychiatry.

An extensive bibliography of recommended books for this course is provided on the PL website.

As usual, please send any questions or comments or cases to us for inclusion in future issues.

And please let your colleagues know about PL. We are relying on our current subscribers to spread the word.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Becoming a master clinician*

Highlights from the Cape Cod summer symposium

The Cape Cod Summer Symposia have been happening for three decades; this year the PL editor conducted the first week long course on basic concepts that are central to PL: How should we diagnose? How should we use medications? How do we understand the role of psychotherapies? Special emphasis was given to the existential approach in psychotherapy.

Highlights of some of the material presented, and the discussion that ensued, are presented here.

“Questionable” evidence: Focus on family history

It was taught that family history and course of illness can inform diagnosis. For instance, if an adult has a family history of bipolar illness in a first degree relative, age of onset of depression before 25 years, and psychotic

features during a depressive episode, a study found that 2/3 of such depressed persons would be found to have a manic episode at some point; in other words, they had bipolar illness. The teaching point was that you can increase your likelihood of correctly identifying bipolar illness, or any diagnosis, by assessing family psychiatric genetics and course features consistent with that illness.

A colleague then asked the following question: I treat children. They all have depression before age 25; many have psychotic features, but it's questionable, because it could have been caused by amphetamines. Many have family history of bipolar illness, but it's questionable. I could diagnose them all bipolar, but it would be on

questionable evidence based on the course and family history.

The PL view is that if one's evidence is truly questionable, then one should not put much weight on it. But our evidence often is much less questionable than we think. For instance, in the case of a child, the parents are usually present for a clinician to interview herself. If the clinician wants to remove doubt, assess the parent with a psychiatric interview to identify whether they've ever had manic symptoms or not.

To focus on family history, it often appears to be the case that clinicians downplay or write off some evidence of psychiatric illness in families. For instance, they'll note that an uncle was reported to have bipolar disorder, and then proceed to diagnose major depressive disorder (MDD). They

don't realize that the whole concept of MDD was based on the notion that it is genetically separate from bipolar illness, and thus it should not happen, or rarely so, in persons with relatives with bipolar illness. Thus, it is important to find out if that uncle truly had bipolar illness or not. How can you do it? The simplest way is to ask the patient to describe what the uncle was like. Suppose the patient says: “He would spend months in bed, not doing anything at all, and then for weeks on end he was all over the place, spending tons of money and visiting prostitutes.” That is not a very questionable history for mania. If the patient doesn't know the relative well, often a family member is present in the waiting room, who can provide that evidence. This is one reason why PL recommends that family members never

“Our evidence often is much less questionable than we think.”

sit in the waiting room if feasible; they should be invited into the office and be part of the diagnostic interview.

There are many studies which have assessed the accuracy of psychiatric family history. They compare "family history" with "family study." In other words, first they asked patients about psychiatric illness in their family members; then they went and interviewed many family members about their own psychiatric symptoms. The conclusion? You won't be surprised: If anything, patients underreport, rather than overreport, psychiatric illness in their families.

Keep in mind that the only two highly genetic psychiatric conditions are bipolar illness and schizophrenia. "Anxiety" and "depression" are not highly genetic, besides being vague symptom definitions (like "fever") rather than diagnoses. Manic-depressive illness is the kind of genetic illness that causes depression. And schizophrenia is the genetic illness that causes chronic delusions. Those are the two main psychiatric conditions to assess in a family history.

Benzodiazepines: What is the abuse risk?

When discussing how to treat high neuroticism, generalized anxiety in DSM lingo, we discussed the risks and benefits of long-term use of serotonin reuptake inhibitors (SRIs) versus benzodiazepines. In relation to the latter, some clinicians expressed concern about their abuse liability. Research was cited stating that their abuse liability is low, if someone has no history of substance abuse. The overall percentages will vary, but in one study, less than 5% of such persons developed an addiction to benzodiazepines. Even if past substance abuse was present, only about 15% of such persons

developed a new addiction to benzodiazepines. This is not to say that these agents are not addictive; they are. But they are not addictive in 85% or more of the persons who take them. Thus this potential risk is not a reason to avoid them nor to be stingy about them, especially in persons with no past substance abuse.

Yet the question was raised whether it was not abuse when someone took benzodiazepines regularly for years, as prescribed, but would not, or could not, come off them. This is a legitimate question. The same could be said regarding amphetamines when taken for ADHD. There certainly is tolerance for benzodiazepines, which will make it difficult to come off after years of regular treatment. The same is the case, perhaps even worse, with SRIs. This doesn't mean that

the individuals are "addicted" to those agents; but they are stuck with them. This is all the

more reason to avoid long-term treatment beyond one year with any of these drugs, whether benzodiazepines or SRIs. There will be a substantial minority of persons in whom such long-term use might be needed in some cases. Perhaps high neuroticism is the most legitimate situation for such use. But even then, attempts should be made to have drug holidays for months at least, or maybe longer, as frequently as possible.

Still this long-term concern about withdrawal syndromes is no reason to avoid giving benzodiazepines short-term, meaning for months, especially in those without past substance abuse.

PL Reflection

To cure sometimes, to heal often, to console always.

Hippocrates

A final point: Many persons in whom benzodiazepines or SRIs are used for anxiety do not have anxiety “disorders.” Anxiety is the most nonspecific symptom; it is the fever of psychiatry. It is often caused by something else, usually mood episodes, sometimes psychosis. Treat the underlying disease, the mood illness for instance, and the anxiety will eventually improve in many persons. In many cases, the benzodiazepines can be used in such settings short-term for symptom relief while the underlying mood disease is getting controlled.

Then when the mood

symptoms improve, the benzodiazepines can be tapered off and anxiety often does not recur. In those cases where anxiety persists despite improvement in mood or psychotic illness, then one might have a true comorbidity, and then, in that minority of patients, long-term use of benzodiazepines might be warranted, despite the reality of withdrawal.

Is ADHD a legitimate diagnosis?

Some evidence was discussed, as summarized in the PL website, about the lack of studies of validators of diagnosis (course, genetics, biological markers) supporting the legitimacy of adult ADHD as a scientifically valid diagnosis. The question was raised whether the same held for childhood ADHD.

The details about the relevant studies are cited in the PL website article. Further discussion of adult ADHD will happen in future PL issues in more

detail. For now, the summary PL view is that adult ADHD is a scientifically invalid diagnosis, and that childhood ADHD mainly represents a developmental phase. These perspectives are explained in the PL website.

One factor that was raised was the experience that apparent adult ADHD often reflects mood temperaments, especially hyperthymia and cyclothymia. In mood temperaments of those

kinds, manic symptoms are always present. Since manic symptoms include

distractibility, those persons often are misdiagnosed as having adult ADHD. In fact, they improve frequently with low-dose mood stabilizers, like lithium 300-600 mg/d or divalproex 250-500 mg/d.

The harms of amphetamines

Some concern was generated when there was a brief review of some of the animal data indicating neurobiological harm with amphetamines, including methylphenidate. This harm involves killing neurons, or cortical atrophy. A brief discussion is present on the PL website.

What should we do with amphetamines, if this kind of neurobiological harm is true? First, it should be noted that these animal effects have neither been proven nor disproven sufficiently in the limited human MRI studies so far. (See PL website for links to the few studies). Thus these

Clinical Tip of the Month

In adults, amphetamines like methylphenidate have a 1 in 1000 risk of sudden cardiac death. We warn patients about lamotrigine, which has a 1 in 5000 risk of Stevens Johnson Syndrome. Yet we do not warn patients about the amphetamine-related sudden cardiac death risk. As a matter of informed consent, we should do so. Avoid amphetamines, especially methylphenidate and its variations, in older persons with severe heart disease or in any one with past heart arrhythmias.

animal data are neither a reason to avoid amphetamines automatically, nor a reason to simply give them out routinely. Rather, the PL view is that patients should be given informed consent. They should be told that these animal data exist, that their relevance to humans is unknown, and that information should be taken into consideration by patients in their decision about whether to take or not take amphetamines for purported ADHD or other purposes (e.g., to increase energy or improve cognition).

Further, patients should be warned that in middle-aged and older adults, amphetamines carry some risk of sudden cardiac death (about 1 in 1000 risk according to a recent study). Again, this is not an absolute contraindication to giving amphetamines to adults, but it is a piece of informed consent that should be given to patients to help them make their own personal risk/benefit calculations.

Existential psychotherapies

A major focus on the course was the use of existential psychotherapies, perhaps the least understood and least used style of psychotherapy in most parts of the world, especially the USA.

The basic principle of existential therapy - if one tries to identify it - is the concept of putting the world "in brackets", that is, not making any judgments of any kind about anything. The therapist doesn't theorize, she doesn't think, she just experiences. The point of the therapy is not to convince the patient about anything, nor to identify any insights. It is simply to be with the patient. The patient isn't sick; the therapist isn't healthy; both are sick and healthy at the same time, and both will change.

This approach of just being with someone else can itself be therapeutic; it can be all that is needed to help the other person, in cases of pure existential psychotherapy. Or, it can be used to engage with the patient or client as part of a larger process, whether it be identification of a psychiatric disease to be treated with medications, or a later shift to a different kind of psychotherapy for a specific purpose, such as couples therapy or psychoanalytic therapy or cognitive behavioral therapy.

In short, existential therapy helps us to connect with the person inside the patient, as Leston Havens said, and that connection is the beginning of any treatment.

"The basic principle of existential therapy...is...not making any judgments of any kind about anything."

Sources

The concept of putting the world "in brackets" was introduced in the late 19th century in philosophy by Edmund Husserl. He saw it as a means of getting at the truth. He called his approach "phenomenology". His ideas soon influenced the founders of existential philosophy, like Karl Jaspers, and thus this way of thinking often is called the "existential/phenomenological" approach. Jaspers trained and worked in Heidelberg, which was the most prominent academic center in psychiatry in the early 20th century. Thus, this approach has also been called the "Heidelberg school of psychopathology."

In the US, the main person who introduced these ideas was the psychologist Rollo May, who had been mentored by the existential theologian Paul Tillich, who himself came from Germany where he had been influenced by a founder of existentialist philosophy, Martin Heidegger.

The other major founder of existentialist philosophy was Karl Jaspers. Jaspers was a psychiatrist, as well as a philosopher, hence he would seem to be an ideal source of existential psychiatry. In fact, he laid the foundation for this approach to psychotherapy. Many ideas we now take for granted were introduced into psychiatry by Jaspers in his classic 1913 book, *General Psychopathology*.

Empathy

Take empathy: The word didn't exist before 1908, and Jaspers was the first to make it central to his approach to psychiatry. Before him, it hadn't been thought as important. Jaspers was the first to place empathy prominently in the tasks of the psychiatrist and psychotherapist. And he didn't do this because he was a nice man (which he was). He did it because empathy is central to existential psychotherapy.

The purpose of the existential approach to psychotherapy is not to provide insights to the patient; it's not to apply some kind of theory. The existential theory is that there is no theory: there is just existence. There are two people, two existences, two human beings who are trying to make sense of their existing worlds. Both change, both the clinician and the patient. If one changes, the other does too. The patient gets better, the clinician might get worse. In any case, therapy is not for one person, it's for both. That's the importance of empathy: you feel and experience what the other person feels; that's both the method and the treatment. If you do so, you as the clinician will feel and change too, not just the patient.

"Psychotherapy, Semrad said, means: To Acknowledge, Bear, and Put Perspective on Affect."

Leston Havens has laid out different ways of achieving empathy, from a technical standpoint, in a few excellent books on psychotherapy. He distinguishes a few types of empathy:

1. *Motor* empathy is when you sit as the patient sits; you look where the patient looks; you move as the patient moves.
2. *Sensory* empathy is when you physically feel what the patient feels, like when you wince when another experiences pain.
3. *Cognitive* empathy is when you think what the patient thinks; you can test this by trying to finish the patient's sentences in your head while he speaks. If you get it right, then you are connected with the patient's thinking.
4. *Affective* empathy is when you feel the emotions that a patient feels.

Many people see empathy only from the affective perspective; but in fact, the other features usually are needed for affective empathy to finally occur.

An 8 word definition of existential psychotherapy

In the symposium, the ideas of Havens' teacher and mentor, the Harvard psychoanalyst Elvin Semrad, were discussed. Semrad provided an 8-word definition of existential psychotherapy that is an excellent ideal of the approach. Psychotherapy, Semrad said, means:

To Acknowledge, Bear, and Put Perspective on Affect.

Future psychotherapy articles will expand on this idea. The basic principle is that *empathizing with suffering reduces it*.

Spirituality

Existentialist philosophy has the reputation for being somewhat dreary. Most people hear about it from the plays or novels of Jean-Paul Sartre or Albert Camus, both of whom were influenced by Heidegger. Sartre's play *No Exit* and Camus' novel *The Stranger* paint an existential picture of a world where nothing has any meaning. This nihilistic variety of existentialism is certainly depressing.

In the symposium, we discussed Karl Jaspers' metaphor for life as a shipwreck. Jaspers emphasized all the limits of life, the limits of failures and defeats, and the ultimate "limit-situation" of death. To be an aware existing person, one has to accept these limits.

In doing so, one is faced with nihilism, the feeling of no meaning.

One symposium participant asked: So isn't this existential psychiatry fatalistic?

It can be. Sartre and Camus were atheists; and their perspective can be seen as putting into doubt any real meaning to living. Their mentor Heidegger was famously inscrutable; he collaborated with the Nazi regime.

Jaspers, in contrast, was the most prominent intellectual who opposed Nazism and remained in Germany throughout that era; he was placed in house arrest and forbidden from writing or teaching.

Existential approaches can be fatalistic, but they also can lead to very moral and courageous stands.

Perhaps the best example here is the psychiatrist Viktor Frankl, who wrote one of the most widely read books ever written in psychiatry, *Man's Search*

for Meaning. This work grew out of Frankl's experience as a prisoner in Nazi concentration camps. If ever there was a scenario where life could be seen as meaningless, it would have to be as a Nazi concentration camp prisoner.

Yet even there, Frankl argued that an existential approach would help us find a meaning in life. Read Frankl's book, and see if you are convinced.

It is not us that have to give life a meaning, Frankl said; it is life which gives its meaning to us. It is there if we will but see it. But we won't see it if

we deny the realities of life, which include death, and evil.

Limits are all around us: failure, evil, harm, death. And within those limits, we can find the meanings of life.

Suffering, for instance, has a good aspect, Frankl argued, because it shows we are alive. The worst scenario in the concentration camp, he observed, was not when a prisoner had extreme suffering and despair; it was when a prisoner had become apathetic, had given up, didn't care any more. Those were the persons who killed themselves or died. The suffering ones survived.

Nietzsche made the famous statement that what doesn't kill you makes you stronger. This is what Jaspers had in mind when he taught that it is through failure that you become who you are. This is what Frankl saw tested in the ultimate cruel experiment of the concentration camps: Those

PL Reflection

It's not a symptom; it's an accomplishment.

Viktor Frankl

who suffered survived. Those who no longer felt anything, including pain, perished.

May's view was that you reached joy only after experiencing despair. Jaspers' view was that you had to travel through the "abyss of nihilism" to reach "existential liberation." Both had spiritual leanings and religious backgrounds, though of very liberal bent. They opposed any specific doctrine of faith in a general sense, but Jaspers in particular held that everyone needed to find his own personal spiritual faith, stemming from his own existence, where he happened to be born and live and the cultural and historical background into which he was placed. For one person, the "philosophical faith"

Jaspers described "*Tillich called psychiatry 'the faith of the faithless.'*"
might occur in the
formal context of
Judaism, for another Islam, for a third
Christianity, for a fourth Buddhism, for a fifth
none of the above.

In other words, for Jaspers and May and Frankl, there is a spiritual aspect to the existential approach. Jaspers called it "philosophical faith"; Frankl called it "medical ministry." The contemporary psychologist Thomas Moore calls it "care of the soul." In all cases, there is this awareness of the limits of existence that leads one to a realization of a larger "transcendence" (to use Jaspers' phrase, obviously also central to the thinking of Emerson), a "higher power" (to use William James' phrase, made famous in Alcoholics Anonymous). This higher power can be seen non-theistically; it can be seen as nature. Or it can be seen theistically.

In any case, once one accepts the obvious fact that my existence is not all there is to the universe, that there is something bigger and larger than me, then one has taken a spiritual

orientation to existence. This approach can help avoid fatalism and nihilism.

The mental health professions are secular, of course, and except for avowedly faith-based counseling, there is an attempt to avoid any talk of spirituality or religion in most approaches to psychotherapies. Tillich called psychiatry "the faith of the faithless." Everyone needs a faith of some kind, these thinkers taught, even a faith in unfaith.

DSM and social constructionism

The first days of the symposium were spent in extensive discussion of the problems with the DSM approach to diagnosis.

The main view presented was that DSM takes a nonscientific approach to diagnosis mainly. This is because it emphasizes social, cultural, professional, legal, and economic aspects to defining psychiatric diagnoses. This is not an opinion, but a fact. DSM codes are central to insurance reimbursement in the US; they are used by lawyers in malpractice lawsuits and in the penal system; they influence interest groups for and against certain psychiatric diagnoses. There is much debate in the public about how to change or not change DSM diagnoses. Scientific research is but one fact among many in the process; not infrequently, the scientific evidence is of less importance than all the other social and cultural professional factors in the process. Recent books by historians have documented this social process in DSM-III in 1980, the basic structure of the current DSM-5 system.

This process whereby many non-scientific factors influence diagnosis definitions is called "social construction." Some use the phrase "pragmatism" to identify the same process: DSM decisions are made based on the practical outcomes of defining

diagnoses this way versus that way. The practical outcomes might have relevance to insurance reimbursement, lawsuits, treatment decisions, and such. But whether or not the scientific evidence supports the validity of a diagnosis - separate from all the other social and cultural considerations - is not the primary factor used to define DSM diagnoses.

This is not meant to simply dismiss all DSM definitions. It is meant to be explicit about what is often unnoticed: DSM is not a purely, or even mainly, scientific document.

This is also not to say that one should not pay attention to social and cultural considerations. But it is important to note that the DSM system is primarily a social and cultural construct.

The main disadvantage to this approach is that since the DSM system is a social construction, and it is explicitly meant to be so, it is not primarily set up based on scientific data. It's not helpful for scientific research.

One notion to consider is that scientific research has failed in many important biological ways over the past few decades. New genes, biological markers or causes, and new pharmacological treatments have been scarce since the 1980s. One factor for this paucity of scientific progress may be that the DSM system, based on social construction, does not correlate well with nature. Genes don't care how we get reimbursed by insurance companies. Brain structure won't follow phenotypes designed with courtrooms in mind. The NIMH leadership has reached the same conclusions, and now will not accept DSM definitions for scientific research grants. Instead, the NIMH leaders will only fund studies that

follow their own proposed approach to diagnosis, called Research Domain Criteria (RDoC), discussed further below.

There was some consternation in the symposium about some of these critiques. Many colleagues agreed, but some wondered:

What is a better option?

One participant noted that the NIMH leadership has provided an option, the RDoC. The RDoC are brain-based; they work from the brain outwards; there are five domains: negative valence, positive valence, cognitive, social systems, and arousal. These domains are based on brain structures that subsume those basic big-picture clinical domains.

"The DSM system is a social construction, and it is explicitly meant to be so."

What the NIMH approach doesn't understand is that scientific diagnoses

can be based on scientific clinical research, and DSM never was a mainly scientific clinical research system. In other words, we can identify clinical diagnoses, and validate them based on the standard research validators (symptoms, genetics, course, biological markers - see PL issue 1). In the symposium, the PL editor described mixed depressive states (see PL issue 2) as a scientifically well-validated description of mood states (which would be part of the "negative valence" and "positive valence" states in the RDoC system). The depressive mixed state concept is more

PL Reflection

But existence is believing
we know for whom we mourn
and who is grieving.

scientifically valid than “major depressive disorder” and it is more clinically useful than RDoC’s “negative” or “positive valence” states.

Clinical examples were provided about the harms of monoamine agonists (so-called antidepressants) and the benefits of dopamine blockers in mixed depressive states, as described in prior PL issues.

A new psychiatry

The symposium went into some detail on the Hippocratic approach to psychopharmacology, as described in the PL website. It was emphasized that the common view that this approach entails “First Do No Harm” is false, that Hippocrates never made this statement, and that in fact the Hippocratic school has nothing to do with a general conservatism about treatment, as that

mistaken phrase implies. Instead the Hippocratic approach mainly entails treating diseases, often aggressively, rather

than symptoms. Conservatism about treatment comes into play once diseases have been ruled out and when one is faced with symptoms, in the absence of disease.

There was some concern about whether diseases exist at all in psychiatric conditions. An ongoing discussion followed about the concept of “postmodernism”, and how psychiatry is strongly affected by postmodernist assumptions, including a denial of the disease concept. Briefly, postmodernist thinking, which has increased in influence in the last half century, involves a rejection of traditional views on truth. Both belief in God and belief in science are rejected; all truths are seen as relative to power. Truths aren't true in any real way; they are just the “discourses” of power. This critique was used by the French

philosopher Michel Foucault to argue that there are no psychiatric diseases, and that all disease concepts, especially in psychiatry, are social constructions.

While many of the critics of psychiatry (anti-psychiatry) are fans of Foucault and are in fact postmodernists, it was noted that there is the paradox that the very mainstream of psychiatry itself, the DSM system, is also postmodernist. It is, and accepts being, a social construction, rather than begin a purely scientific search for truth.

Some participants were critical of this critique and remained skeptical about diseases in psychiatry. A discussion was given of neurosyphilis, which is clearly a medical disease, but which was indistinguishable in many of its symptoms from manic and depressive and psychotic episodes. It was claimed that schizophrenia and manic-depressive illness (recurrent

severe unipolar depression and bipolar illness) were both diseases, as are obsessive-compulsive disease and autism. The view was that these are diseases as other medical conditions are diseases, in the standard concept of abnormalities of organs of the body that are internally produced (whether genetically or through environmental interactions with biological susceptibility) and which then produce stereotypic clinical syndromes. This discussion wasn't fully convincing to some participants, although it was convincing to others.

A discussion was also conducted of what we mean by “science” to clarify that the claims made here were not based on simplistic notions of scientific truth (often called “positivism”) but take into account the complexities of the scientific process,

such as the production and rejection of hypotheses, the probabilistic nature of inductive confirmations of hypotheses, and social influences on science (such as the profit motive in the case of the pharmaceutical industry).

The goal of this approach to psychiatry, one that goes beyond simple DSM diagnoses and use of drugs, is a *new psychiatry*, one that puts the 20th century behind, and one that is ready to be scientific but not simplistic. The easy solutions of eclecticism are put aside for the hard decisions of scientific and humanistic thinking. The nihilism of pure social construction is rejected. This includes being willing to be biological when faced with a disease, but being willing to be existential when faced with the limits of living, in the absence of disease. And it means being willing to be humanistic under all conditions.

Becoming a master clinician

What does it mean to be a master clinician? The goal is not to be average. It's to be better than average. DSM is written for the

lowest common denominator of practice. FDA indications and pharmaceutical marketing are aimed at herding clinicians to practice the same way.

There's nothing wrong with standards. There's plenty wrong with standardizing.

The old saying is true: A clinician who treats two patients identically harms both.

To modify a comment by Leston Havens: Be scholar enough to know the rules. Be clinician enough to break them.

So what is a master clinician? In the mental health professions, it means knowing DSM but

"There's nothing wrong with standards. There's plenty wrong with standardizing."

not using it exclusively or even primarily in diagnostic judgments. The master clinician would use a diagnostic hierarchy (see PL website), and not diagnose every symptom as a separate "disorder", and then give a different drug for it. Rather, polysymptomatic conditions, like manic-depressive illness and schizophrenia, would be identified first and treated alone, with the view that most symptoms would resolve when the underlying cause was treated. It means knowing the drugs, but not using them routinely for symptoms. They should be used preferably for underlying diseases causing symptoms, of which only a few are proven so far to exist based on extensive biological research, namely: schizophrenia, manic-depressive illness (which means recurrent unipolar depression plus bipolar illness), obsessive-compulsive disease, and autism. Besides those conditions, medications should be seen as purely symptomatic, and only modestly beneficial, and thus with benefit/harm ratios that

are borderline at best. Short-term use at the lowest doses possible would be the

general approach. In the diseases, on the other hand, even "toxic" medications like lithium would be used very assertively, because the benefits are extensive and outweigh higher potential risks than is seen with some of the symptomatic agents (such as serotonin reuptake inhibitors).

In the majority of clinical situations, where symptoms are present but diseases are not, the master clinician can use existential approaches to psychotherapy to connect with the human being who has come to her as a patient. These approaches may be sufficient sometimes as the only "treatment" needed. Sometimes, they may allow enough connection to identify other problems that can be addressed non-biologically,

such as other specific psychotherapies or even social and cultural interventions (moving one's place of residence; addressing effects of crime and poverty to the extent feasible in a clinical setting).

The Hippocratic ideal was to cure sometimes, to heal often, and to console always. The disease-oriented drug treatment approach cures sometimes (though permanently); the symptom-oriented conservative drug approach heals often (though temporarily); the existential/humanistic approach to the person consoles always.

The PL Bottom Line

- The master clinician doesn't rely on DSM diagnoses, and doesn't prescribe drugs for symptoms.
- The preferred approach is to base diagnoses on clinical research only, and to use drugs most extensively for diseases, such as schizophrenia or manic-depressive illness.

- All other drug use is symptomatic, and should be minimized both in dose and duration.
- Most patients present with symptoms, but not diseases.
- They can be helped with existential psychotherapeutic methods to engage the person inside the patient.
- Existential therapy consists of having no theories about anything. Its main method is empathy
- There is a 8 word definition of existential psychotherapy: To acknowledge, bear, and put perspective on affect.
- Empathizing with suffering reduces it.
- The recognition of our limits can lead to a spiritual perspective about being part of a larger universe.

Sources: Links to relevant articles and an extensive bibliography of books are provided on the web

PL Reflection

Getting acquainted with ourselves is unsettling. There are forbidden thoughts but also commonplace ones. I have often remarked that when the psychotherapist opens us up, he finds what the surgeon finds, all the usual organs. The unique contour of our being only shapes a universal content. It is hard to see ourselves because the individuality we may prize is hardly there.

We are all much more alike than we are different.

Looking in the mirror we see everyone.

*Leston Havens
Coming to Life*

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THE PSYCHIATRY LETTER

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On PTSD

The question of trauma has been central to psychiatric practice for a century. The issue has become culturally important both with the rise of feminism, and attention to childhood sexual abuse, and with continued experience with wars, where military combat trauma remains a major problem.

The special article this month examines the concept of trauma as it has evolved historically and as it has progressed in clinical practice today. Most of the focus is on civilian trauma. Future issues will address trauma specific to military settings.

The importance of distinguishing stressful life events from traumata is emphasized. We examine ways in which PTSD can be identified and distinguished from other conditions. We describe how most traumatic experiences do not lead to later PTSD, which leads to the importance of baseline biological susceptibility and the concept of resilience. The PL emphasis is on avoiding using medications excessively for PTSD, which is common practice.

As usual citations and references can be found on the web version of the newsletter.

The classic study of the month examines a unique test of whether the presence of trauma predicts PTSD. The drug of the month is propranolol, a versatile drug, which has potential uses in PTSD and other important arousal settings, such as akathisia. The case of the month examines a scenario in which stressful life events are misinterpreted as traumata, and where a mood disease is misdiagnosed as PTSD.

Keep reading, and send us your comments.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: When trauma is, and is not, PTSD

Sometimes ignored, sometimes exaggerated

The concept of trauma has been a central feature of psychiatry and psychology ever since a century ago, when a Viennese neurologist concluded that many of his young female patients with hysteria had experienced childhood sexual abuse.

Freud's observation, which he later modified to mean fantasies of childhood sexual experience, opened the gates to a century of attention to experiences of childhood, especially traumatic ones. The concept of trauma soon was extended to adults too, mainly in soldiers. In fact, a major impetus to the rise and acceptance of Freudian thinking had to do with shell shock in World War I. German and Austrian government officials realized that traditional psychiatric methods didn't explain or help those soldiers who had developed intense fear

and depression, whereas psychoanalytic ideas seemed tailor-made for them. During the war period, the German authorities even sponsored one of the first and largest psychoanalytic congresses.

Hysteria, shell shock, war neurosis - it all became mutated in the bureaucratic Orwellian language of DSM-III's radical revision of 1980, to post-traumatic stress disorder (PTSD).

Ever since Freud, the profession has waxed and waned between explaining practically everything, and practically nothing, with variations of PTSD. We still need to come to terms with what trauma means and implies, and what it doesn't.

In the beginning

Let's start in the beginning - with Freud and his observations and theories.

As a neurologist, Freud was well versed in hysteria. This condition involved clear neurological symptoms, like paralysis, without any clear neurological cause. Freud's teacher, Charcot, thought that there were lesions in the spinal cord or brain that would explain hysteria. He never managed to find those lesions, but his teaching impressed the young Freud as to the importance of hysteria. When Freud was visiting France to study with Charcot, he also became exposed to the work of Pierre Janet and Hippolyte Bernheim. Janet saw hysterical symptoms as part of a dissociation process, whereby symptoms becomes separated from the emotions that caused them. In contrast to Charcot, Janet thought that hysterical symptoms had an emotional, not a

physical, cause. Bernheim was part of the Nancy school of hypnosis; his group showed that hysterical

symptoms could be affected by hypnosis. The fact that a psychological treatment, hypnosis, could impact physical symptoms of hysteria argued against Charcot's theory.

Young Freud put all this together: Psychological causes could produce physical symptoms, and they were treatable with psychological interventions.

He went back to Vienna and started hypnotizing his patients with hysteria. Freud wasn't very successful with hypnosis, though, and he invented the free association method. He just let his patients talk. Once his (mostly female) patients began to go in any direction they wished in their talk, they started talking about sexual experiences, often in childhood, often with father-figures.

Thus was born psychoanalysis. In a general sense, Freud came to the conclusion that childhood emotional experiences cause adult psychological symptoms. In a specific sense, Freud concluded that those childhood experiences were sexual in nature. Initially, he believed that those childhood sexual experiences actually happened in real life; eventually, faced with extensive and complex sexual descriptions in the free associations of his patients, Freud concluded that most of those childhood sexual experiences were psychological in nature, not physical. In other words, they were fantasies, not actual events.

We now know that childhood sexual trauma happens in about 10-20% of the general population (less in males, more in females), but the psychoanalytic theory is that childhood sexual fantasies occur in 100% of the general population.

The Kaiser's psychoanalysis

Before World War I began in 1914, Freud was becoming infamous, not famous. He began publishing his theories around the turn of the century; after about 15 years, he was becoming more well-known, but mainly as a crank thinker, a man with the weird idea that children are sexually depraved, and that's why adults are anxious and depressed. He was rejected by the mainstream medical and psychiatric establishment.

World War I ended Freud's isolation. Soldiers suffered "shell shock"; they couldn't function on the front because of emotional problems. Standard medicine and psychiatry, based on biological theories, couldn't explain shell shock in male soldiers, just as it had failed to explain hysteria in women.

Freud had an explanation; it was the same explanation as in hysteria, except the cause wasn't childhood traumatic experience, but adult traumatic experience.

Immediately, the German military brass realized that the new theory could help them win the war. The German government in fact funded the largest psychoanalytic congress up to that point, in 1917 in Berlin. Suddenly, the crank with the sexual theory was the favorite theorist of the German military establishment.

The war ended soon thereafter, but Freud's theories suddenly had become acceptable. His popularity soared in the 1920s and into the 1930s. Then came World War II, and the Americanization of trauma.

Men under stress

The lessons of shell shock in World War I were not lost on the planners of World War II. When the next war occurred, psychoanalysis was ready. It had become

part of the mainstream in psychiatry, especially in the US, not a crank fringe theory. When American generals began to draft soldiers, they hired Harry Stack Sullivan, a leading psychoanalyst in Washington DC, to put draftees through extensive psychoanalytic evaluation. Sullivan's group excluded anyone with any hint of any "perversion", which essentially meant any kind of presumed abnormality of psychological development according to Freudian theory. (For instance, homosexuality was a sexual perversion and thus a reason for exclusion from entry into the military). The result: The rates of military trauma leading to emotional problems were even higher in the highly selected Sullivanian soldiers

in the US military than they had been in World War I.

The generals fired Sullivan, and took all comers. Military traumas declined in frequency. Another American psychiatrist was hired to oversee the military selection and treatment of soldiers - Roy Grinker Sr, a psychoanalyst who had personally trained with Freud. Grinker took a more eclectic approach to his job, and excluded only the most severely psychiatrically ill draftees. He treated soldiers on the front with amyntal interviews, where barbiturates were used to facilitate free associations, producing some reduction in emotional symptoms. After the war, he published the first textbook on military trauma, *Men Under Stress*, which would form the basis for later work on soldiers in the Vietnam War, and thereby was an important source for the development of the concept of Post-Traumatic Stress Disorder (PTSD) in DSM-III in 1980.

The birth of PTSD

When DSM-III radically changed diagnoses in American psychiatry, one of its main goals was to remove directly Freudian or psychoanalytic causes from diagnostic definitions. The term "neurosis" was removed in general for that reason. In contrast, psychoanalytic ideas were reintroduced in psychiatric diagnoses more descriptively with new diagnostic terms that had never existed before, such as borderline personality disorder and PTSD.

The original definition of PTSD included the important description that the traumatic experience must be something that was outside the bounds of usual human experience. This definition was used for two reasons: one was that

military trauma, as in Vietnam, was an important influence on the drafters of DSM-III's definition of PTSD, and military trauma, by definition, is not a routine experience that happens to the general population; it is a unique experience that happens to some soldiers during periods of war. Another factor was the (mistaken) belief that childhood sexual trauma was uncommon.

In the years that followed DSM-III, the concept of PTSD evolved during a period of relative peace with no active wars from the end of Vietnam in 1975 until the start of Middle Eastern wars after 2001. Instead of its military application, PTSD was applied mostly to domestic trauma, usually sexual in nature and typically related to childhood. At the same time, PTSD work had become central to feminist-inspired theories in psychiatry.

Research from these sources led to the observation that childhood sexual trauma, and indeed adult sexual trauma, was much more common than previously appreciated. It was reported to occur in about 10-20% of the population at least, and probably more if one takes into account biases in memory, or reporting, of such events.

As a result, by DSM-IV in 1994, a strong movement existed to remove the descriptor limiting trauma to unusual human experiences.

This apparently small change had huge effects.

Life event or trauma?

The matter has not changed with DSM-5. Now trauma is defined as any terrible event that causes PTSD symptoms. This tautological definition has led to a common conflation of life events with trauma.

The concept of trauma, as originally derived from the experience with hysteria and shell shock, didn't apply to any human experience. It applied to very troubling human experiences, such as rape and murder.

But trauma as defined by DSM-IV and DSM-5 opened the door to a much broader interpretation by adding the phrase "serious injury", so that the definition reads: "...exposure to threatened death, serious injury, or sexual violence..."

Studies on PTSD using current definitions report that the most common traumata are car accidents. Clinicians have been using a very wide definition, applying the PTSD concept to even common adverse events such as losing a job, or getting a job, or getting divorced, or getting married, or the death of a pet, or the birth of a child.

Another way of seeing the matter is that what has been termed "life events" are now seen as traumata. Life events is a more neutral descriptor for the experiences described above. It has been shown in extensive research that clinical depressive episodes are preceded by life events in the prior 6-12 months in the vast majority of cases. As noted, such life events are not unusual experiences, but rather the typical stresses of life. Those who prefer to take a social or psychological orientation to psychiatry see those life events as "causes" of the depression that follows. A similar perspective is seen with proponents of PTSD: the traumata are "causes" of PTSD.

The problem is that everyone experiences those life events; but 90% of the population never develops clinical depression.

Similarly with PTSD, about 80-90% of persons exposed to severe trauma do *not* develop PTSD.

This means that the underlying biological susceptibility of the individual to depressive episodes or to PTSD is the deciding factor, not the occurrence of life events or trauma.

So the concept of trauma has been expanded in clinical practice to include many life events. By so doing, the importance of the "trauma" recedes, and one is faced instead with the question why most people who experience "trauma" never develop PTSD.

Resilience

This evolution has led to a shift in the PTSD literature from a sole focus on risk factors to protective factors.

The transition is not solely because of the immense broadening of the concept of trauma to include almost all life events. Even in studies of sexual trauma for instance, or major unusual experiences such as the 9/11 attacks in New York,

researchers find that about 80-90% of persons exposed to such severe trauma do *not* develop long-term PTSD.

What are the protective factors that keep such persons mentally healthy?

The basic term used to explain such protection from PTSD is "resilience," a phrase that has become part of popular culture now.

A scientific approach to the concept of resilience would focus on personality, or temperament, as the baseline susceptibility of a person to PTSD, which would then interact with traumata, or life

events. Some people are more susceptible, and some less so, to PTSD, given the same traumatic experience. This baseline susceptibility often is seen as being related to personality traits.

Research on this topic suggests, to summarize it briefly, that depressive-type personality traits predispose to PTSD: if one is nervous or anxious or sad (e.g., has the mood temperament of dysthymia or the illness of recurrent unipolar depression), one is more likely to develop PTSD. In contrast manic-like personality traits appear to protect against PTSD: if one is high-energy, sociable, has lots of friends, is future-oriented, is humorous, and is other-oriented - then one is less likely to develop PTSD. The psychological literature tends to examine these "positive" traits one by one, and it has been seen as part of a general approach to emphasizing strengths and positive aspects of one's personality. (Hence the "positive psychology" movement). These traits can also be seen in the clinical tradition as part of the manic side of mood

symptoms, which can be positive and beneficial. Hence these protective personality traits can be seen in the mood temperaments of hyperthymia (constant mild manic symptoms) or cyclothymia, or even in frank bipolar illness. In one study, for instance, compared to non-bipolar control groups, persons with bipolar illness were less prone to PTSD after the 9/11 attacks in New York.

Resilience is not a thing, but a descriptor for features of personality and/or mood that protect against responding to life events or traumata in an anxious or depressive manner.

Assessing PTSD today

One of the biggest mistakes in clinical practice, in the PL view, is to mistake life events for trauma, and then to mistake trauma for PTSD, and then to diagnose PTSD when it doesn't exist. Trauma, even if present, doesn't usually lead to PTSD.

Let's review the clinical relevance of these two basic concepts.

If a person has an apparently harsh life event, this by itself doesn't qualify to presume that person has PTSD. Instead, one should look at the other three diagnostic validators (besides symptoms), as described in the first PL issue: course of illness, genetics, biological markers/treatment response. Does the person have family genetics of manic-depressive illness or severe depressive disease? If so, current depressive symptoms likely stem from the same biological cause, not from PTSD. Does the person have past repeated depressive episodes with many different life stressors? Then the current depression likely is another manifestation of the underlying depressive disease, with the life events being "triggers", not traumatic causes, of the underlying depressive disease.

If someone has no prior depressive episode and no family genetics of severe mood disease and then has a sudden extreme traumatic experience, such as military combat or sexual trauma, then new depressive and anxiety symptoms likely do represent PTSD. Similarly, if someone has childhood sexual or extreme physical abuse, and no family genetics for mood disease, then lifelong anxiety and depressive symptoms likely are related to PTSD.

Classic PTSD symptoms are dissociative - flashbacks and nightmares - and these do not happen by themselves in non-PTSD conditions like manic-depressive illness. The presence of

severe dissociative symptoms by themselves would increase the likelihood of PTSD. However, it should be noted that dissociative experiences of a milder nature, like depersonalization, can happen with panic attacks and marked anxiety; and such anxiety can be caused by depressive or even manic episodes; thus even in the presence of dissociative symptoms, one should rule out severe mood episodes and pay attention to other clues for a non-PTSD diagnosis such as psychiatric genetics and the course of illness.

How do you treat?

If PTSD is correctly diagnosed, what should you do? There is extensive research now with many medications in randomized trials, and the general results are that most medications in PTSD are modestly effective at best. Their effects are symptomatic only, which means they don't get at the cause, and they only superficially help the painful symptoms. This is better than nothing, but one shouldn't have an inflated expectation of the effects of medications in PTSD: they are symptomatic, temporary and modest.

The real treatment, as Freud discovered, is psychotherapy. There may be different ways to conceive how to conduct this psychotherapy; the Freudian approach is insight-oriented, but other approaches may also help. The supportive and empathic aspects of psychotherapy are also important. Benefits are not rapid, and require long-term treatment, as Freud emphasized. In some persons, improvement is only modest, but in others, major benefits can occur.

Clinicians should be careful not to overuse medications in PTSD, since benefits are minimal

"Clinicians should be careful not to overuse medications in PTSD, since benefits are minimal..."

and side effects correspondingly will outweigh the modest benefits. Drug effects if present are only short-term in any case. Long-term improvement, and more than minimal benefit, will be obtained by psychotherapy mainly. Clinicians should put the emphasis there rather than on medications.

In doing so, clinicians should be careful to avoid overdiagnosis of PTSD by mistaking all life events with trauma, and they should pay close attention to genetics and course of illness to make sure that they are not missing manic-depressive illness or other psychiatric conditions. In the case of manic-depressive illness, in particular, the distinction is especially important because the treatments are opposite: medications are central and psychotherapies are less effective in manic-depressive illness, whereas medications are peripheral and psychotherapies are central to treatment of PTSD.

The PL Bottom Line

- A major problem today is that many stressful life events are seen as trauma.
- If most life events are viewed as causal traumata, PTSD will be overdiagnosed.
- Almost 90% of people who experience trauma do not develop PTSD.
- The underlying biological susceptibility of a person is the deciding factor, not trauma.
- Resilience, often related to manic symptoms, reflects low underlying susceptibility
- Medications should be used conservatively if at all; they are effective modestly at best.
- Psychotherapies should be the main emphasis in treatment of PTSD.

Classic study of the month: *Where's the link between trauma and PTSD?*

Is PTSD caused by traumatic stress? J. A. Bodkin et al, Journal of Anxiety Disorders, 2007, Volume 21, Pages 176-182

The same amount of apparent PTSD occurs whether or not trauma is present

This short study raises the important question of how central trauma really is to the presence of apparent PTSD symptoms. Specifically, the study suggests that the reaction to trauma is more important than the occurrence of the trauma itself. Further, in persons without trauma, anxiety and depressive symptoms that approximate PTSD can occur as part of clinical depression unrelated to PTSD.

In this study, 103 patients, who had come to a psychiatric clinic for treatment of diagnosed major depressive disorder (MDD), were examined. They presented for treatment with antidepressants in clinical trials for severe depression. The clinical researchers then examined these patients in two ways. First researchers assessed whether the subjects met DSM-IV criteria for PTSD.

Then two different blinded researchers assessed whether the subjects met the DSM-IV criterion A for presence of a severe trauma.

54 subjects were judged by both raters to have experienced severe trauma. Of this group 78% (n=42) met full criteria for PTSD.

36 subjects were judged by both raters as *not* having experienced severe trauma. Of this group, 78% (n=28) met full criteria for PTSD.

In other words, exactly the same percentage of patients (78%) met full criteria for PTSD whether

or not a severe trauma, using the broad PTSD definition of trauma, was present.

Interpretation

The PTSD criterion A for trauma is as follows:

“(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others (2) the person's response involved intense fear, helplessness, or horror.”

This kind of stressful life experience does not lead to PTSD in many persons, as described in the special article. That is why it was present in many persons in this study who did not have PTSD.

Further, except for specific dissociative experiences like flashbacks, many remaining PTSD symptoms often reflect a state of arousal and anxiety that are present in clinical depressive episodes in persons who do not have PTSD. This is why PTSD symptoms were present in those who were judged not to have experienced severe trauma.

The PL Bottom Line

- The apparent presence of trauma doesn't mean someone has PTSD.
- The presence of PTSD-like arousal and anxiety doesn't mean someone has PTSD.

PL Reflection

You're only given a little spark of madness; you mustn't lose it.

Robin Williams

Drug of the Month: *Propranolol*

A most versatile drug

Propranolol is the first of the beta-blocker class of medications used mainly for hypertension. It has many potential psychotropic uses as well, including for PTSD.

Clinical efficacy and inefficacy

Focusing on psychotropic uses, some studies have found that if beta-blockers are given in the emergency room setting soon after an acute trauma, later PTSD symptoms may be lessened.

If given later, beta-blockers can reduce anxiety and physiological symptoms of PTSD. Most beta-blockers affect the peripheral nervous system, reducing the sympathetic drive, thereby decreasing arousal and anxiety. Propranolol also enters the central nervous system, and thus can reduce anxiety directly through effects on the brain.

A specific kind of severe anxiety for which propranolol appears to be helpful is akathisia, marked psychomotor restlessness that occurs as a side effect of dopamine blocking medications.

This agent also helps tremor, such as can be induced by lithium or valproate.

In older persons, especially those with medical illnesses, beta-blockers have some risk of causing depression.

Biological mechanism

Propranolol causes central and peripheral blockade of Beta-receptors on noradrenergic neurons.

Side effects and dosing

PL strongly recommends using the generic slow release version of this agent, propranolol ER, since the standard generic agent has a very short half-life of only 1-4 hours and thus needs to be dosed multiple times daily, which is not practical for most persons. Further, the ER formulation can be given at night, so that sedating effects help sleep and do not cause problems in the daytime.

Fast Facts: Propranolol ER

Typical dose: 60-120 mg/d.

Biological mechanism: centrally acting Beta-blocker

Typical side effects: sedation

Less common but important side effects: fainting

Medically important side effects: Bradycardia

Clinically proven efficacy: Treatment of akathisia, anxiety, PTSD, tremor, migraine, antihypertensive

Other side effects besides sedation are potential fainting or dizziness from excessive blood pressure reduction or from bradycardia.

This agent reduces the heart rate, so bradycardia is the

main concern. Resting pulse should be assessed before using this medication and it should not be prescribed if baseline pulse is 60 beats/minute or lower.

Dosing should start at 60 mg at night, then increased to 80 mg at night, and further increased if needed as long as the pulse stays around or above 60 beats per minute.

Attention should be paid to some risk of masking diabetic ketoacidosis symptoms and/or worsening of obstructive pulmonary disease. Hence in diabetes and obstructive lung disease, these agents should be avoided or used with caution.

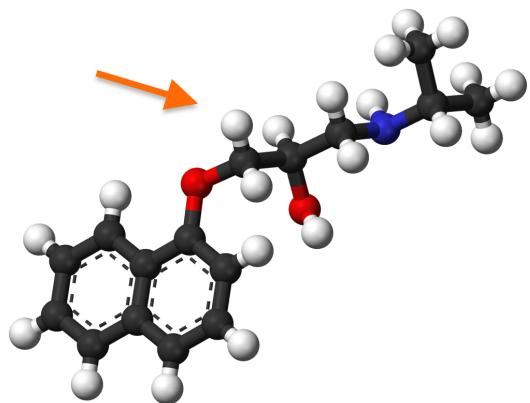


Fig 1. Beta-blockers contain at least one aromatic ring and an ethanamine (arrow). However, contrasting more polar counterparts (e.g. atenolol), propranolol structure contains an additional ring, typically increasing lipophilicity (K_{ow}) and blood-brain-barrier permeability. The brain/plasma concentration ratio reaches 26 for propranolol but only 0.2 for atenolol. Other lipophilic beta-blockers include metoprolol and oxprenolol. However their beta-1-selectivity or intrinsic sympathomimetic activity, respectively, limits the psychotropic clinical use.

The PL Bottom Line

- Propranolol ER is a versatile medication, which can be helpful for anxiety.
- Its use in akathisia is important to allow for effective use of dopamine blockers.

Case of the month:

Life events, not trauma

A 25-year-old female is diagnosed with anxiety, depression, and PTSD. As a child, she was raised in a supportive family with no known sexual or physical abuse. When she went to school, though, she experienced bullying and had conflicts with some female peers. In college, she felt out of place and had a clinical depressive episode at age 18. She met a young man whom she married and who has been very supportive. In the last few years, she has experienced continued anxiety and

depression, although no definable flashbacks and nightmares. Her most recent period of worsening of symptoms relates to the passing of an aunt, to whom she was very close. Also, her husband recently lost his job, which caused her to be worried about their finances. Their family is helping to support them.

Her family genetics involve severe depression in multiple family members going back a few generations, including one person who received ECT and was put into a state hospital for decades.

Staying with course of her illness, she has definable clinical depressive episodes since age 18, usually lasting about 2-3 months. In between those episodes she always was mildly depressed in mood, but didn't meet full clinical depressive episode definitions. She had not cut herself or made any suicide attempts. She had no dissociative experiences.

Her clinician saw her as having "complex PTSD" with these multiple life stressors causing her anxiety and depressive symptoms. Multiple SRIs and amphetamines and benzodiazepines produced limited benefit. Her current medications were citalopram 20 mg/d and Adderall.

The PL diagnosis and clinical impression

The PL diagnosis is recurrent unipolar depressive illness (also known as manic-depressive illness, see PL June 2015 issue). The family genetics of severe mood disease reflects the original concept of manic-depressive illness. Recurrent severe depressive episodes beginning early in life, around age 18, and being short in duration (2-3 months) reflects the course of illness of what is now called bipolar illness (a variety of manic-depressive disease). Baseline mood symptoms seem to represent dysthymia, a mood temperament that occurs in persons or families with manic-depression. She has no specific features of PTSD

as classically described, i.e., no identifiable trauma and no dissociative symptoms.

Even if she had PTSD, she was not receiving adequate psychotherapy for it, but rather extensive medication treatment, which is not very effective for that condition.

The PL recommendation was to taper off citalopram and Adderall and to replace them with whatever mood-stabilizing agent she could tolerate or was willing to take. She was willing to take lamotrigine, and a fluoxetine cross-titration was instituted to help with SRI withdrawal (since she had been on those agents for years). Since she had no drug allergies, lamotrigine was deemed acceptably safe if dosed very slowly (25 mg every 2 weeks). Over 3-6 months, her mood improved more than it had improved in the past.

The PL Bottom Line

- This case provides an example of the misinterpretation of life events as traumata.
- Genetics and course of illness provide the definitive diagnostic evidence.

PL Reflection

What will you have: Wise madness or foolish sanity?

Don Quixote

Curbside consults:

Questions and cases from you

Question: In the July 2015 issue, summarizing the Cape Cod symposium, PL argued that there is a need for:

“...being willing to be biological when faced with a disease, but being willing to be existential when faced with the limits of living.”

This idea helped me to appreciate that understanding "the limits of living" from that existential view is essential to understanding how ascribing suffering to the limits of living is not dismissing them; it is not a failure of empathy.

I focus on interacting with colleagues in primary care. The quote above nails the central dilemma. Far more than 50% of consults which I receive as a psychiatrist revolve around a single question: "How bipolar is she?" Or, put another way: "In addition to trauma, does she also have some bipolarity?" Or, in your language: Are these just "the limits of living" (albeit harsh limits, which so many patients experience), or is there also some biological component?

In residents' shorthand, PTSD yes; but is there also something else, or is it just PTSD?

PL: These are exactly the right questions to ask. The PL perspective is that PTSD is overdiagnosed for two reasons: we misinterpret stressful life events with the concept of trauma, and the anxiety and arousal symptoms of apparent PTSD happen in clinical depression (and hence are part of manic-depressive disease, rather than PTSD). So a further question might be:

Are we really certain the patient has PTSD to begin with? Or could it just be bipolar illness? Or could it be neither?

The concept of the “limits of living” raises the important option that a person might have many stressful life experiences, and even have anxiety and depressive symptoms associated with those life experiences, and yet not have PTSD or any variety of a mood disease. In other words, the PL approach is to avoid labeling each of those symptoms as a “disorder” (e.g., PTSD or MDD), and ask the question: does the overall clinical picture meet the concept of PTSD or manic-depressive disease? Those concepts are not only about symptoms, but about a course of illness and family genetics and (sometimes) treatment effects.

Often, neither clinical picture really fits, and this is where PL thinks clinicians need to get more comfortable with the notion of “none of the above,” and think about seeing patients’ problems as just that: life problems. Like PTSD, the main recommendation would then be psychotherapies, although specific existential approaches might be most helpful in such circumstances of life problems in the absence of definable disease. In either case, extensive medication use targeted to symptoms, which is common practice today,

would be opposed to the PL approach. By using less medications, we also would send an important psychological message to patients that it is important to focus on psychotherapies as the central treatment for PTSD.

PL Reflection

The experience of being disastrously wrong is salutary; no economist should be denied it, and not many are. The best, most elegant and most applauded designs can fail, and greatly to your surprise if, in persuading others of their excellence, you have persuaded yourself.

John Kenneth Galbraith

Clinical Tip of the Month

A strict approach to PTSD would be to limit the diagnosis to someone who has experienced sexual trauma in childhood or adulthood, or severe physical trauma in childhood, or military combat trauma in adulthood. All other cases of painful life experiences would not be considered part of the PTSD syndrome, but rather psychosocial stressors that could trigger mood episodes or symptoms in persons with underlying biological susceptibility to mood conditions, such as manic-depressive illness or neurotic depression.

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THE PSYCHIATRY LETTER

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Schizoaffective illness

This issue addresses some common clinical problems: schizoaffective illness, substance abuse, and premenstrual symptoms.

The special article examines the concept of schizoaffective illness and describes how it is not a separate disease. Three important subtypes are described: namely schizoaffective illness as a mild version of schizophrenia, or a severe version of bipolar illness, or the chance comorbidity of schizophrenia and manic-depressive illness.

The study of the month examines the first unique documentation, in a re-analysis of a randomized clinical trial of paroxetine for childhood depression, of exactly how the pharmaceutical industry “spins” interpretations of data. The recent paper received some media attention, deservedly, and we review some of its details.

The drug of the month is gabapentin, which has many uses but is misused when it is wrongly believed to be a “mood stabilizer.”

The case of the month examines a case of premenstrual symptoms which aren't simply the same thing with the word “disorder” after it. A more nuanced clinical analysis is offered and the concept of a diagnostic hierarchy is applied to identify the illness which caused premenstrual symptoms in the case.

As usual complete citations and references can be found on the web version of the newsletter.

Keep reading, and send us your comments.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: Schizoaffective illness

Real, but not a separate disease

If you work in an inpatient setting or an outpatient setting with severe mental illnesses, it's likely that a common diagnosis you see is schizoaffective illness (SI). What does this diagnosis mean? What does it imply terms of treatment? Is it a real thing? These are all questions that are important for clinical practice. In this special article, PL examines how to understand schizoaffective illness, and important clinical pitfalls.

Five models

Our understanding of SI can be organized in five different theories. One approach holds that SI is its own illness, separate from others, as appears to be the case superficially by its separate diagnostic criteria in DSM-5. A second model holds that SI represents a middle clinical picture on a psychotic continuum that extends from bipolar disorder to schizophrenia; in other words, this model rejects the Kraepelinian dichotomy of bipolar disorder and schizophrenia. A third model argues that SI represents the comorbidity of affective disorders and schizophrenia, thereby maintaining the Kraepelinian dichotomy and explaining overlap symptoms as chance co-occurrence. A fourth theory views SI as a variant of bipolar illness, and a fifth as a variant of schizophrenia.

Origins

For most clinicians, the term "schizoaffective" simply applies to

individuals with continuous psychotic and mood symptoms. Unlike mood conditions, psychotic symptoms aren't brief. And unlike schizophrenia, mood symptoms aren't absent. Clinically, many patients seem to fall into this overlap region. In fact, the original paper describing the occurrence of such patients with such overlap was published in 1933. Indeed, Kraepelin himself observed that a good number of patients had such overlap of manic-depressive and dementia praecox symptoms. Hence, the fact that such overlap occurs is almost universally accepted, even by Kraepelin, who originated the idea that mood and psychotic conditions differ.

"By itself, the presence of overlap doesn't invalidate the diagnoses of schizophrenia and manic-depressive illness."

By itself, the presence of overlap doesn't invalidate the diagnoses of schizophrenia and manic-depressive illness. This is partly because phenomenology is only one of four diagnostic validators (along with course, genetics, and treatment effects). This is also partly because a difference in symptoms is not an all-or-nothing phenomenon. In other words, to say that schizophrenia and manic-depressive illness differ in symptoms isn't to say that they never overlap. It only means that they usually don't overlap. And indeed, excellent epidemiological studies have shown that patients with mood and psychotic symptoms tend to differentiate into two big groups, one with mainly mood symptoms and one with mainly

psychotic symptoms, although there is some overlap.

It is sometimes argued that the mere existence of SI is a counterexample to the Kraepelinian dichotomy of schizophrenia and manic-depressive illness. As should be clear from the above considerations, this isn't the case. Some overlap is expected; and symptoms are only one aspect of diagnostic validation. To refute the Kraepelinian diagnostic schema, one would also need to look at genetic, course, and treatment response.

Genetics

SI isn't found mainly in families of persons with SI. Rather, various studies suggest a unique pattern. In some studies of families of persons with bipolar illness, there is an increased prevalence of schizoaffective illness, bipolar type. In some studies of families of persons with schizophrenia, there is an increased prevalence of schizoaffective illness, depressed type. And in a number of studies comparing both major groups, SI is more prevalent in families of persons with schizophrenia or bipolar illness than in control populations or than in families of persons with SI.

These results are consistent with three possibilities. In some persons, schizoaffective illness, bipolar type appears to be a more severe variant of bipolar illness. In others, schizoaffective illness, depressed type appears to be a less severe variant of schizophrenia. In still others, seems to run in both families of

"Schizoaffective illness may simply represent the comorbidity of having, by chance, schizophrenia and manic-depressive illness at the same time."

persons with both schizophrenia and manic-depressive illness. In this last group, two explanations seem possible:

- (1) It may be a counterexample to the Kraepelinian dichotomy between mood illness and schizophrenia: they should all be seen as one continuum.
- (2) Schizoaffective illness may simply represent the comorbidity of having, by chance, schizophrenia and manic-depressive illness at the same time, just as one might have diabetes and asthma at the same time.

Course

SI appears to have an intermediate course between bipolar illness and schizophrenia. It's more severe than the former, less so than the latter. These outcomes would be consistent with both subtypes of being a mild version of schizophrenia or a severe version of bipolar illness. These course data could also support the continuum view. However, there's not a completely unique course to this illness, different than both schizophrenia or bipolar illness, and thus course data aren't consistent with the concept that schizoaffective illness is a uniquely separate disease.

Treatment Response

This is the least specific diagnostic validator. There are few studies of treatment of SI, but it is generally thought that these patients require long-term treatment with antipsychotic agents, as in schizophrenia, and long-term treatment

with either mood stabilizers (bipolar type) or antidepressants (unipolar depressed type) as in the corresponding affective disorders. Again, this treatment response pattern is consistent with all four models except the separate illness model.

The Judgment

What are we to conclude? What appears most clear is that, its appearance in DSM-III-5 notwithstanding, schizoaffective illness does NOT represent a separate illness distinct from schizophrenia and manic-depressive illness. Studies of symptomatology vary, but excellent studies tend to find a difference in symptoms in psychotic and affective populations that more or less falls along the lines of Kraepelin's dichotomy. While there are overlap areas, such overlap is empirically expected in a biological distribution of any group.

"Schizoaffective illness does NOT represent a separate illness distinct from schizophrenia and manic-depressive illness."

Prevalence of SI is low (contrary to clinical experience)

If SI represents a comorbidity of schizophrenia and manic-depressive illness, one would expect an epidemiological prevalence that is significantly lower than the other two. In other words, SI should be infrequent, since comorbidity shouldn't be overly frequent by chance. Despite clinical impressions otherwise, epidemiological prevalence studies demonstrate that SI is diagnosable infrequently in the general community, in less than 0.5% of the population, much lower than accepted

prevalence rates for schizophrenia (1%) or bipolar disease (2-4%).

Three types of schizoaffective illness

Now we have a way of thinking about schizoaffective illness that allows us to identify these three basic types of patients, and then to target treatments differentially.

1. Patients who have mainly mood symptoms, usually of the bipolar type, with some added psychosis: The main focus should be to make sure that these patients receive mood stabilizers. The most common clinical pitfall is to provide antipsychotics without mood stabilizers, which leads to insufficient response.
2. Patients who have mainly psychotic symptoms of schizophrenia, with some added depressive episodes: There is a better outcome than with traditional schizophrenia, and antipsychotics can be expected to be more effective. Additional antidepressants (monoamine agonist) use may help.
3. Patients who have truly equal a psychotic and affective symptoms: PL recommend seeing those patients as having a chance comorbidity of schizophrenia and manic-depressive illness. In those cases, adequate and aggressive treatment with both mood stabilizer and antipsychotic is equally important.

The PL Bottom Line

- Schizoaffective illness is not a legitimate separate disease.
- There are three subtypes, two of which represent subtypes of other diseases: a) a severe variant of bipolar illness, b) a mild variant of schizophrenia

- The third subtype of schizoaffective illness can be understood as the chance comorbidity of schizophrenia and manic-depressive illness happening at the same time.
- Treatment of the first two subtypes should emphasize the main underlying disease.

Three varieties of schizoaffective illness

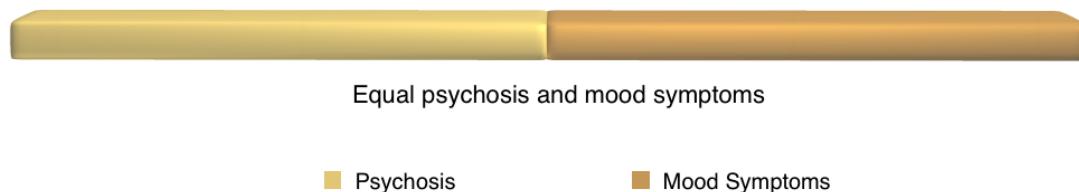
1. Schizoaffective illness, bipolar type: A severe variant of bipolar illness



2. Schizoaffective illness, depressed type: A milder variant of schizophrenia



3. Schizoaffective illness: Comorbidity of schizophrenia and manic-depressive illness



Clinical Tip of the Month

Whenever you see a case of schizoaffective illness, divide it into three types: 1) A severe variant of bipolar illness, in which case mood stabilizers are essential; 2) A mild variant of schizophrenia, in which case antipsychotics are the main treatment; 3) The chance comorbidity of both conditions, in which case both types of medications usually are needed.

Selected references

KS Kendler et al, The Roscommon family study, *Arch Gen Psych*, 1993, 50:645-52. KS Kendler et al, The structure of psychosis, *Arch Gen Psych*, 1998, 55:492-9. MT Tsuang, JC

PL Reflection

Nearly all men can stand adversity. But if you want to test a man's character, give him power.

Current study of the month: *Paroxetine in depression - A reanalysis 14 years later finds the truth wasn't told*

Restoring Study 329: Efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence.
J. Le Noury et al, British Medical Journal, 2015, Volume 351, h4320

Documentation of how companies “spin” randomized trials

This is a disturbing study that isn't surprising. It took over 100,000 hours of work to get access to the actual data from a research study from 2001, conducted by Smith Kline Beecham (SKB) on paroxetine for major depressive disorder (MDD) in children. That published study reported benefit. Over a decade later, a reanalysis with the same data reports no benefit.

The difference partly is about what we mean by “benefit.” There was about a two point improvement with paroxetine over placebo. This is a small “benefit”, but the original paper made a big deal about it because it was “statistically significant.” This is a mistake because a benefit that is very small is still very small, even if it's real. Yet it wasn't even statistically significant, we now know, after 100,000 hours of digging: The original statistical analyses that were planned before the study began showed that it wasn't statistically significant. Yet the authors of the first paper went on to use other statistical comparisons that found statistical significance in some weeks of the study, and they emphasized those outcomes. They also emphasized four outcomes that were statistically significant even though they weren't part of the original study plan. Called “post-hoc”, those outcomes could have occurred by chance at a higher likelihood than the study ever acknowledged.

In other words, in the original paper, the authors worked hard to show positive results with their

statistics in the interests of the study drug. This makes sense when you realize that its manufacturer, SKB, was seeking FDA indication which would translate into billions of dollars of profit. The original study was ghostwritten by a company hired by SKB, not by the academic “authors”, who only revised it.

“SRI withdrawal produced more suicidality..”

Further, the original paper reported low rates of worsened suicidality (increased ideation or attempts or self-harm), and dismissed those results because they weren't “statistically significant”, which again is wrong since the study wasn't designed to assess those outcomes, and thus was “underpowered” (didn't have enough subjects) to test for statistical significance (which means the effect of chance on a result that is sufficiently powered to assess that outcome). The reanalysis re-examined the actual patient charts in part of the sample and found that there were twice as many cases of worsened suicidality than originally reported (11/93, 11.8%, vs 5/93, 5.4%) and this was much more than placebo (2/93, 2.2%).

Part of the reason for more cases of suicidality in the reanalysis has to do with patients who became more suicidal when they were in paroxetine withdrawal, i.e., as they were switched from paroxetine to placebo. The original study didn't count these patients as having effects related to paroxetine. This is important, though, because we know that SRI withdrawal is a major clinical problem, that patients often do and sometimes

should stop their SRIs, and agents like paroxetine produce withdrawal-related marked agitation, anxiety, impulsivity, and now we can add, even suicidality. In other words, SRI withdrawal produced more suicidality.

PL has conducted a further analysis, using the same data above but not presented in the current BMJ analysis. Converting those raw numbers to relative risks, we find the following: The relative risk (RR) of worsened suicidality with paroxetine versus placebo in the new re-analysis is 5.50 (95% confidence intervals 1.25, 24.1). This compares to RR using the original 1994 publication of 5.00 (95% confidence intervals 0.59, 42.0).

You'll notice that the basic effect of PL's examination of this new BMJ reanalysis is the same as in the original 2001 paper. There was a relative risk of about 5 in both analyses, meaning about a 5-fold increased risk of suicidality with paroxetine over placebo. But, in the 2001 paper, SKB and its authors dismissed the results because it was "statistically nonsignificant," meaning that it could have occurred by chance more than 5% of the time. As mentioned, this isn't legitimate statistically since the study wasn't designed to assess suicidality, thus one could have results that don't meet statistical significance in those equations because there aren't enough people in the study to assess an infrequent outcome (i.e., suicidality in 5-10% of the sample).

With the new BMJ reanalysis where the number of suicidal outcomes is doubled in the paroxetine group (and doubled in the placebo group), we have the same relative risk of 5-fold increase, but now the increase in frequency of outcomes produces confidence intervals that do not include the null value of one. What this means is that the results are statistically significant with the new analysis, if we care about statistical significance.

In other words, the strategy of the original paper to ignore these results now isn't tenable.

The clinical bottom line is the same as the FDA black box warning: SRIs can worsen suicidality in some children. The scientific bottom line is the same as we knew, but this analysis proves with the same database as previously published by SKB: Pharmaceutical industry clinical trials are ghostwritten in such a way that they overstate drug benefits and minimize drug harms. There needs to be independent scientific analysis of those data before we can understand them fully.

The PL Bottom Line

- The original paroxetine study misrepresented a small clinical benefit as more important than it was, by emphasizing statistical significance in ways that weren't legitimate.
- The original study didn't report the full extent of suicidal side effects, downplaying this harm by relying on statistical non-significance when it shouldn't have.
- SRI withdrawal can cause suicidality.
- You can lie with statistics. You can tell the truth with statistics.
- Clinicians shouldn't rely on ghost-authored studies by the pharmaceutical industry in which databases are never accessible publicly for verification by independent researchers.

PL Reflection

How can you tell the difference between hypomania and normal happiness? Hypomania is recurrent. Happiness is not.

Drug of the Month: *Gabapentin*

Many uses, but NOT a “mood stabilizer”

Gabapentin is a medication that has many uses, especially for anxiety and insomnia, but it is frequently misused as if it was a mood stabilizer that could be used by itself in bipolar illness. It's important to know when to use it and also to realize that it shouldn't be used primarily as a mood stabilizer.

Clinical efficacy and inefficacy

Gabapentin was first FDA indicated for epilepsy. Very quickly it began to be used for many non-indicated purposes.

Some of this use outside of epilepsy was based on a certain amount of clinical wisdom, with the observation that gabapentin was effective for anxiety and pain. These anxiety and pain symptoms often

occurred in the context of depression, however, and this led to the misinterpretation by many clinicians that this medication might be effective for mood illnesses per se. The PL editor was one of those who published clinical experience suggesting possible benefits of mood conditions. The company which marketed this medication in the 1990s then began to market those uses to clinicians, which is outside of federal regulations. This led to a backlash from the FDA and those who are critical of the pharmaceutical industry.

In the last decade, the opposite scenario evolved. Critics began to claim that gabapentin was useless for anything except epilepsy. The truth is somewhere in between.

Gabapentin is experiencing something of a renaissance. It's being used for anxiety, insomnia, menopausal symptoms, chronic pain syndrome, and once again mood and bipolar illness.

It's the PL view that all of these uses are potentially valid, but it's very important *not* to use this medication as a primary mood stabilizer in bipolar illness. It was studied about a decade ago in multiple studies of acute mania, and it was proven to be equivalent to placebo. It has never been proven to be effective for bipolar depression

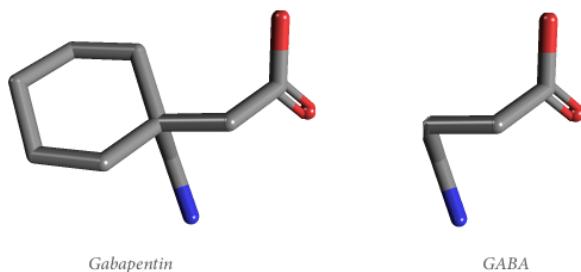
or in prophylaxis of mood episodes. Therefore it is inappropriate to use this medication as if it was similar to lithium or valproate or lamotrigine. This is a mistake:

It is not effective for bipolar illness.

Nevertheless it is useful for anxiety, whether symptomatically or as part of a larger anxiety illness. It's sedating and probably helpful for insomnia in some persons, although it has not been carefully studied in that condition. It's very well proven for pain syndromes and also beneficial for persons with substance abuse who may have anxiety-related self-medication.

Biological mechanism

Gabapentin stimulates a receptor subunit of GABA, which likely produces its anxiety benefits. It is not definitively known if this mechanism is the reason for its other benefits such as anticonvulsant effects.



Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) and GABA (4-aminobutanoic acid) structures. Gabapentin contains an additional 5-carbon closed chain, forming a non-aromatic ring. Despite similarity, gabapentin agonism relates only to specific types of GABAB receptors.

Side effects and dosing

The main benefit of this medication is that it has very few side effects, and none that are known to be medically important or harmful long-term. Its main nuisance side effects are nausea and sedation. Dosing has a very broad range, which can be good in terms of being able to reduce the dose greatly to a point that is tolerable for most people. Sensitive individuals usually begin at 100 mg nightly, but for the average patient, 300 mg is a standard starting dose. For anxiety and pain and insomnia, typical final dose will be about 300 to 900 mg nightly. PL recommends giving all the medication at night, even though it has a short half-life of about four hours. This short half-life may be relevant for anxiety, in which case multiple daily dosing may be needed. If given for other purposes, a single evening dose may be sufficient.

The PL Bottom Line

- Gabapentin is a versatile medication, which can be helpful for anxiety and insomnia.
- It is proven ineffective for mania and should NOT be given as a "mood stabilizer."

PL Reflection

We have the strength enough to endure the troubles of others.

Case of the month:

"PMDD" which isn't

This case came from one of our colleagues:

A 26 year-old female without prior psychiatric history presents for a consultation upon the recommendation of primary care. Both primary care and gynecology have diagnosed pre-menstrual dysphoric disorder (PMDD). In 2014, primary care prescribed Sarafem (fluoxetine) for several months, "but it didn't do anything." Primary care also recommended this consultation for an ADHD evaluation. The patient has taken a friend's ADHD medication (Adderall 5-10mg) and "it brings me up to par. It just really helps with the lows and the attention." The patient describes a long history, since teenage years, of alternating mood cycles. She only became aware of them in 2012 when she experienced several months of continuous depressive symptoms after a family death. She reports that about 14 days before menses she develops significant depressive symptoms, especially very low energy ("it just completely dives"), poor motivation ("don't even want to get out of bed"), no desire to socialize and very low mood. At the same time, attention and thinking are poor ("I feel like there is this film over my brain, a hard time thinking and articulating things"). In contrast, the other two weeks of the month (at menses and onward), she experiences the opposite: "I'm just motivated, doing a lot better. It's the way I should be feeling all month long." She reports being productive at work, bright and optimistic, "but I think my mood is usually optimistic." The patient reports chronic sleep impairment and racing thoughts since teenage years: "I have always been a night-owl... My brain is incredibly more active at night time. I have a hard time shutting my mind off in the evenings." There are periods where sleep is

worse and she averages 6 hours at night, (1am-7:30am), but she still has good energy. She denies past manic episodes. In reference to the 2 weeks of elevated mood, energy, and thinking, she denies these as above her baseline: "I feel like this is how I should be. I just feel more organized. I have more motivation to do the small things like working out or doing chores."

She recently had another consultation with a psychiatrist who agreed with the PMDD diagnosis but referred her back to her gynecologist. "He said there is nothing behaviorally he could do for me. He said what was happening was a chemical process and I should go back to gynecology." Past medical history is notable for past ovarian cysts s/p excision x 2 (emergency surgery after a rupture). She has taken several oral contraceptives but each caused various psychiatric side effects: "a few months where I felt depressed 24/7."

Family history is as follows: Maternal aunt: was "treated for some depression throughout her life." Father "is like me in a lot of ways, hyper focused sometimes and stays up late;" also a "procrastinator like me." Brother is diagnosed with ADHD and uses stimulants, "but I think he just uses it for a high stress job."

She had no behavioral or academic problems throughout schooling, with a high school GPA of 3.5. She was active with many hobbies including tennis, soccer, and softball. Mother has told patient that she has suspected patient was periodically depressed in high school.

She denies any physical symptoms associated with menses - no bowel changes, cramping, bloating, heavy bleeding, or headaches. Extensive laboratory testing for TSH, FSH, prolactin, and cortisol are all within normal limits.

During the consultation, her mental status examination was notable for: Hyperactivity (restless, fast and quick movements); pressured speech but interruptible; mood "pretty great!"; mildly euphoric affect - very animated, gregarious; and mild tangentiality requiring some redirection.

The colleague who sent this case had the following overall clinical impression:

The case reflects a long history of mood cycles, which likely have less to do with her menses than with bipolar illness. Pre-menstrual dysphoric disorder is unlikely here because of (1) severity of symptoms between pre- and post menses cycles (2) lack of any physiologic symptoms associated with menses (no bloating or cramping) (3) chronic symptoms of insomnia and racing thoughts (which have nothing to do with PMDD but are a frequent feature of untreated bipolar) (4) family history being suspicious for mood cycling, likely in father (5) lack of response to Prozac, and (6) oral contraceptives induced depression. Timing of cycles may not be as clear-cut around menses as the patient believes, but hormonal exacerbations are likely happening. There is no indication that ADHD is present.

Questions for PL: (1) Is PMDD a valid scientific construct? What about PMS? (2) If this patient actually has underlying bipolar (type 2, rapid cycling?), what does the literature say about hormonal influences of mood cycles? (3) What is the approach for medication management in this patient who disagrees that anything other than PMDD could be occurring? 4) Is ADHD present?

PL commentary: The PL view is that PMDD may be a valid scientific construct, but we caution against the general process of adding the word "disorder" to a collection of symptoms and assuming that *ipso facto* it is valid. There certainly are premenstrual symptoms of mood/anxiety/hot

flashes/bloating and so on. These symptoms can be caused by other conditions - like manic-depressive illness - or they can occur by themselves as part of the normal process of menstruation. The key issue in our view is to differentiate those two circumstances. In other words, we need to apply the concept of diagnostic hierarchy: Does the patient have anything else that could cause premenstrual symptoms? (You could call "PMS" the presence of the symptoms; this doesn't answer the question of whether it is occurring by itself or caused by something else).

Mood cycles in bipolar illness often are triggered by stressors, not just psychosocial ones, but also biological ones, and hormonal changes around menstrual periods are common biological triggers of mood cycles in bipolar illness. Since they occur monthly, PMS-related mood episodes are rapid-cycling by definition (≥ 4 mood episodes yearly).

Again applying the diagnostic hierarchy concept, ADD isn't present since distractibility is a consequence of the mood episodes, not a separate "disorder," just as "fever disorder" isn't present during pneumonia. Benefit with Adderall isn't diagnostic of ADD because attention improves in everyone with amphetamines. This would be like saying decreased anxiety with benzodiazepines, which occurs in all human beings, means that everyone has an "anxiety disorder."

Regarding the diagnosis of bipolar illness, the question is whether her 2 non-depressed weeks per month represent normal happiness or hypomanic episodes. One hint is that hypomania is recurrent, happiness is not (a favorite quote of Dr Hagop Akiskal). 6 hours nightly of sleep with good energy is biologically abnormal (sleep studies indicate that about 9 hours of sleep is the biological norm, although culturally most of us don't get it). This is decreased need for sleep, a

manic symptom; it is not normal. This symptom, along with increased activities and racing thoughts support the higher probability of hypomania rather than normal happiness. The biology of this condition is supported further by her father's apparent similar symptoms.

If we can agree on the bipolar diagnosis, with a rapid cycling course and type II subtype, then the PL recommendation is straightforward, like any other person with bipolar illness: Use mood stabilizers. Since this is a rapid-cycling course, multiple mood stabilizers will likely be needed, and lamotrigine in particular has been shown to be ineffective in rapid-cycling. Since many patients are concerned about weight gain, PL might recommend carbamazepine first, because it doesn't have weight gain. If a second agent is needed, lithium at low doses may be sufficient. Dopamine blockers don't combine well with carbamazepine because the latter reduces blood levels of the former, rendering them less effective. Another approach would be to start with lamotrigine, see how much benefit is gained, and then add lithium or dopamine blockers which don't have weight gain, like aripiprazole or ziprasidone or lurasidone, at low doses preferably.

How could you convince this person to take this approach? Some people are beyond convincing. But here are some strategies: Tell her *not* to search this matter randomly on the Internet. The PL approach is not mainstream and if she goes by majority vote, she'll be directed against the recommendations made here. Recommend the PL website for a rationale for these ideas. Talk to the patient about the concept of a diagnostic hierarchy, using unimpeachable medical examples such as pneumonia and fever. Make it a pragmatic decision: If it doesn't work, she can see someone else to take other approaches. For many people, this rationale can be persuasive.

Curbside consults:

Questions from you

Question: Why do you champion extended-release lithium over immediate-release lithium?

PL: PL doesn't "champion" any formulation of lithium. The most important thing to know about lithium is that it should be dosed only once daily, not multiple times daily. Its half life is about 24 hours and there is no reason to dose it more than once a day. Long-term outcome studies show that multiple daily dosing is a major predictor of long-term chronic kidney impairment. This issue is much much more important than whether immediate or extended release dosing is used. PL recommends that readers use whichever formulation they prefer, as long as they give them once daily only.

The extended release formulation cuts off the initial peak of dosing. In the standard formulation, this initial peak might cause more short-term side effects and/or brief exposure of the kidney to high lithium levels. PL doesn't feel strongly about this point, which is conceptual, and not proven in empirical studies. If you feel strongly about using immediate-release lithium for other reasons, such as cost, that's fine. The more important matter is to dose it once daily rather than multiple times daily.

Question: A 79 year-old woman presents with 10 years of treatment with venlafaxine XR 75 mg/d for perimenopausal hot flashes. When she tried to come off venlafaxine, she felt much worse, with

return of hot flashes and marked agitation. She went to see an expert consultant, who told her she just needed to resume venlafaxine. She now believes that her post-menopausal hot flashes still remain with her, and that she needs venlafaxine for the rest of her life. Is this correct?

PL: No. She did not have return of perimenopausal hot flashes in her late 70s when she went off venlafaxine. Rather, she experienced classic serotonin withdrawal syndrome. SRI withdrawal is worst with venlafaxine and paroxetine, which have the shortest half-lives, and it is least with fluoxetine, which has the longest half-life. She received inadequate advice from the expert consultant, who should have recommended that she be cross-tapered using fluoxetine. This could be done by adding 10 mg/d of fluoxetine, waiting one week, then reducing venlafaxine to 37.5 mg/d for 2 weeks, then 37.5 mg every other day for 2 weeks, and then stopping it. Fluoxetine could then be continued for one more month, then reduced to every other day for one month, and then stopped. The importance of coming off venlafaxine in older persons is that it has been associated with fatal overdoses and risk of cardiac arrhythmias. For these reasons, UK regulators have contraindicated it in persons with cardiac disease or hypertension. PL agrees that the cardiac dangers of venlafaxine are underappreciated in the US, and that it should not be given at all to most older persons, since cardiac disease and hypertension are quite common in the elderly.

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THE PSYCHIATRY LETTER

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The ADD controversy

It is said that in every controversy there are three sides: one side, the opposite - and the truth. Perhaps no topic attracts more conflicting perspectives than ADD. The PL website has laid out its perspective, but many details must be explained to address many different aspects of the topic. In this issue, we begin that process, though this is not the end of the matter. Further discussions will be needed to address different questions and viewpoints, and the complexities that arise in any analysis of this matter.

The special article provides our overall summary of the ADD concept in children. We examine its diagnostic validity and conclude it represents a developmental delay, not a permanent disease. This conclusion entails short-term treatment, if any, not automatic commitment to long-term medication treatment, as is commonly the case today.

The classic study of the month examines the most definitive randomized trial of childhood ADD, the NIMH-funded "MTA" study, and addresses some misconceptions about its results.

The drug of the month is methylphenidate and its variants, and important risks, including neurotoxicity, are explored.

The case of the month examines a case of childhood ADD that improved by stopping amphetamines and instead treating anxiety symptoms.

As usual, citations and references can be found on the web version of the newsletter.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Childhood ADD*

A developmental phase, not a permanent disease

Attention deficit disorder (ADD) is a common diagnosis made in children and, increasingly, in adults. In this special article, we'll focus on whether it is a valid concept, and if so what it means diagnostically. Then we'll think about what those considerations imply for treatment decisions.

Since this topic is complex, we will address it in more than one PL issue as a special article.

ADD - not ADHD

A first basic idea is that PL prefers to drop the "H" which is commonly used in the term "ADHD". Hyperactivity is a common misconception in the diagnosis of ADD, especially in children. If you say a child is "hyperactive" and thus has ADHD, you would diagnose every manic child with ADHD. Of course, that's another debate, which many proponents of ADHD solve by denying that there is any, or much, bipolar illness in children. That's another topic for another occasion.

For now, let's just ask the question: What do we mean by "hyperactivity"? Do we mean increased energy? If so, increased energy is not a diagnostic criterion of ADHD, and it never has been. But it is a core diagnostic criterion for mania. Do we mean decreased need for sleep? This is not a diagnostic criterion for ADHD, but it is a central diagnostic criterion of mania. Does increased energy happen as a diagnostic criterion of any psychiatric diagnosis besides mania/hypomania? No.

So the problem with the word "hyperactivity" is that it frequently connotes increased energy,

which is usually part of decreased need for sleep, and these symptoms are not part of the ADHD syndrome, but rather only occur in bipolar illness as part of manic or hypomanic episodes.

So what is meant by hyperactivity in ADHD, if we can't use the term to refer to increased energy? What seems to be meant is psychomotor agitation: children don't sit still. Why don't they sit still? Is it because they have increased energy? We already established this is not the case, because increased energy would define them as having mania, not ADHD. Instead, the general view is that children don't sit still because they can't focus, they're distractible, that's the first "D" in ADHD. They're in school for 6-8 hours day, expected to sit at a desk and focus on a teacher, and they can't focus, so they have a hard time sitting at the desk.

"...apparent 'hyperactivity' isn't hyperactivity at all but rather psychomotor agitation"

In other words, the apparent "hyperactivity" isn't hyperactivity at all but rather psychomotor agitation that's an effect of the main psychopathological problem: distractibility. And this psychomotor agitation isn't always present. Some children can't focus, but they manage to stay seated. In adults, since they are no longer in schools and are not usually forced to sit at a desk 6-8 hours daily, there is no "hyperactivity" or psychomotor agitation in most people. ADD is distractibility, pure and simple, in adults, with the associated cognitive impairment of executive dysfunction and disorganization.

So, an initial common error is to diagnose "ADHD" in children mainly based on "hyperactivity" without asking whether this

reflects increased energy, in which case the diagnosis should be mania instead, not ADHD.

One way to avoid this common error is to refuse to go along with the unscientific insistence of DSM on using the term "ADHD" and instead to use the term "ADD" so as to put the emphasis of the diagnosis where the science shows it to be: in cognitive impairment, not increased energy.

There is no "paradoxical" effect of "stimulants"

Another benefit of realizing that "hyperactivity" is not a scientifically sound aspect of ADD is that it is no longer "paradoxical" that "stimulants" reduce hyperactivity. PL apologizes for all the quotes, but the problem is that these

English terms are used by clinicians despite a lack of scientific meaning to the words. There is no paradox to decrease of hyperactivity with stimulants because a) there is no hyperactivity and b) "stimulants" aren't stimulants.

We just explained above how there is no hyperactivity in ADD, if by that term is meant increased energy. There is psychomotor agitation in some children secondary to being unable to sit still for long periods of time, usually in school settings, as a result of their marked cognitive impairment of distractibility.

Now we can add that "stimulants" aren't stimulants. What do they stimulate? How do they stimulate anything? We are referring to amphetamines, including methylphenidate, which is an amphetamine (see the Drug of the Month). These agents are dopamine agonists (and some also have norepinephrine agonism). This is a kind of biological "stimulation" but we don't call SRIs serotonin "stimulants" because they increase serotonin activity.

"...stimulants' aren't stimulants....The more correct term is that they are dopamine agonists..."

Instead the term "stimulants" seems to imply a clinical meaning. Patients feel stimulated. What does this mean? They have more energy. That's right; we know that amphetamines increase energy even in normal persons. But we also know that amphetamines markedly improve attention. So is there any paradox to their benefit in ADD, a condition of poor attention? If you have poor attention, and you take a drug that improves attention, and then you sit still because now you can focus, where is the paradox? Since these children are not high in energy to begin with, there is no paradox that a drug which increases energy makes them less agitated. It makes sense when we realize that the agitation is secondary to poor attention, which is improved by the dopamine agonists.

A disease or a developmental phase?

The presence of a diagnosis doesn't entail the presence of a disease. This is especially the case with DSM, where hundreds of diagnoses are included but the majority are not diseases of the body or brain. A diagnosis, if valid scientifically, basically reflects a clinical syndrome that can be distinguished from other clinical syndromes. This scientific validity is based on the classic diagnostic validators of symptoms, genetics, course, and treatment response, as discussed in prior PL issues and the PL website. Childhood ADD can be claimed to differ from other childhood clinical syndromes based on these diagnostic validators. It may be a valid diagnosis, but is it a disease of the body?

One should note that it isn't enough to show changes in the brain. There are changes in the brain with any clinical presentation because all thoughts and feelings are mediated by the brain. PET scans and even structural MRI of Republicans and Democrats, of men and women,

differ; but political preference and gender are not diseases.

A special danger exists in assuming disease processes in children since childhood is a period of biological and psychological development. The child is a runner in motion; taking a picture at one point in time to claim a disease process may not hold true a year later. The importance of development in understanding ADD is brought out by some excellent work examining the brain in children with ADD using MRI and PET scans, not just cross-sectionally but prospectively (P Shaw et al, Proc Nat Acad Sciences, 2007, 104: 19649). In that study, compared to matched controls, children with ADD showed evidence of brain abnormalities (decreased blood flow, reduced cortical thickness) in some regions (like dorsolateral prefrontal and ventromedial frontal cortex). These abnormalities were present around age 7-8 but then normalized by about age 11-12. In sum, there was a 2-3 year delay in cortical maturation, especially in the prefrontal cortex, in ADD children versus matched non-ADD controls.

The straightforward interpretation of this research is that ADD is a developmental delay, not a permanent disease. It represents normal childhood, slowed down by a few years.

Readers probably wonder about the effects of treatments in this research. Medication effects were not examined, nor would they be definitive since these studies are not randomized trials. About half of children diagnosable with ADD are treated with medications, thus one cannot assume that the improvement seen in this study was due to medication effects. It could be due to natural

"The main interpretation of this research is that ADD represents a developmental delay, not a permanent disease."

history as well, or solely. If so, then the question is raised whether the main thing to do with this developmental phase delay is to help symptomatically for a brief period of time, not more than 2-3 years, and then leave children alone.

This evidence for developmental delay also is consistent with the older ADD literature (before the introduction of Strattera, atomoxetine, and the subsequent rise of adult ADD) that indicated

that about 90% of children diagnosable with ADD were no longer diagnosable by age 18. In other words, since this is not a disease but a developmental delay in which there is natural recovery, the vast majority of children with ADD will "grow out" of it.

This concept contrasts with popular belief in the existence of adult ADD, to be addressed in next month's PL issue.

The PL Bottom Line

- ADD is characterized by the core feature of inattention. Increased energy is not a feature of the syndrome.
- Hence there is no "paradoxical" effect of "stimulants." These agents simply improve attention, which improves behavior.
- Childhood ADD is a developmental delay, not a permanent disease.
- Treatment for ADD can be given for short duration, if at all, in childhood and need not be continued into adulthood in most persons.

Further reading

Much of the material presented here is discussed in detail with full citations in Vergne et al, Adult ADHD and amphetamines: A new paradigm. Acta Neuropsychiatrica, 2011, 1: 591-598.

Classic study of the month:***Multimodal Treatment of ADD (MTA): The longest randomized trial of amphetamines is misunderstood***

Multimodal treatment of children with ADHD. Archives General Psychiatry, 1999, 56:1073-1086

Amphetamines were less effective than commonly believed

This classic NIMH-funded study is the longest and largest randomized trial of the efficacy of amphetamines in childhood ADD. It is cited widely as showing more benefit with those medications than with psychosocial interventions. In fact, this is not the case for functional outcomes. Further, the study provides important safety data which contradict other widely held beliefs; namely, it shows that substance abuse rates do not decline with amphetamine treatment of ADD, and further it provides evidence of shortened height as a side effect of this medication class in growing children.

Children aged 7-10 with ADD were recruited (mean age 8.5 years, total sample = 579). They were double-blind randomized to one of four arms of treatment: medication (73% methylphenidate, 27% other amphetamines), intensive behavioral management, both, or neither ("standard community care"). Average dose of methylphenidate was 30.5 mg/d. It was well tolerated with 86% of children having no or mild side effects.

At the end of 14 months of double-blind treatment, those children who received methylphenidate were almost one inch shorter than those who did not receive it (4.25 vs 6.19 cm difference, equal to 0.76 inch difference).

In a range of 19 outcomes, benefits were seen in 10 outcomes. ADD symptoms improved more with medications than with behavioral

management. Both treatment groups did better in most cases than standard community care.

However, *functional improvement was not statistically significantly different between medications and behavioral management*. These functions included: academic achievement, oppositional/aggressive behaviors, social skills, and parent/child relations.

This is a key finding: in the longest randomized trial of amphetamines versus behavioral management, it is NOT true that amphetamines were more effective for functional outcomes. It is true that amphetamines were more effective for symptoms of ADD: namely, children were felt or were observed to be more attentive and less agitated.

But when it comes to whether they did better in school, or had better social relationships at school or home, behavioral interventions were just as good as medications, and better than standard community care.

The importance of this matter is that one often hears statements by ADHD experts to the effect that the MTA study showed that amphetamines were superior to psychosocial interventions in general. This is not true as stated. For functional outcomes, which is a key rationale for prescribing, amphetamines were *not* more effective than behavioral interventions.

After the one-year randomized study, patients were allowed to receive whatever treatment they or their clinicians wanted, in an open unblinded

non-randomized manner, for two more years. Now keep in mind that at the 2 and 3 year outcomes, the results are no longer randomized, and thus there is possibility of “confounding bias”, which means that others factors may influence results besides the treatment given (this is the whole point of randomizations, to control for other confounding factors such that the randomized arms can be seen as causal in their effects on outcomes, as discussed in the April 2015 PL issue). Nonetheless, despite needing to think about confounding factors, 2-3 year outcomes provide important information on long-term efficacy and safety of amphetamines versus behavioral interventions for ADD.

At 3 year follow-up, with subjects now at about 12 years old (mean 11.9 years), all groups showed similar improvement. In other words, the amphetamine group no longer was better than other groups for symptoms, nor were medication and behavioral intervention arms more effective than community care for functional outcomes. All groups had similar outcomes. Now the authors went to great lengths to keep you from drawing the wrong inference that medications are ineffective. They wrote: “It would be incorrect to conclude from these results that treatment makes no difference or is not worth pursuing.” They are right, because of confounding bias; the results are no longer randomized, anyone can get any treatment they wish, which means that some of the non-medication arm subjects would now be receiving medications, and some of the medication arm subjects would now be receiving behavioral interventions. It is worthwhile noting exactly how this played out:

“One can avoid the need to use amphetamines at all, even for the long term, in one-half of children if adequate behavioral interventions are provided.”

In the behavioral arm, where patients initially were randomized only to behavioral interventions, and zero amphetamine use, 3-year outcome found that 45% of patients had begun to receive amphetamines, added to their behavioral interventions.

In the combination arm, where 100% of subjects were randomized to receive amphetamines plus behavioral management, 3-year outcome found that medication use had decreased to 71% of patients. In the standard community care arm, where doctors could do whatever they wanted, medication use stayed stable at 3 years (going from 60% to 62%).

What does this tell us?

One way of looking at it is that in all treatment arms, medication use stabilized out at about 1/2 to 2/3 of subjects. In other words, patients and doctors judged that medications were needed and helpful in many, but not all, patients.

Another way of looking at these results involves focusing on the behavioral intervention arm. Three year outcomes suggest that if one tries to provide good behavioral intervention to patients, without any amphetamines at all, only about one-half of ADD children eventually will need medications. Put another way, *one can avoid the need to use amphetamines at all, even for the long-term, in one-half of children, if adequate behavioral interventions are provided.*

What about side effects at three years?

The MTA results are interpreted usually as good news, because the 0.75 inch growth impairment plateaued at 3 years; there was no further difference in height between medication and non-

medication groups. The authors and many experts often cite these data to assert that we need not worry about shortened height as a long-term risk with amphetamines.

But why are they willing to interpret these non-randomized 3-year results as showing no further differences for height, whereas they were not willing to interpret these same non-randomized 3-year results as showing no differences for efficacy?

They are inconsistent: You can't have one interpretation without the other. If the results cannot be interpreted as showing lack of efficacy with medications (since all groups had similar outcomes at 3 years), they also cannot be interpreted as showing lack of harm with medications (since all groups had similar height changes at 3 years).

Put differently, the results do NOT show that there is no height risk; they simply are uninformative since the 3-year results are non-randomized and there is similar medication use in all four groups, and thus one can no longer draw causal inferences about medication effects between groups.

All we can say is that when assessed during randomized treatment, amphetamines shorten height by almost one inch per year. We do not know if this effect persists or goes away after multiple years.

There is another 2-3 year analysis that deserves more attention than it receives: the effect of amphetamine prescription on substance abuse. It is commonly stated, based on observational data, that amphetamine prescription leads to *less* substance abuse in persons with ADD. But observational data are non-randomized data, and non-randomized data are prone to confounding bias, as discussed above. Thus, one cannot draw

causal inferences. If, in adolescents with ADD, those who received amphetamines had less substance abuse than those who didn't receive amphetamines, it may have been because clinicians gave amphetamines mainly to those who didn't have evidence of substance abuse. The causal link can go in any direction. Only randomization can allow causal assertions in a simple manner (again see the April 2015 PL issue).

The MTA study is useful in this regard again because it is the longest randomized trial of amphetamines. Its non-randomized outcomes at 2 and 3 years are more dependable than most studies, since they follow up on an initial randomized period of treatment of one year, which is much better than studies that are purely observational from the get-go.

"When assessed during randomized treatment, amphetamines shorten height by almost one inch per year."

With that context, let's ask what happened in MTA with substance abuse. At one year, in the pure randomized follow-up period, there was no difference in substance abuse rates between amphetamine-treated children and those treated with behavioral interventions. In other words, the most definitive interpretation is that amphetamines were neutral. They did not worsen substance abuse rates, but they also *did not improve* substance abuse rates, contrary to common claims. At 3 years of follow-up, again there were no differences between the groups, but this doesn't mean that there was no risk, for the same reasons given up previously regarding similarities in efficacy and height at 3 years. At 2 years of follow-up, there was *more* substance abuse in amphetamine-treated children than in non-amphetamine treated children. This finding in the MTA study contradicts the common claim that amphetamines reduce substance abuse. In fact, using the best data on the topic, which is the MTA study, the most

objective interpretation of these data is that amphetamines do not reduce the risk of substance abuse. They may have no effect, or they may *increase* risk, but there is no evidence in this study that they decrease risk of substance abuse.

The PL Bottom Line

- The MTA study is the longest, randomized trial of amphetamines in childhood ADD, with a one year randomized period, and 2 more years of nonrandomized outcomes.
- The main finding, contrary to the emphasis of the authors and experts, is that amphetamines

are NOT more effective than behavioral interventions for functional outcomes in ADD, such as academic achievement and social relationships.

- Amphetamines were shown to shorten height by about 3/4 inch in one year.
- Substance abuse was not decreased with amphetamine treatment, and was increased at 2 year outcomes.
- If behavioral management is given, medications can be avoided entirely in almost one-half of children for the long-term.

PL Reflection

Our knowledge is just enough to obscure our ignorance.

William Gowers MD

Clinical Tip of the Month

Anxiety, not ADD, is a common cause of inattention in children

When diagnosing ADD in children, do not focus on hyperactivity. Rather the central clinical diagnostic feature should be inattention. Even then, the diagnosis shouldn't be made in the setting of other conditions that cause inattention, most importantly: anxiety, depression, mania, and psychosis. The most common set of symptoms in children that produces inattention is anxiety. Anxiety itself often is an early prodrome to other conditions, such as mood and psychotic illnesses. Both of the latter conditions are worsened with amphetamines, so care should be given to recognizing anxiety in children as an important cause of inattention. Since most clinicians avoid benzodiazepines in children, SRIs are commonly used for anxiety, but SRIs can worsen mood and psychotic conditions, thus they should be used in low doses and not continued long-term, meaning for years and years, if possible. Long-term use produces major problems with serotonin withdrawal syndrome when the one ultimately needs to come off those agents some day. Further, the long-term effects of SRIs on sexual development, if continued throughout adolescence, are not known. In short, with children, don't routinely diagnose ADD with inattention, and certainly not for hyperactivity. Consider anxiety and other syndromes, but even then, minimize dosing and duration of medication treatment as much as possible. Remember it's a developmental delay, not a permanent disease. Medication treatment isn't always necessary, especially for the long-term.

Drug of the Month: *Methylphenidate and its variants*

Methylphenidate is an amphetamine

The most widely used amphetamine agent is methylphenidate. In fact, all prescribed amphetamines are variants of either methylphenidate or dextroamphetamine. In this issue we focus on methylphenidate and its variants; in the next PL issue, the focus will shift to dextroamphetamine and its variants.

Clinical efficacy and inefficacy

Methylphenidate and its variants have been shown to be effective in ADD, as well as in major depressive episodes. They also produce weight loss and increase sexual libido. They have been found to cause mania and/or worsen bipolar illness.

“Benefit” in ADD for attention is not surprising, since methylphenidate has been shown to be effective in normal individuals to improve attention. In other words, since some inattention is normal, methylphenidate “works” in everyone, and efficacy is not indicative of presence of an illness.

Biological mechanism

This agent is a dopamine reuptake inhibitor and directly stimulates dopamine and norepinephrine receptors. Thus, it increases both dopamine and norepinephrine activity.

For some reason, there is a common misconception that methylphenidate is NOT an amphetamine. It clearly is an amphetamine, based both on its pharmacological structure and its biological effects. As seen in the figure, it has the same basic structure as dextroamphetamine and dopamine. It also has the same basic biological effect of dopamine agonism as is the case with dextroamphetamine. The only

difference is that it also has noradrenergic effects. But this additional effect doesn't remove or cancel out its basic dopaminergic effect, which is part and parcel of its basic amphetamine structure.

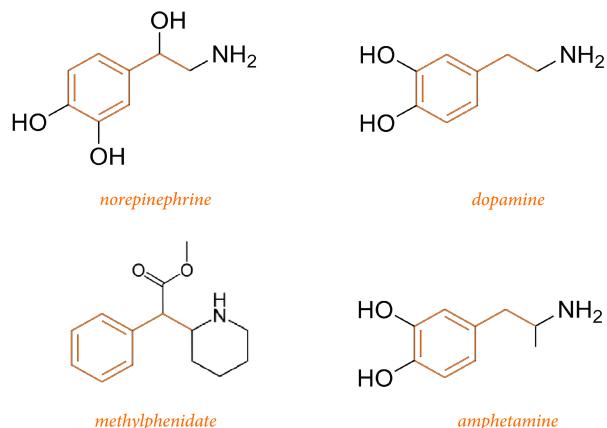


Fig 1. Note the structure similarity between norepinephrine, dopamine, methylphenidate and amphetamine. All share the 4-ethylphenyl structure, in orange.

Neurotoxicity

Many animal studies have shown that methylphenidate is harmful to neurons, causing atrophy. This has been shown over and over again in many rat studies. The question often raised is whether this effect occurs in humans. The short answer is that it hasn't been studied in any way that can answer the question. A few small studies exist in adolescents, none of which are followed more than a few years, and all in non-randomized observational settings. Those studies mostly report no cortical atrophy, although some analyses do indicate more atrophy. In any case, because of confounding bias, those studies cannot answer the question. We would need randomized neuroimaging studies, which have never been conducted. Another factor is that animal studies indicate that the most harm occurs if

methylphenidate is given early in childhood and continued into adulthood. There has never been even a non-randomized observational study of neuroimaging in human adults who have been exposed to amphetamines in childhood continuously into adulthood.

Side effects and dosing

Besides neurotoxicity in animals, methylphenidate is known to have cardiotoxicity, specifically cardiac arrhythmias. This risk may be lower in children than in adults. In adults, a recent analysis found that there was almost a doubling of risk of sudden cardiac death due to ventricular arrhythmias with methylphenidate. The authors tried to explain this result away given the observational setting, and the presence of confounding factors should prevent definitive judgments pro or con. Nonetheless, these are the best data we now possess, and they do indicate some risk as far as we can accept those data. The PL editor has analyzed the results to calculate an absolute frequency of risk, which was about 1:1000. In other words, if these results are correct, methylphenidate can cause sudden cardiac death in 1 in 1000 adults. Other studies do not find evidence of such risk, so that at present one cannot be definitive.

In sum, it is not the case that this medication is proven safe in children and adults, as is commonly repeated by some experts.

Fast Facts: Methylphenidate

Typical dose: 10-60 mg/d

Variants: Focalin, dex-methylphenidate; Concerta, methylphenidate ER

Biological mechanism: Dopaminergic and noradrenergic agonist

Typical side effects: insomnia, anxiety, jitteriness

Less common but important side effects: mania

Medically important side effects: ventricular arrhythmia, neurotoxicity

Clinically proven efficacy: Treatment of ADD and non-bipolar depressive episodes

The PL Bottom Line

- Methylphenidate is an amphetamine
- It is effective for attention in everyone, not just persons with ADD.
- It is proven neurotoxic in animals, and human studies do not prove

or disprove that risk.

- It is possibly cardiotoxic in adults with 1:1000 risk.
- It is not proven safe in children and adults such that one can prescribe it without any concerns.

Further reading

Much of the material presented here is discussed in detail with full citations in Vergne et al, Adult ADHD and amphetamines: A new paradigm. Acta Neuropsychiatrica, 2011, 1: 591-598. Other citations are available on the web newsletter.

PL Reflection

On the wish to use medications and the role of pharmaceutical marketing, in Germany circa 1876:

“The chemical industry of our days produces various substances for which no market can yet be found....We know that a great number of physicians, without rhyme or reason, go after every new remedy that is recommended to them. If an industrialist is but shrewd enough to advertise sufficiently, he usually succeeds in increasing the sale of his product – for some time at least – and thus enriching himself.”

R Buchheim

“Über die Aufgaben und die Stellung der Pharmakologie an den deutschen Hoschshulen” Arch Exp Pathol Pharmakol 5: 261, 1876.

Case of the month:*Childhood ADD worsened by stimulants*

A 10 year-old male is brought by his mother for consultation. He has been treated with Focalin, Concerta, Adderall, methylphenidate, and Dexedrine. He also has received aripiprazole and olanzapine, added to the above agents. His main problems involved not being able to pay attention in school, and being aggressive and agitated toward other children. In two years of treatment, he had not improved, and was forced to change schools multiple times. At one point, while at a restaurant with his parents, he bolted out the door and tried to run down the street. On other occasions, he tried to open the car door on the highway. His parents were concerned about these impulsive behaviors, which had not improved with multiple amphetamines.

He was markedly anxious and had marked insomnia, but his family denied increased or a high level of energy. They also denied any observable depressive symptoms such as suicidality or noticeable sadness or anhedonia.

He was adopted and biological family history was unknown. He lived in an intact and loving family with two parents and an older adopted sister, who had no psychiatric problems and was very successful in school and social life.

He was observed to be very short for his age, and very thin.

On mental status examination, he was polite but played mostly with a video game, answering questions briefly. He was frustrated about his poor social and academic skills and how it harmed his friendships with his peers. He expressed this frustration appropriately and rationally during the interview. He said he wanted to come off his

current medications of methylphenidate 60 mg/d and aripiprazole 5 mg/d.

The PL diagnosis was that anxiety symptoms were present, which could explain all of his attentional impairment, which could further explain his school-related agitation. The worsened impulsivity was attributed to the harmful manic-like effects of amphetamines. The recommendation made was to stop both methylphenidate and aripiprazole. Since the latter has some dopamine agonist effects, it could be contributing to the worsening impulsivity. Two treatment options were given for symptomatic purposes: very low dose SRI for anxiety, or low dose risperidone for pure anti-dopamine effects to target impulsivity. The diagnosis was unknown since family history was unknown and because of his young age. It is typical for anxiety symptoms to be the earliest manifestation of other psychopathology, such as later depressive or bipolar illness.

The PL approach in children is to use medications minimally for symptoms, provide as many behavioral interventions as possible at school and home to improve function, and then to observe the evolution of the illness until a more definitive diagnosis could be made.

Within weeks of stopping methylphenidate, his parents reported that he was much calmer, less anxious, and less agitated. He began to eat more and was putting on needed weight. A few months later, he became somewhat anxious, and the family chose to start SRI treatment. The PL recommendation was 10 mg fluoxetine given twice weekly. This is because fluoxetine has a very long half life of one week and thus it can be dosed weekly. This approach would give the lowest amount of SRI feasible, and also the child would not see himself as being medicated daily. Within

weeks, his anxiety resolved and his behavior improved notably.

At one year follow-up, taking only fluoxetine 10 mg 1-2 times weekly and no other medications, he had grown a number of inches and was closer in stature to his peers, which markedly improved his self-esteem. He had gained weight and was normal in his body mass index. He was doing very well in a private school with sufficient attention to providing behavioral assistance for executive dysfunction. His peer and family relationships had improved markedly.

Curbside consults:

Questions from you

Question: Do you have a preferred antidepressant for major depressive disorder? Do you endorse the approach in Stahl's textbook to choose the agent by symptom subtype?

PL: PL prefers to take the approach of subtyping based on mixed states versus melancholia versus neurotic depression, as explained in the PL website. Antidepressants would be avoided in mixed states altogether. The bipolar/unipolar distinction is less important than the above three basic depressive subtypes, in the PL viewpoint. This subtyping is not symptomatic alone, but takes into account genetics and course of illness to separate manic-depressive illness (e.g., mixed states and recurrent melancholia) from other depressive states (e.g., neurotic depression). Since MDD is not a clinically valid disease, as explained on the PL website, PL does not recommend simply using "antidepressants" (monoamine agonists) for depressive episodes. If used, PL views the scientific literature as indicating no notable differences in efficacy among modern monoamine agonists. Thus, if used, PL recommends choosing among monoamine agonists based mostly on side effects.

PL Reflection

I did not want to become a doctor, I wanted to write. But medicine gave me what I most wanted: life in the raw; it exposed me to every emotion of which man is capable; it excited the novelist in me. Even 40 years later, I recall certain faces and phrases. I saw how men died, how they bore pain; I saw what hope looked like, fear and relief; I saw despair; I saw courage and steadfastness. I saw faith which seemed unwarranted, and gallantry when ironic jokes were made to hide terror.

W. Somerset Maugham

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THE PSYCHIATRY LETTER

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The ADD controversy - Part II

This issue continues with the theme of Attention Deficit Disorder (ADD), which was also the theme of the last issue of PL, in October 2015. The prior issue focused on ADD in childhood. This issue turns to the topic of ADD in adulthood.

The special article provides our overall summary of the ADD concept in adults. We examine its diagnostic validity in particular.

The classic study of the month examines a widely cited study regarding the prevalence and validity of adult ADD: the National Comorbidity Survey (NCS). PL raises the question of whether the very high co-occurrence of mood illness with reported adult ADD reflects the constant coexistence of two separate diseases, or the presence of concentration impairment caused by mood illness.

The drug of the month is atomoxetine, the first agent FDA-indicated for adult ADD. The case of the month examines a case of apparent adult ADD, with "comorbid" depression, that did not improve with amphetamines and antidepressants.

As usual citations and references can be found on the web version of the newsletter.

As noted in the side bar, PL is pleased to announce that we can begin to offer CME and CEU credits to physicians and nurses and psychologists beginning with the January 2016 issue. We hope this will provide our readers with another reason to continue reading PL. We are coming up on our one year anniversary with the January issue, and your subscription will be up for renewal soon or in the coming year. We hope you renew and take advantage of CME/CEU credits through your reading.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special article: *Adult ADD examined*

Why it's normal to be inattentive

Last month's special article focused on childhood ADD. We come now to adult ADD.

It is worth noting that the concept hardly existed before Eli Lilly marketed the drug Strattera (atomoxetine) for it about a decade ago. Before then, the general consensus of researchers was that ADD did not persist into adulthood in the vast majority of persons. 9 prospective studies were conducted before Strattera came to the US market in 2003; in a total of 718 persons followed for 13-25 years from childhood into adulthood, from a mean of age 10 to age 25, the prevalence of ADD fell by 90%. In other words, only 10% of children with ADD continued to have it in their mid 20s. This observation contrasts with the common opinion these days that the majority of children with ADD will continue to have it as adults. Post-strattera research, often funded by pharmaceutical companies marketing adult ADD, report higher rates of persistence into adulthood, but even then, the full ADD syndrome is reported to be present in only about 40% of children followed to age 18-20. In other words, the majority still lose the diagnosis by early adulthood. Now the claim is made that despite syndromic remission, ADD symptoms still persist and cause functional impairment. But, even if so, it is worth noting that all studies show that the majority of children with ADD have syndromal remission by about age 18: they no longer meet ADD criteria.

Again, the question of treatment comes up. In general, in these studies, some children are treated and some are not, and the studies do not assess outcomes based on treatment in any systematic fashion, nor are they randomized. Thus

they cannot answer this question, but since a good number of the study subjects are untreated, it cannot be assumed that the results are the effect of treatment. Natural history still remains an important possible interpretation of the results.

The most cited recent data represent the National Comorbidity Survey (NCS) epidemiological study in the US, which found that about 3% of adults are diagnosable with ADD, which means that they meet criteria as adults in a current cross-sectional assessment as part of the NCS study, and that they retrospectively met those criteria as children.

"Why should pneumonia always happen with 'fever disorder'?"

The classic article of the month in this issue examines that study in detail. The key aspect discussed there is the finding that 45% of those who met adult ADD criteria also met bipolar disorder criteria and 39% of those who met adult ADD criteria also met major depressive disorder (MDD) criteria. In other words, 84% of those who can be diagnosed with current adult ADD are also diagnosable with current bipolar disorder or MDD. Here is the question: What causes what? Are they just unlucky, and every time they have one disease they have two diseases? Or does the ADD cause depression, as many ADD experts assume? Does ADD also cause recurrent manic episodes? This would seem biologically implausible.

At least in the case of bipolar illness, the proponents of the adult ADD diagnosis haven't explained why almost half those patients also have manic episodes. They haven't explained why we should believe they have two diseases, when one disease could explain all the symptoms, since a

cardinal feature of mania is distractibility. Why should pneumonia always happen with “fever disorder”?

ADD at age 41

One of the most interesting studies (RG Klein et al, Archives Gen Psych Dec 2012, 69: 1295-1303) that can add to this literature was a recent publication that represents the longest prospective outcome of ADD: a 33 year outcome study following children diagnosed with ADD at age 8, and compared with matched controls who did not have ADD. They were all followed to age 41. Here is an interesting observation: ADD was diagnosable in the control group in 5% as adults. These were children who were NOT assessed to have ADD as children, but simply chosen at random from matched controls, and then they met the criteria 30 years later.

NCS study for adults who had persistence of childhood ADD.

Here is one potential explanation: the 5% who did not have ADD in childhood but met adult criteria are simply adults who have statistically abnormal attention spans. They don't have a disease, and they don't have a developmental delay of the maturing brain; they are just at an extreme of the normal curve for the cognitive trait for attention. Recall that most psychological and biological traits are distributed on a normal curve in the general population, as shown in the figure. Most of us are at or near the 50th percentile. At 2 standard deviations from the middle of the curve, on each end, there is about 2% of the population. This is not disease, and it is not “disorder”. Some people are short, some are tall; some are skinny, some are not; some are shy, some are extroverted;

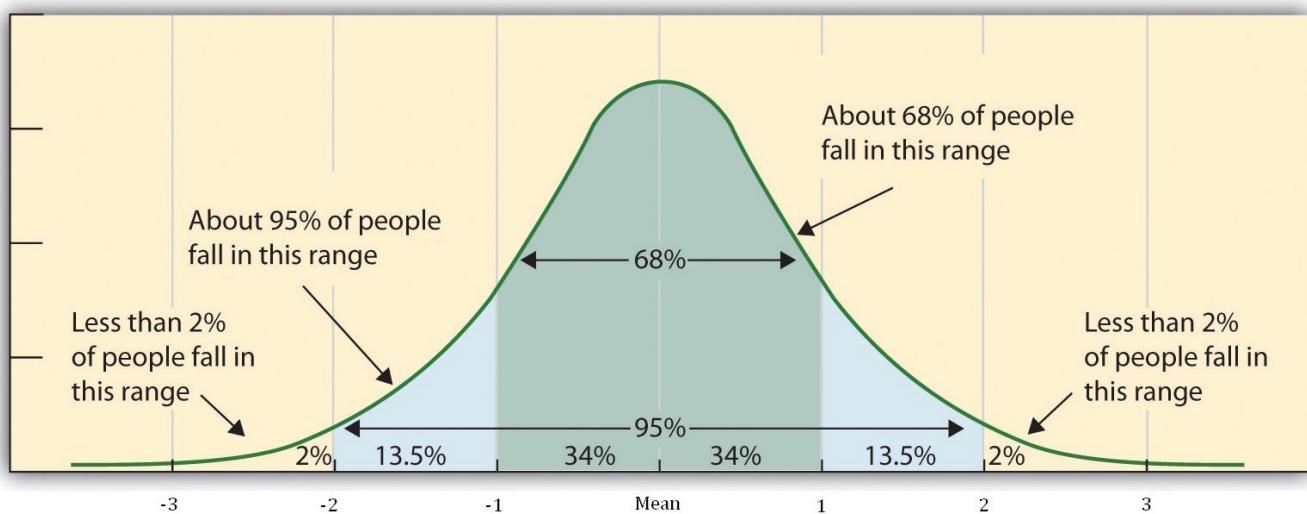


Fig 1. Sufficiently large samples of parameters with well-defined expected values and variance, including at psychometrics, tend to the Gaussian distribution, also known as bell curve. Central limit theorem. Horizontal axis, standard deviation.

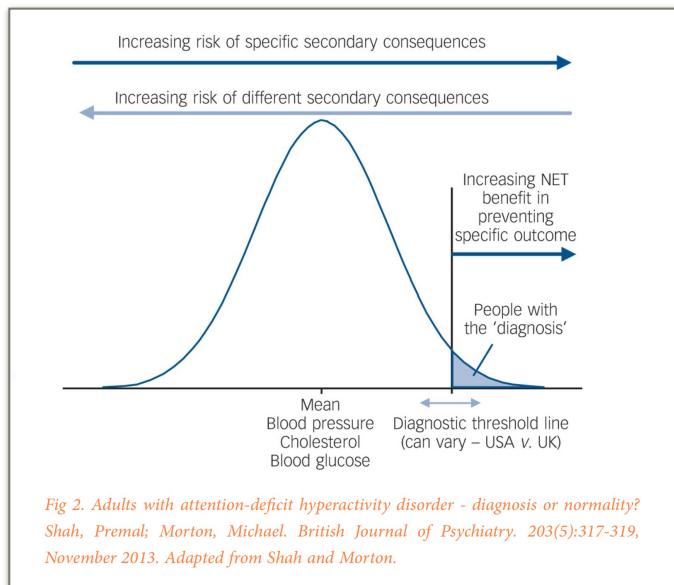
How is this possible? This is not adult ADD, because the diagnosis is supposed to reflect persistence of childhood ADD, but this group did not have childhood ADD, and yet it is almost twice as large as the prevalence claimed in the

some are hyper focused in attention, some are distractible. 4-5% in fact.

So what is “adult ADD”? Could it just be the extreme of the psychological trait of attention, which is not a bad thing.

Too much attention disorder

If we think about attention as a cognitive trait with a normal curve, you might ask the question: Are we humans supposed to be highly attentive? Nature seems to have evolved in such a way that many of the “symptoms” which we treat are in fact quite normal when present to a mild to moderate degree. It’s normal to be somewhat anxious. It’s normal at times to be sad. It’s normal even to be somewhat illogical in our thought processes. These are all proven to be common traits in the normal population. All are distributed as in an inverted U-shaped curve. What about attention? Is it normal to be a little inattentive?



Of course it is. What would life be like if you focused on every little thing that crossed your mind? You would have this idea, then that, then another; you would focus on one, then the other, then the next. It is normal to filter sensations and thoughts, and focus on some but not others. Inattention is normal. When we have no filter, and attend too much to all our thoughts and feelings, we are psychotic. That is the nature of the thought disorder of schizophrenia. It is not an accident that amphetamines are used as an animal model of psychosis. Too much attention is psychotic. That’s why we are selected to be normally inattentive. And some people are more inattentive than others. That is expected for any

normal psychological trait. It’s not a disease; it’s an extreme of a natural trait.

One might say that even if this is the case, inattention should be treated if it is causing functional impairment. This may be defensible, or perhaps not. We treat the extreme of the normal trait of blood pressure, but not because it causes functional impairment. In fact, it is

famous for having no symptoms at all, for being “silent”. We treat high blood pressure because it later causes certain diseases, like coronary artery disease or stroke. What future diseases does inattention cause? None that we know of.

Still, one might argue for treatment for current functional

impairment. But as discussed the last PL issue’s Classic Study of the Month (the MTA study), even if this is the case, non-medication treatments are as effective as medication treatments for functional improvement of ADD.

A final comment: In the 33 year prospective study, 78% of subjects with childhood ADD were no longer diagnosable with it as adults. Again, the older literature seems closer to the truth that the majority of children with ADD (about 80% in this study) will not have it as adults. Clinicians need not feel impelled, as is the case these days, to continue amphetamine medications long-term for decades and decades, on the assumption that once the ADD diagnosis is made, then long-term treatment is entailed.

Mood temperaments

A final important clinical consideration in analyzing apparent adult ADD is the concept of mood temperaments.

This concept is highly under appreciated in contemporary psychiatry. The terms dysthymia and cyclothymia are in DSM, and are thus known, but they are misused or not used at all. Most commonly, dysthymia is used as a “comorbidity” along with MDD or other conditions. In contrast, cyclothymia is not used as a comorbidity, but is thought to be exclusive of the diagnoses of MDD or bipolar illness.

The mood temperament of “hyperthymia”, or mild constant manic symptoms, is not known by most clinicians, mainly because it is not included in DSM. All three terms, described in more detail in the PL website, were originally developed about 100 years ago by Kahlbaum and Kraepelin, and later expanded by Ernst Kretschmer, to reflect biological and genetic variants of the diseases of severe depression or manic-depression. They were present as mild forms of those diseases in relatives of persons who had the full disease. In many persons with the full disease states, those mood temperaments also were present in between the clinical episodes of depression or mania. In other words, they are not comorbidities because mood temperaments are not diseases in themselves; they are personality traits in persons, or their relatives, who have mood diseases.

If you are depressed all the time mildly, or manic all the time mildly, or back and forth between mild depression and mild mania all the time, you will not have good concentration. This is because concentration is impaired in both manic and depressive states.

Hence it is commonly the case that adult ADD is mistakenly diagnosed in persons with hyperthymic personality, or cyclothymic personality, or dysthymia. The affective symptoms are chronic, and hence the attentional impairment is constant. But the causal source may be the affective temperament, not a separate disease of adult ADD. The PL experience is that these patients improve in their affective symptoms, including inattention, with low-dose mood stabilizers whereas amphetamines either provide only partial or inconsistent benefit.

The PL Bottom Line

- Adult ADD likely reflects an extreme of the natural trait of attention.
- The best evidence that adult ADD is not likely to be a valid independent disease entity is that it almost always occurs with mood illnesses, which themselves cause inattention.
- In the longest follow up into middle age, similar inattention is seen in adults without past ADD as in adults with childhood ADD.
- Apparent adult ADD often reflects mood temperaments, like hyperthymia and cyclothymia.

Further reading

Much of the material presented here is discussed in detail with full citations in D Vergne et al, Adult ADHD and amphetamines: A new paradigm. *Acta Neuropsychiatrica*, 2011, 1: 591-598.

Classic study of the month

A widely-cited study doesn't show what the authors claim

Patterns and Predictors of Attention-Deficit/Hyperactivity Disorder Persistence into Adulthood: Results from the National Comorbidity Survey Replication. R. C. Kessler et al, Biological Psychiatry 2005;57:1442-1451

Most adult ADD represents mood diagnoses

Recently one of the authors of this paper gave a talk about ADD in which he cited this study to support the validity of adult ADD. This paper is an analysis of the National Comorbidity Survey (NCS) epidemiological study. In the NCS project, researchers knocked on doors all across the United States to identify the frequency of various DSM-based psychiatric diagnoses. This is the study that is used for basic citation of frequency of many diagnoses. In this analysis, the NCS lead researchers collaborated with ADD experts to identify the frequency of ADD diagnosis in the young to middle age adult population of the US, based on a sample of 3197 subjects, aged 18-44.

Overall, they found that ADD was diagnosable in 3% of this general population sample. This was defined as persistence of childhood ADD. To clarify, 8.1% of the NCS adult sample was identified as having been diagnosable retrospectively with childhood ADD. Of this group, ADD persisted into adulthood in 36.3%. So the overall adult prevalence rate was 2.94%.

This study is the basis for many claims. One is the idea that ADD is common in adults, happening in about 3% of the general population. Further, it supports the claim that ADD persists in a substantial portion of children into adulthood, namely about one-third of persons.

Note that if we take these results at face value, one could turn the interpretation around and conclude that most children - namely 2/3 - with

ADD will *not* have persistence into adulthood. These days, many clinicians practice as if the majority, or almost all, cases of ADD in children or adolescents will persist into adulthood. It is routine practice to continue amphetamines for childhood ADD into young adulthood. Once the growing child enters college, amphetamines are not stopped. They often are continued well past college, into the decade of the 20s. Yet, this study, so often cited by supporters of the adult ADD diagnosis, shows that the reverse should be the case: In 2/3 of children and adolescents, amphetamines should be stopped before they reach the age of 18, if such treatment is based on the claim that they will continue to meet the diagnostic definition of adult ADD.

The most important finding in this NCS analysis, though, is one that the authors don't emphasize. The researchers looked at "comorbidities" of adult ADD, based on the careful identification of other DSM diagnoses, which was the main purpose of the NCS epidemiological study.

In this analysis of comorbidities, the NCS study found that persons diagnosable with adult ADD could also be diagnosed at the same time with the following diagnoses in the percentages provided in Table 3 of the paper (page 1447):

Major depressive disorder - 39.2%

Bipolar disorder - 44.9%

Dysthymia - 56.4%

The absolute frequency of these diagnoses was 15.0% for MDD, 10.4% for bipolar disorder, and 7.6% for dysthymia.

We will put off the discussion of dysthymia for now, for later discussion in this article on the subject of mood temperaments. It is notable, though, that over one-half of all cases of apparent adult ADD involved the mood temperament of dysthymia. Since depressive symptoms include poor concentration, this "comorbidity" becomes a major logical problem. How can you say that people have a chronic cognitive condition of poor attention (the claim of adult ADD) when they have another chronic cognitive condition of poor attention (dysthymia)?

Turning to other conditions among the adult ADD subjects, there were high rates of other diagnoses, as well, especially anxiety disorders (49.9%, post-traumatic stress disorder, PTSD; 34.4% generalized anxiety disorder, GAD) and substance abuse (40.2% alcohol abuse, 31.4% other drug abuse).

Now one can certainly claim, as the authors do, that these are "associations" with adult ADD; namely, that if you have the adult ADD diagnosis, you'll also run into other problems, such as abusing drugs or alcohol. This is not unreasonable; the same interpretation exists with mood illness, for instance, where many patients abuse substances as a result of having mood illness (often as self-medication).

In the list of comorbidities, many overlap with each other; for instance, one can have PTSD and also meet criteria for GAD and dysthymia. But two diagnoses are exclusive; you cannot make one

if the other is present: MDD and bipolar disorder.

If we look at those two exclusive mood diagnoses, MDD was present in about 39% and bipolar disorder was present in about 45%. Since they are mutually exclusive, this means that a total of 84% of all subjects with adult ADD also met criteria for either MDD or bipolar disorder.

Now, here is the key question: Is this a mere association?

There are three possibilities: 1) there is no such thing as adult ADD: almost all the time (84% of cases), it is caused by depression or mania; 2) adult ADD causes depression or mania almost all the time (84% of cases); 3) adult ADD cases are unlucky; almost every time they get the ADD diagnosis (84% of cases), they also get an independent and unrelated disease of depression or mania.

The third possibility is biologically implausible. Nature doesn't tend to give two diseases every time to patients who are unlucky enough to get one disease. You don't get diabetes 84% of the time that you get diagnosed with cancer.

That leaves the other two causal possibilities: either the mood illnesses cause apparent "adult ADD", or adult ADD causes the apparent mood illnesses.

The last claim is made by ADD experts, when pressed on this issue. Adult ADD is such a terrible experience, they claim, that patients become depressed a lot, hence the 39% prevalence of apparent MDD. They also become quite anxious about half the time, and have terrible life experiences, hence the 34-50% prevalence of GAD and PTSD.

Adult ADD explains almost everything - except...

There is a deep flaw in this rationale: ADD proponents cannot claim that adult ADD causes mania. They cannot explain away the 45% prevalence of bipolar illness, which means that those subjects experienced manic or hypomanic episodes. There is no biological or clinical rationale that can claim that adult ADD causes manic or hypomanic episodes.

This leaves only one other possibility. Even if interpreted mostly charitably, about one-half of apparent cases of adult ADD likely represent manic or hypomanic episodes, i.e., bipolar illness.

It is well known that depression and anxiety both are mental states that impair concentration and cognitive function. Thus, if we allow that at least some of those apparent cases of ADD were caused by anxiety or depressive illnesses, as opposed to the reverse, then we can make the following claim: Almost half of all cases apparent adult ADD are caused by bipolar illness, and another subgroup are caused by depressive and anxiety illnesses.

This analysis would lead to a conservative interpretation that the majority of cases of claimed adult ADD are caused by either bipolar or depressive or anxiety illnesses.

In other words, the 3% prevalence rate of adult ADD is not what it seems. Independent adult ADD, not attributable to another psychiatric cause, would be a minority of that 3% prevalence, perhaps about 1/3 or so, leading to about a 1% true adult ADD prevalence rate.

This 1% or so rate would be consistent with the concept of an extreme of a normal trait. As noted

in the special article, attention is a normal cognitive trait, which, like most physical traits, is distributed on a statistical normal curve. This means that 95% of observations occur within 2 standard deviations in either direction from the 50th percentile. In other words 2.5% of the population will be at one extreme or the other. 1% would be observed at over 2 standard deviations from the mean. This observation would be expected with any normal trait; it doesn't reflect a disease process necessarily.

"This analysis would lead to a conservative interpretation that the majority of cases of claimed adult ADD are caused by either bipolar or depressive or anxiety illnesses."

One could take another view. If we accept that anxiety and depressive states cause inattention and cognitive impairment, and we consider those conditions as primary to apparent ADD, then we could say that almost all cases of apparent adult ADD reflect either bipolar illness, depression, or anxiety conditions.

In this latter interpretation, adult ADD more or less disappears as a concept.

When the PL editor raised the bipolar "comorbidity" aspect of the NCS study with one of the NCS authors recently, the NCS author wasn't even willing to admit the 45% comorbidity rate. This reaction is an example of how human beings ignore data that conflict with their beliefs.

The PL Bottom Line

- About one-half of adult ADD involves co-occurrence with manic/hypomanic states.
- About 84% of all cases of adult ADD co-occur with either mania or depression.
- About one-third to one half of cases of adult ADD involve co-occurrence of anxiety conditions (PTSD or GAD).

- The most plausible explanation of these apparent “comorbidities” is that at least half, and probably the majority, of cases of apparent adult ADD in fact reflect cognitive symptoms of bipolar illness and/or depressive or anxiety states.
- Over one-half of apparent adult ADD cases occurred in persons with dysthymia, another chronic condition associated with attentional impairment.

- In short, the claim of an independent ADD disease is not supported by the many other conditions documented in the NCS study which cause attentional impairment.

PL Reflection

I believe we may safely affirm, that the inexperienced and presumptuous band of medical tyros, let loose upon the world, destroys more of human life in one year, than all the Robinhoods, Cartouches and Mccheaths do in a century....I wish to see a reform, an abandonment of hypothesis for sober facts, the first degree of value set on clinical observation, and the lowest on visionary theories.

*Thomas Jefferson
letter to Dr Caspar Wistar
1807*

Clinical Tip of the Month:

Diagnose the causes of attentional impairment, not adult ADD

When faced with a case of apparent adult ADD, either diagnosed by others or self-diagnosed by the patient, apply the concept of a diagnostic hierarchy. Is a mood illness - a clinical depressive or manic/hypomanic episode - present? If so treat it directly, with a mood stabilizer or monoamine agonist (antidepressant), and see if the attentional symptoms improve. If a mood illness is not present, see if an anxiety condition is present, most commonly “generalized anxiety” or obsessive-compulsive disease. If present, treat them with anxiolytics, and see if the attentional symptoms improve. If neither mood or anxiety conditions are present, see if a mood temperament is present: dysthymia, cyclothymia, or hyperthymia (mild manic symptoms as part of temperament, see PL website). If they are present, treat with low doses of mood stabilizers or monoamine agonists, and see if attentional symptoms improve. If the above differential diagnosis is applied, very few if any patients will remain who could be claimed to have adult ADD. With the above approach, amphetamines would rarely, if ever, be justified for the sole purpose of treating attentional symptoms occurring in the absence of any other possible causal condition.

Drug of the Month: *Atomoxetine*

An antidepressant masquerading as an ADD drug

This medication is a norepinephrine reuptake inhibitor, initially developed as an antidepressant. It was brought to the market as the first drug for adult ADD, rather than one of the last for depression. It differs notably from other “stimulants” though in its mechanism and risks.

Clinical efficacy and inefficacy

In early clinical trials, this agent was found to be effective in major depressive episodes. It was noted that it shared

its basic mechanism of pure norepinephrine effects with desipramine, which had been proven effective in childhood ADD. Eli Lilly, the company which was developing atomoxetine, made an economic decision to shift to ADD, rather than major depressive disorder (MDD), but even in ADD, there were multiple other agents, mostly amphetamines, that were FDA-indicated in children. However, no agents were FDA-indicated in adults for ADD. Indeed, the whole concept of adult ADD was not used much, and it was not part of DSM-IV.

After obtaining academic support, Eli Lilly convinced the FDA to provide the first indication for ADD in adults. The latter designation was then added to DSM-5.

Biological mechanism

Atomoxetine blocks reuptake of norepinephrine at the synapse. Unlike other “stimulants” it does not have direct or indirect agonism of dopamine activity.

Side effects and dosing

The main side effect of this agent, as with the other pure noradrenergic drug desipramine, is anxiety and feeling agitated or overstimulated.

Desipramine, which is a tricyclic antidepressant, was also associated with cardiac arrhythmias, but this has not been the case with atomoxetine.

Fast Facts: Atomoxetine (Strattera)

Typical dose: 40-80 mg/d (range: 10-100 mg/d)

Biological mechanism: Norepinephrine reuptake inhibitor

Typical side effects: anxiety, insomnia

Less common but important side effects: none

Medically important side effects: none

Clinically proven efficacy: Treatment of major depressive episodes and ADD

The clinical trials with atomoxetine showed some cases of increased suicidal thoughts with this agent, versus no cases with placebo, which led to a FDA black-box warning in 2005.

The PL Bottom Line

- Atomoxetine is an antidepressant masquerading as a “stimulant” for adult ADD.
- It is a norepinephrine reuptake inhibitor, like desipramine, which tends to cause anxiety.

PL Reflection

And what goal could be more sacred than that of caring for a brother in distress, especially when the affliction is distinctly human and therefore more obvious than others, and when it respects neither reason nor rank nor riches?

Emil Kraepelin

Case of the month:

Not ADD, not chronic fatigue, not “depression”

A 23 year-old female seeks consultation for unremitting depression and ADD. She had been first diagnosed at age 15 with chronic fatigue syndrome. A medical workup for possible causes of exhaustion was negative. Eventually her doctors decided to treat her with amphetamine stimulants to give her energy. Since age 16, she has taken one amphetamine or another, beginning with methylphenidate, later Concerta, and later Adderall.

In the past year, she began to see psychiatrists, who changed her diagnosis from chronic fatigue syndrome to major depressive disorder. They continued Adderall and added various serotonin reuptake inhibitors (duloxetine, fluoxetine, sertraline) without success. She was changed eventually to bupropion.

On evaluation, she was taking Adderall 20 mg twice daily plus bupropion SR 150 mg twice daily.

Besides exhaustion, her parents report that she has marked insomnia and notable cognitive impairment. Her sleep is quite poor: she stays up very late, and has multiple awakenings in the night, followed by tiredness during the day. Her cognition is poor also, with very impaired working and verbal and short term memory. She has been slowed down in her college studies to the point that despite 5 years of college, she has only completed her sophomore year. She has a great deal of trouble organizing herself for her college work and paying attention in class and in memorizing material for tests.

Adderall gives her “30 minutes glimpses of normality”. After she takes the medication, she

reports that she feels “like myself” for about half an hour, with improved concentration and energy and mood, but then she goes back into her usual depressed, low energy, poor concentration state.

She has these depressive symptoms continually, but 2-3 times per week, she has about 1-2 hours of spontaneous high energy states: “I feel elated, happy, like I can convince anyone to do anything. I try to do things, but it doesn’t last long enough for me to do anything. My thoughts go fast, I talk a lot, I feel super smart briefly, and then I’m back to my usual unhappy slowed down state.”

She reports repeated suicidal thoughts and wishes she was dead, but she has not tried to harm herself.

She and her family deny past manic or hypomanic episodes lasting 4 days or longer.

One psychiatrist suggested that she had type II bipolar illness, but he continued Adderall and added lithium 900 mg/d immediately. She stopped lithium after two days due to heart palpitations.

Family history provides evidence for a paternal aunt with severe depression that required ECT. All other illness is denied.

Medical history is otherwise normal and she has no drug allergies, nor does she abuse alcohol or drugs. She has no trauma history. She has had no psychiatric hospitalizations or suicide attempts or self-harm or dissociative or psychotic states, and no eating disorder symptoms.

The PL diagnosis is that she is experiencing current mixed depressive states, as described in the PL February 2015 issue. The broader

diagnosis is manic-depressive illness, or one might use the term bipolar spectrum illness. These diagnoses reflect brief manic states that occur as part of recurrent depressive episodes. The illness is not pure depression, since manic symptoms are present, nor does it represent classic bipolar illness, since full manic or hypomanic episodes are not present. Hence the concept of bipolar spectrum illness can be used to reflect being in the middle of the spectrum between pure depression and full manic or hypomanic episodes.

The PL recommendation was to taper off Adderall and bupropion and to resume lithium again, this time in slow titration and in the absence of any antidepressants/amphetamines. This recommendation is explained below:

Readers should keep in mind that all amphetamines are antidepressants. They were introduced as the first class of antidepressants in the 1930s. Thus, like all antidepressants, they can have negative effects in bipolar illness of causing/worsening mania, or causing/worsening long-term rapid-cycling. In the case of mixed depression, as discussed on the PL website and in the February 2015 issue, antidepressants seem to worsen mixed states, thus causing more depressive and manic symptoms. They especially seem to worsen suicidality and impulsivity. In an analysis of mixed depression as described by Koukopoulos, antidepressants caused three times more suicide attempts in person with mixed depression when compared with those treated without antidepressants.

Further, as mood-destabilizing agents, amphetamines and antidepressants counteract the benefits of mood stabilizers, like lithium. Thus, it is not enough to just add lithium. Adderall and bupropion need to be stopped also. Further,

readers will recall that bupropion is an amphetamine in its pharmacological structure - all the more reason to stop it.

This patient's apparent "adult ADD" had not improved with amphetamines because it was driven by her mixed depression. Until the mixed depression improves, the "ADD" will not improve. Since amphetamines worsen mixed depression, cognitive ADD-like symptoms persist.

Lithium is the best agent to choose partly because of its direct suicide prevention benefit, given that this patient has clear suicidal ideation and notable risk for suicide.

Specific PL recommendations were as follows:

Reduce Adderall to 20 mg daily for 2 weeks, then 20 mg every other day for 2 weeks, then stopped. Reduce bupropion to 150 mg daily for 2 weeks, then stopped. At the same time, begin lithium at 300 mg at night for 1 week, then 600 mg at night for one week, then 900 mg at night, seeking a level close to 0.8. The PL expectation would be that the patient would get worse before getting better, with amphetamine withdrawal leading to worsened energy and concentration and possible clinical depression. This could be the course for a few months, but then the patient would be expected to improve gradually on lithium alone, possibly with later combination with dopamine blockers and/or other mood-stabilizing anticonvulsants such as lamotrigine.

PL Reflection

Nearly all men die of their treatments, not their diseases.

Moliere (1673)

Curbside consults:*Questions from you*

Question: What are your thoughts on the common combination of amphetamines and benzodiazepines? This is so very common and even worse in patients with substance abuse.

PL: This common combination makes sense, in a rather absurd way. Amphetamines cause anxiety, which is then treated with benzodiazepines. Another relevant reason for the combination is that anxiety states, as discussed above, often cause impaired concentration. Such patients then get mistakenly diagnosed with adult ADD, and treated with amphetamines, which worsen the underlying anxiety that caused the inattention to begin with, hence the addition of benzodiazepines. In short, the effect is mistaken for the cause, and inattention is treated with amphetamines which worsen the causal anxiety, leading to further treatment with benzodiazepines.

Both classes of agents are addictive potentially, but at least in animal models, amphetamines appear to produce more addictive behavior than benzodiazepines. Certainly the former have more evidence of neurotoxicity harm, as reviewed in last month's PL issue, than the latter.

Thus, the PL perspective is that if a patient has an anxiety condition, that is not due to some other diagnosis like a mood illness, then it is reasonable to treat that anxiety condition with benzodiazepines. If such anxiety states cause poor concentration, then those inattention symptoms should improve with benzodiazepines alone, without the need to add amphetamines. The use of amphetamines in persons with anxiety conditions is self-defeating, as is the case with using those agents in bipolar illness. Amphetamines worsen anxiety and manic states, hence they worsen anxiety and bipolar illnesses. The only condition which they do not worsen is pure depression, where they had been used for years as primary antidepressants.

As reviewed in the classic article above, it is reasonable to conclude that most apparent cases of adult ADD in fact represent inattention symptoms caused by other diseases, most commonly bipolar illness, but also anxiety conditions. Thus, if anxiety diagnoses are made, the PL recommendation is that adult ADD should not be diagnosed, and the anxiety condition be treated, with benzodiazepines or in some cases with serotonin reuptake inhibitors. In most cases, attentional symptoms then resolve with treatment of the underlying cause, without ever needing to use amphetamines.

PL Reflection

The young physician starts life with twenty drugs for each disease, and the old physician ends life with one drug for twenty diseases.

William Osler

Historical insights

Emil Kraepelin looks back at the prior 100 years of psychiatry in 1917.

Compare his observations with the next 100 years.

If we compare the situation of mental patients today with the circumstances that prevailed a century ago, the revolution that has been accomplished comes into clear focus....One by one prejudices have been overcome, abuses and cruel practices eliminated, new means found to alleviate mental diseases. Spearheading this advance was the growing body of scientific knowledge relating to the nature and etiology of insanity and deriving from study of data in different fields of investigation and from overall progress of the science of medicine. Unrelenting effort on the part of a large number of alienists gradually transformed the sad lot of the mentally ill, with the result that today we are actually nearing the end of our struggle. To be sure there are still many defects to be remedied and improvements to be made, but we are not being presumptuous in stating that we have discovered the approach to be followed henceforth in psychiatry.

Our satisfaction over the progress already made is tinged with regret. When we consider the extraordinary sacrifices made by those responsible for the evolution of psychiatry, we are constrained to lament the fact that all the hopes tied to it can never be fulfilled. We must openly admit that the vast majority of patients placed in our institutions are according to what we know forever lost, that even the best of care can never restore them to

perfect health. Our treatment probably makes life endurable for a vast number of mental cripples whose plight would otherwise be intolerable, but only rarely does it effect a cure....

We must therefore ask if there are other, more promising, approaches. The answer is a resounding yes. Most promising is the prevention of insanity... The nature of most mental disorders is now obscured. But no one will deny that further research will uncover new facts in so young a science as ours; in this respect the diseases produced by syphilis are an object lesson. It is logical to assume that we shall succeed in uncovering the causes of many other types of insanity that can be prevented - perhaps even cured - though at present we have not the slightest clue; a case in point was cretinism before the discovery of the thyroid treatment....

The great war in which we are now engaged has compelled us to recognize the fact that science can forge for us a host of effective weapons for use against a hostile world. Should it be otherwise if we are fighting an internal enemy seeking to destroy the very fabric of our existence?

PL comment: Kraepelin, a great late 19th century psychiatric leader, identified the basic distinction between schizophrenia (dementia praecox) and manic-depressive illness. These are his reflections near the end of his career, in 1917. Emil Kraepelin, One Hundred Years of Psychiatry, NY, Citadel Press, 1962, pp 150-152.

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THE PSYCHIATRY LETTER

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The End of the Beginning

This issue represents the end of the first year of the existence of this newsletter. We would like to thank you who are reading these lines in the weeks after its publication because you have been a loyal and sympathetic audience for this effort.

This newsletter has gone from crawling to walking and we hope to see it off and running into the future. We hope you stay with it into its second year of existence and beyond.

As noted in the last issue, an exciting aspect to this second year of life for PL is the ability to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to our readers. This will apply to psychiatrists and nurses and psychologists. Our next step will be to obtain CEU accreditation for social workers; we will notify you when we have obtained such accreditation.

In honor of the first year anniversary of the newsletter, which coincides with the end of the old year and the birth of a new year, the December newsletter is a special issue with a Top Ten list of events, studies, and topics in psychiatry in the past year.

In the next issue, January 2016, we will return to our usual format, with, for the first time, CME/CEU credit availability. We hope you take advantage of those credits for your needs.

If you find PL helpful to you and your patients, please let others know so that more clinicians and patients may benefit.

Happy new year to you and yours,

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article I: Top Ten List of 2015

Our review of key topics in psychiatry this year

The New Year reviving old Desires
The thoughtful Soul to solitude retires
Where Jesus upon the Bough puts out
And Moses from the Ground suspires.
Omar Khayyam (adapted by Edward Fitzgerald)

What's important?

At the beginning of a new year, and the end of an old, PL turns to the tradition of thinking about what happened in the past year and identifying the most important topics or debates or studies in the mental health professions. In so doing, PL defines what is important not necessarily as what is right or what PL thinks matters, but rather what has been in public discussion. In this review, PL provides its perspective frankly, not necessarily with all the evidence for its conclusions. On the PL website and in PL issues cited, relevant links are provided to articles which provide further elaboration.

Number 10: How effective is ketamine?

Recently, many clinicians have been swept away with enthusiasm for ketamine, a NMDA receptor antagonist. This drug, which is mainly used in intravenous form, had been part of traditional anesthesia treatments for many years. When given to patients with treatment-resistant depression (TRD) or bipolar depression, some small randomized trials have reported benefit for the acute clinical depressive episode. The main claim was that IV ketamine produced "rapid" response within days to weeks, unlike traditional oral monoamine agonists, which require weeks to months for efficacy.

....Ketamine is addictive in animal studies. It also is neurotoxic, causing neuronal cell death in animal studies."

To PL, this "rapidity" of response is uninteresting. The problem in the treatment of the vast majority of patients with depressive conditions is not that response is too slow; the main problem is that response occurs acutely but is not maintained for the long-term. (See the PL website for a discussion of the STAR*D study which is the basis for this judgment). There is NO evidence of any long-term benefit with ketamine, and certainly not in randomized comparison to other proven effective alternatives like lithium.

Thus, the PL view is that ketamine is much ado about nothing.

Many are beginning to identify and decry the rise of "ketamine clinics", often staffed by physicians who are not mental health professionals, with profits from out of pocket payment by patients.

Even if ketamine worked in any important manner, its intravenous use would hamper its practical utility. Some clinicians have taken to intramuscular or even intranasal administration. These uses are unproven.

A final point: Ketamine is addictive in animal studies. It also is neurotoxic, causing neuronal cell death in animal studies. Human studies are few in number, varied in result, and do not outweigh the animal data.

It is understandable that many patients and clinicians want a simple solution to a complex problem. The problem: Many patients with DSM-defined "major depressive disorder" (MDD) do not respond to standard "antidepressants." The simplistic solution: Get a better antidepressant.

The alternative solution: Get a better diagnosis than MDD, which is unscientific in its core, as discussed on the PL website, and then we might find that many of our available drugs can work quite well, short and long-term, for more scientifically valid definitions of depressive conditions.

As for ketamine: It is likely that it sounds too good to be true because it is.

Number 9: Do benzodiazepines cause dementia?

A study in the past year reported that benzodiazepines were associated with increased risk of dementia. As reviewed in the May 2015 PL issue, this conclusion is not definitive since the study was observational, not randomized. Thus, many confounding factors could have influenced the result. The study controlled for many of those confounding factors but it could not control for all of them. The interpretation is less straightforward when we add in the fact that a number of animal studies show the opposite, namely that benzodiazepines are neuroprotective and keep neurons alive longer.

The PL verdict: Clinicians need not make major decisions yet on whether or not to use benzodiazepines, especially in older persons, on this possible association.

Number 8: How can we stop suicide in soldiers?

It is now a well known statistic. Every hour, a US soldier back in civilian life kills himself. Why is this happening? How can we stop it? A number of major Veterans Administration funded studies have looked at this matter, one of which was reviewed in the August 2015 PL issue. Obviously

PTSD is the main culprit, but associated factors are present which increase the risk of suicide in some veterans versus others. The fact that veterans have been trained to kill and are expert with firearms certainly is a key general risk factor.

In the larger literature on PTSD, PL emphasizes the importance of personality traits, factors which are present in individuals before, during, and after war-related trauma. Depressive and anxiety traits increase the risk of PTSD; manic traits decrease the risk of PTSD. Thus, if soldiers have dysthymia or high neuroticism as part of their personality, before going to combat, they are more likely to have severe PTSD upon their return. In contrast, those with hyperthymic temperament are less likely to have severe PTSD upon return.

How is this relevant to preventing suicide in veterans?

"Lithium is the only drug proven to prevent suicide."

One aspect would be more attention to affective temperament in the screening of civilians who want to enter the military. Currently, systematic assessment of affective temperament does not occur in psychiatric evaluations of those entering the military.

Number 7: Use lithium to prevent military suicide

Another important solution to this devastating problem of veteran suicide deserves its own separate place on the Top Ten list. This topic has been ignored by policymakers: Lithium is the only drug proven to prevent suicide. It should be given more widely to veterans with suicidal ideation. It can be effective for suicide prevention even in low doses, according to some data, like 300 mg/d or even less. Thus, it can be given in tolerable dosing to almost anyone.

PL has come to this conclusion regarding lithium for suicide prevention: There is no minimum effective dose. Thus almost everyone should be able to take it.

Number 6: Diabetes is a major risk factor for dementia.

Recent studies have found a strong correlation between diabetes and dementia, with more than a doubling of risk. This kind of effect has also been found in the past with depression as a risk factor for dementia.

These observations are clinically important. Clinicians frequently give olanzapine or quetiapine, the most common dopamine blockers that cause diabetes, to middle aged persons, who enter their 50s and 60s with increasing risk of dementia. The iatrogenic causation of diabetes with these agents will multiply the long-term risk of dementia in such persons.

Often those agents are used to treat depressive symptoms, but other dopamine blockers, like aripiprazole and ziprasidone, can do so without risk of causing diabetes.

Number 5: Should we be more active in diagnosing and treating adult ADD and binge eating disorder and DMDD?

Here PL lumps together a number of invented DSM-5 diagnoses, which have been reviewed in prior issues on the PL website. The PL judgment is that these purported diagnoses have little to no scientific validity, and thus their diagnosis and treatment is not a scientifically meaningful process. Readers will note that the treatments for adult ADD and binge eating disorder mostly involve amphetamines, which provide symptomatic benefit in both cases but this benefit also occurs in normal populations (everyone

concentrates more and eats less with amphetamines). Hence such "benefit" does not imply diagnostic validity. As reviewed in detail in the October 2015 PL issue, and on the PL website, amphetamines also are harmful with neurotoxicity, meaning causing neuronal death, in animal studies, without clear confirmation or refutation in the limited available human studies.

Regarding dysphoric mood dysregulation disorder (DMDD), a publication after DSM-5 noted that there had never been any study of its prevalence or diagnostic validity or treatment. The concept was invented to discourage clinicians from diagnosing bipolar illness in children. Separately from where readers stand on whether and how bipolar illness should be diagnosed in children, PL feels that it is not a scientific process to invent one purported diagnosis to prevent clinicians from making another one. Future issues will address the controversial topic of childhood bipolar illness.

"Be cautious about all dopamine blockers and neurotoxicity"

Number 4: Do antipsychotics harm the brain?

Yes, they do, according to human studies in the past few years. Those studies mostly involve traditional dopamine blockers, like haloperidol, and many experts state or assume that new dopamine blockers will not have that risk. They often cite animal studies which report neuroprotection with newer dopamine blockers. Those animal studies often are conducted by the pharmaceutical companies that produce those agents. Because of the problem of non publication of negative studies, we cannot know how many animal studies have been conducted by pharmaceutical companies which show neurotoxicity with their dopamine blockers. They are under no obligation to publish those studies.

The PL verdict: Be cautious about all dopamine blockers and neurotoxicity. The older ones now are known to cause that effect, the newer ones have neither been proven nor disproven to do so.

Is this a reason NOT to prescribe dopamine blockers? No. Even with the older agents, the chronic psychotic illness of schizophrenia was associated with more neuronal damage than was associated with the dopamine blockers. In other words, the drugs are harmful somewhat to the brain, but the disease is even more harmful.

Number 3: Do antidepressants work?

As reviewed in detail in PL website, the PL verdict is as follows:

Antidepressants work. MDD doesn't work.

The problem is not that "antidepressants" don't work in general, or are marginally better than placebo in general, which is what the anti-psychiatric critics claim. The issue is not a general one at all. The important factor is that antidepressants work better for certain kinds of depressive presentations, and less for other ones. This is because MDD is a mixture of many kinds of depressive conditions, and when we lump together the higher and lower amounts of antidepressant benefits for the many depressive conditions mixed up in MDD, we get a "marginal" overall effect, which is clinically meaningless. What is important clinically is to better identify depressive conditions so that we can target antidepressants more effectively.

As reviewed in February 2015 PL issue, monoamine agonists (a better term than antidepressants) are NOT effective in mixed depression, and are less effective in melancholic depression. They are effective in neurotic

depression, but not more so than placebo. In other words, those patients always improve to some extent, whether or not they receive monoamine agonists. These medications are effective acutely in depression that is not mixed, not melancholic, and not neurotic, in other words, in fewer cases than are commonly assumed. Long-term preventive efficacy also is less well-established than is appreciated by many clinicians. Future PL issues will examine the STAR*D study and other data to explicate this topic.

Number 2: Light boxes aren't just for winter.

A fascinating randomized trial found that the use of a light box was effective for the acute depressive episode in persons who did NOT have seasonal depression. In fact, light box treatment was more effective than fluoxetine (Prozac) acutely. This finding raises the new possibility that light boxes could be used for acute depression treatment even outside of classic fall/winter depression. PL urges caution with the fact that if used in the spring and summer, in susceptible persons, light box therapy can cause mania, like any antidepressant treatment.

"What is important clinically is to better identify depressive conditions so that we can target antidepressants more effectively."

Number 1: Should we be excited about the human genome project and genetics?

"Personalized medicine" is the slogan of current health care policy. Everyone is talking about it. In medicine, uses are focused mostly on oncology, which we can hope will produce more effective treatments. The question has been raised whether this research is able to produce any benefit in psychiatric conditions, with most focus being on schizophrenia and bipolar illness and

“MDD”. Many experts and clinicians are hopeful for a pharmacogenetics breakthrough.

Miracles have long been awaited in our field, as the historical insights section below will remind us. This is not to say that this work in pharmacogenomics isn't useful, but only to say that we should be cautiously optimistic.

The PL concern regarding MDD returns to the problem of DSM-5; if the diagnosis is based on social and professional judgments, not scientific ones, we can't expect genetics to follow the profession's lead.

So far, a few disease genes have been replicated in schizophrenia and bipolar illness. Little progress has occurred with MDD, which PL would expect to be the case.

Treatment predictor genes may have some promise, if disease states are identified more validly. PL hopes that future research will produce such genetic predictors. So far, none are on the horizon, but we will keep our eyes open in the new year and years to come for any future advances.

The PL Bottom Line for 2015

- Ketamine probably is not going to prove to be clinically useful.

- Diabetes is a major preventable cause of dementia, especially when related to some antipsychotics.
- Benzodiazepines, in contrast, are not major or clear risk factors for dementia.
- Use a light box in any kind of acute depression, but beware of mania.
- Veterans are more likely to develop PTSD if they have depressive affective temperaments, and less likely if they have manic affective temperaments.
- Use low-dose lithium to prevent suicide in veterans.
- Dopamine blockers probably are neurotoxic, especially the older ones, but this does not entail stopping their use in schizophrenia.
- New DSM-5 diagnoses that are not scientifically valid should not receive clinical attention.
- Antidepressants “work” in the right kinds of depression, but not other kinds.
- Genetic research will not provide a miracle around the corner, but, combined with more scientifically valid diagnosis, one can hope for some progress in predictors of treatment response.

PL Reflection

Is not disease the rule of existence? There is not a lily pad floating on the river but has been riddled by insects. Almost every shrub and tree has its gall, oftentimes esteemed its chief ornament and scarcely to be distinguished from the fruit. If misery loves company, misery has company enough. Now, at midsummer, find me a perfect leaf or fruit.

Henry David Thoreau

Special Article II: Historical Top Five List

Other years, once new, teach us some old lessons

Every year we focus on the 12 months that passed. A longer time horizon can provide a better focus, perhaps, about insights that have stood the test of time, not just for one new year but for many many years. In this article, PL analyzes a Top Five list of insights from the history of psychiatry.

Number 5: 1927 - The first and only Nobel prize given to a psychiatrist for a psychiatric treatment

PL Note: Julius von Wagner-Jauregg was a medical school classmate and for a time a research colleague of Sigmund Freud. While Freud struggled in private practice, Wagner-Jauregg rose quickly in academic stature to become chairman of the department of psychiatry at the University of Vienna. In later years, though they opposed each other on many occasions (including in court), they had qualified respect for each other, exchanging birthday greetings yearly. Throughout his life, Freud hoped to obtain the Nobel Prize, for which he was nominated but rejected. Wagner-Jauregg, now forgotten, obtained the prize for malaria therapy for neurosyphilis, a treatment that seems odd to us now, but had, in fact, an important historical impact on psychiatry, mostly for the better. Historian Edward Shorter (A History of Psychiatry, pp 194-196) tells this story:

In 1883, during his residency at the asylum, Wagner-Jauregg noted that a female patient who had contracted erysipelas, a streptococcal infection, experienced a remission of her psychosis. This piqued his interest in the relationship between fever and madness, which had long been a subject of medical inquiry. In 1887, Wagner-Jauregg wrote an article speculating that it might be possible to treat psychosis through the use of fever. He mentioned neurosyphilis as being potentially treatable....

"...neurosyphilis...a clinical picture that customarily amounted to a death sentence"

In 1890 the German microbiologist Robert Koch developed a vaccine, tuberculin, that was supposedly effective against tuberculosis. Wagner-Jauregg injected tuberculin into several patients whose psychotic symptoms were caused by neurosyphilis, with the aim of giving them a tuberculous fever. (It was thought that fever itself arrested the progress of neurosyphilis on the ground that the syphilis spirochetes are heat-sensitive). By 1909 he was regularly obtaining long-term remissions of the symptoms of neurosyphilis through the use of tuberculin. Yet he discontinued his experiments with tuberculin because it was considered to be toxic.

Wagner-Jauregg then returned to the possibility of giving paretics a fever with malaria, which, unlike other possible infections, had the advantage of being controllable with quinine. In June 1917, he learned that one of his patients, a soldier sent back from the Macedonian front with shell-shock, seemed to have malaria. An assistant physician asked Wagner if the patient should be given quinine. No, said Wagner, who decided upon the spot to inject some of the soldier's blood into his neurosyphilitics.

In May 1917, a 37 year-old actor with the initials T.M. had been readmitted to the clinic with the now advanced symptoms of neurosyphilis, including weakness of memory, fits, and pupils that were unequal in size and unresponsive to light, a clinical picture that customarily amounted to a death sentence. There being nothing to lose...Wagner-Jauregg inoculated T.M. with malaria. Three weeks later, the patient had his first febrile attack, and after nine such attacks was given quinine. Astonishingly, after the sixth

malaria attack, the syphilitic fits came to an end. [Wagner-Jauregg later wrote]: 'In the course of the following months, there was gradual improvement to the point of abolition of all of the patient's symptoms...' A year later Wagner-Jauregg gave the first report of his work, describing the effect of the malaria-cure upon a total of nine patients. This was an epochal moment...Wagner-Jauregg's fever "cure" (it did not cure but it did restore an almost normal life to patients who otherwise would have died demented) broke the therapeutic nihilism that had dominated psychiatry in previous generations. If one could halt the neurosyphilitic psychoses, perhaps psychotic illness from other causes was treatable as well. Wagner-Jauregg received the Nobel Prize for this work in 1927.

Number 4: 1954 - Don't believe the patient.

PL Note: The most widely read psychiatric textbook of the mid 20th century was Clinical Psychiatry, written by three British psychiatric academic leaders, two of whom were of Continental origin. Willy Mayer-Gross from Germany and Martin Roth from Austria (both influenced by the great German psychiatrist Karl Jaspers) had emigrated and worked in the UK for most of their adult lives. Together with Eliot Slater, they produced, in the opinion of the PL editor, the most comprehensive and clear-headed psychiatric textbook of the last 50 years. The last edition, published in 1969, predates most of the new medications, which would lead later generations to forget about this treasure trove of psychiatric wisdom. This excerpt (p 36) gives a taste of their insights into the psychiatric interview:

Only in the course of time can the psychiatrist develop the art of eliciting by tactful questioning all he has to know. Long training is needed to learn how to overcome the patient's resistance, to be aware of where his tale is biased, where information has been withheld and where it has been coloured by an emotional attitude. The

"It is even more important to know what the facts are than to know what the patient makes of them."

beginner is inclined to take every statement the patient makes at its face value. In this he has been encouraged by psychoanalytic teaching that fabrications and even deliberate falsifications have their value as symptoms. He must, however, beware of an *uncritical credulity*. It is the objective world in which we live and to which the subjective world must pay deference. It is even more important to know what the facts are than to know what the patient makes of them.

Number 3: 1845 - Your treatments may make sense to you, but that doesn't mean they work.

PL Note: For two millennia, almost all physicians agreed that bleeding was an appropriate treatment for almost all conditions, including insanity. This was based on widespread acceptance of the four humor theory of disease. Here we have a good description of the state of the art in the mid 19th century, written by Esquirol, a successor to the great Philippe Pinel of Paris, founder of the moral therapy approach to insanity which led to removal of chains. Pinel's humanism was based on a biological theory of insanity being a disease of the brain, and thus he taught skepticism about the widespread bleeding which was the accepted mainstream standard of care

of two thousand years. Yet even in his circle, bleeding and other evacuations predominated, as described in Esquirol's textbook, Mental Maladies (pp 404-405). As you read about these treatments, widely accepted by the most advanced clinicians of that era, think about what treatments these days are accepted widely and yet may prove to be mere beliefs as opposed to scientific facts:

Administration of medicines...calls for careful reflection...So easy it is for us to permit ourselves to be imposed upon by the violence of symptoms. The same medicines should not be ordered indiscriminately to all maniacs and during all periods of the malady.....

At the outset of mania, during its first symptoms, if gastric symptoms are present...we may employ

emetics....If indications of plethora are present, we employ and repeat blood-letting. We apply leeches behind the ears, or upon the temples; cupping glasses to the back of the neck; and frequently a small number of leeches to the anus.....

We must be cautious respecting sanguine evacuations. By enfeebling maniacs, we run the risk of throwing them into dementia. 'Bleeding,' says Pinel, ' is an unusual evacuation....How numerous are the maniacs who have never lost blood, and been cured; how many have been bled, but still remain incurable!'

We employ tepid baths, and continue them for two, three, and four hours; repeating them two and three times a day, by giving a bath every time that the delirium and fury is renewed, if the subject is of a dry and irritable temperament. While the patient is in the bath, we apply cold water constantly to the head...We insist upon the use of cold, diluent and slightly laxative drinks. Lastly, we unload the large intestine by enemata, at first emollient, then purgative. The diet should be cautiously restricted.

Number 2: 1878 - Pay attention to mild symptoms, even hypomania.

PL Note: Daniel Tuke was a British physician whose treatise on mental illness, *Insanity in Ancient and Modern Life*, is full of insights that still ring true today. Here he describes the importance of paying attention to mild mood symptoms, especially hypomanic ones. These days, many clinicians use the term "hypomania" as a way to minimize the importance of manic-depressive disease, as if manic symptoms only matter when they are severe. Tuke reminds us that mild manic symptoms are important to diagnose:

Warnings of danger are very frequently, if not always, associated with the inability to sleep. The

foe is insidious, and, true to his character, loves to assail us in the dark. He comes upon us in the night....

Emotional warnings there are also, which are of grave import, and ought to be regarded with suspicion by those to whom they occur. Among these may be enumerated slight depression of spirits, especially if this alternates with a sense of exaltation and buoyancy....The buoyancy of spirits...is less likely to excite apprehension among friends than despondency; but it is most important to remember that exuberant spirits, mental exhilaration, loquacity, when unusual to the individual, are fully as serious indications as are the opposite states of mind....

"...exuberant spirits...are fully as serious indications as are the opposite states of mind"

Unfortunately, when action is taken, mistakes in business have been made, or legal documents have been signed which involve serious consequence, family disputes have been occasioned, friendships have been broken, and a great deal of misery caused in various ways, all of which might have been prevented by arresting the symptoms by timely treatment, or failing this, arresting the patient himself and sending him to an asylum in an early stage of the disorder....

Number 1: 1930 - An analysis with Freud was "a fine thing for normal people"

PL Note: The historian of psychoanalysis, Paul Roazen, had made it his business to identify and interview all of Freud's living ex-patients in the 1960s and 1970s. In his book, *How Freud Worked*, Roazen brings Freud the clinician to life, and reveals some astonishing facts about what he believed and how he practiced. Here is an excerpt of the experience of one of Freud's ex-patients, herself a psychoanalyst, as interviewed by Roazen in 1966 (pp 167-187):

Dr Irmgard Putnam...struck me as one of the most unusually detached and brainy of all the former patients of Freud's that I ever

met....Although Dr. Putnam had once been a practicing analyst in Boston, by the time I had met her she was 71 years old and living in a quietly elegant New York City apartment....In 1925 Dr. Putnam spent not quite a year in analysis with Jung...Thinking back on her contact with both Jung and Freud, Dr. Putnam thought that 'one could not have imagined any two people more different.'

[By 1930 she had arranged therapy with Freud himself]. She felt Freud was very attentive, as if she were his 'first patient.' While she was in treatment with Jung, he had wanted to talk primarily about what he was interested in....Freud was 'different'; he talked about 'everything under the sun' - but he 'analyzed' her 'too'....Although the analysis was never lost sight of, a great deal else came into the picture. He spoke about Communism and opera, for instance....Yet the analysis was undertaken in the 'strictest' fashion; there was nothing 'social' about it, and only what was relevant got introduced....

Dr. Putnam knew that Freud had been disillusioned with his early analyses, which had once looked so successful but had turned out not to be. He talked about having become skeptical himself, especially about the therapeutic value of psychoanalysis....When something happened in Dr. Putnam's analysis that was 'classical', he would say, "Didn't I tell you that psychoanalysis was a fine thing for normal people,' and he would laugh....

Dr. Putnam felt in the course of her own analysis that everything was her own responsibility, and she did not resent what Freud expected of her. Before she saw Freud it had never occurred to her not to 'project like other people,' seeing in others her own weak points. The lesson she took away from her psychoanalysis with Freud was that you should not find faults elsewhere, but rather be preoccupied with what you yourself are doing. Even if the other person was in the wrong, what counts is what you are able to do with the situation. She had the healthy-minded conviction that 'anything can be made somewhat better or worse....'

"Didn't I tell you that psychoanalysis was a fine thing for normal people..."

I asked Dr. Putnam if she thought she had been helped by her therapy with Freud, and her answer was unequivocal: 'Definitely.' He had considered her 'normal,' but she of course, like everybody, had 'problems.'

The PL Bottom Line

- Psychosis can be cured.
- Don't believe what the patient says at face value.
- "Standard of care" treatments can be false.
- Hypomania is not innocuous; mild manic symptoms are diagnostically and therapeutically important.
- Psychoanalytic therapy may be most helpful to normal persons.

PL Reflection

We do go about curing a substantial number of ailments...But there is another part of the mystique. It's the great secret of doctors, known only to their wives, but still hidden from the public. Most things get better by themselves; most things, in fact, are better in the morning.

Lewis Thomas MD

Top Study of 2015: *Psychiatric conditions cause physical diseases*

Association of Mental Disorders With Subsequent Chronic Physical Conditions. K. M. Scott et al, *JAMA Psychiatry*.

Published online December 23, 2015. doi:10.1001/jamapsychiatry.2015.2688

An international study provides data for ending stigma

In searching for the most impactful paper of 2015, PL went to the most highly cited general psychiatry journal, JAMA Psychiatry (formerly Archives of General Psychiatry). There one finds a list of the most widely read articles, among which the top article listed was this one, which had just been published online 6 days before PL found it. In about a week, this paper had already been read more frequently than other papers on in JAMA Psychiatry from earlier in the year.

This high level of attention led PL to choose it as the top paper of the year, not because we think it is the best or the most creative or impactful for the long run, but because it has had an impact. Thus, PL wants to bring the paper to the attention of our readers.

This study was headed by many of the same researchers (like Ronald Kessler PhD) who ran classic epidemiological studies in psychiatry, such as the National Comorbidity Survey (NCS). In this study, researchers in 17 countries conducted epidemiological surveys of the frequencies of psychiatric conditions, using DSM-IV diagnoses, in 47,609 people, and they did so repeatedly 18 times over a decade (2001-2011).

They then asked the persons who were interviewed about whether they had been diagnosed with a list of medical illnesses, and at what age they had been so diagnosed or had first experienced symptoms. This analysis describes

"When any psychiatric diagnosis was present, the risk of cancer was increased by an odds of 30%."

the frequency of medical illnesses occurring AFTER onset of psychiatric diagnoses.

The key limitation to the study is that medical diagnoses are based completely on the self-report of patients, and were not independently verified or based on medical chart evidence. Another limitation, present with all such observational data, is that other confounding factors could exist and explain the association of mental and physical illnesses.

With those caveats in mind, using statistical regression modeling, the researchers found that mood conditions, anxiety conditions, and substance abuse each could explain about 3-13% of cases of a range of physical illnesses, such as cancer, diabetes, chronic lung disease, heart disease, and asthma.

When any psychiatric diagnosis was present, the risk of cancer was increased by an odds of 30% (odds ratio 1.3, 95% confidence intervals 1.1-1.5). The same was the case for diabetes. Heart disease risk was increased 70%, and chronic lung disease risk (presumably secondary to mediators like cigarette smoking) was doubled.

Many physicians focus on "physical" illnesses as if "mental" illnesses are unrelated. This report, within the constraints of its limitations as an observational study, reverses this discriminatory belief: If you want to control physical diseases better, diagnose and treat psychiatric conditions better.

Curbside Consults

Questions and cases from you

Question: I have not found lamotrigine to be helpful in treating hyperthymic or cyclothymic temperaments. What is your experience?

PL: This is a good question, and the discussion of affective temperaments for now can be found on the PL website. Future issues will discuss this topic in more detail. To put it briefly, readers are familiar with dysthymia, or mild depressive symptoms. But they likely are not familiar with the opposite state of mild manic symptoms, called hyperthymia. Cyclothymia represents the alternation between the two. In the classic German literature, especially in the work of Ernst Kretschmer in the early 20th century, these temperaments were seen as variants of manic-depressive illness (MDI). They were biologically and genetically related to that disease. They were not different conditions, as DSM sets it up, nor were they diseases in themselves. They were personality constructs, a constellation of traits seen in a certain way in persons with MDI, *in between their episodes*. These affective temperaments also were seen in relatives of persons with MDI.

With that basic definition, we can see the rationale for the PL approach to treating affective temperaments: the use of low doses of mood stabilizers. The treatment type is the same as in MDI, namely mood stabilizers, but since affective temperaments are the mildest shade of MDI,

then lower doses can be effective for them. There is some evidence to support this hypothesis in an observational study with divalproex in cyclothymia, and in some research with dysthymia, but so far there are no published treatment studies of hyperthymia.

Lamotrigine has been proven to be ineffective for acute mania. It does not work for manic symptoms directly. It also is less effective in prevention of manic than depressive episodes. Thus, of the four major mood stabilizers (lithium, divalproex, carbamazepine, and lamotrigine), the one agent that has a major weak spot, in the case of mostly manic presentations, is lamotrigine. If this is the case, then this agent is not likely to be effective for hyperthymic temperament, which is a purely manic condition. Nor is it likely to be as effective in cyclothymia, where manic symptoms are frequent, as opposed to the three other alternative mood stabilizers.

No studies yet exist on this topic, but your experience is consistent with the PL experience, and thus we don't recommend lamotrigine as the primary treatment for hyperthymic or cyclothymic temperaments. Instead low dose divalproex or lithium seem most effective for those conditions.

PL Reflection

Psychiatry is neurology without physical signs, and calls for diagnostic virtuosity of the highest order.

Henry George Miller MD 1970

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THE PSYCHIATRY LETTER

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"Treatment-resistant" depression

This issue represents the beginning of the second year of PL. It is the first issue in which we provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to our readers. This will apply to psychiatrists and nurses, and to psychologists in most states. Please check the website for links to obtain your credits.

The first CME article is on "treatment-resistant" depression (TRD), which in the PL analysis, often blames the illness instead of the drugs. The Classic Article of the Month describes the STAR*D study results, focusing on treatment-resistant results and long-term outcomes. The Drug of the Month is selegiline patch, a monoamine oxidase inhibitor which is commonly misinterpreted as being effective for refractory depression.

This issue adds two new columns. The first, suggested by our colleague Dr. Richard Berlin, is called "By the Numbers"; there PL will provide probabilities, of response or outcomes or other clinical features, that clinicians can cite to patients in their clinical practice. This month, By the Numbers provides data on antidepressant outcomes in major depressive disorder. The second new column is called "Clinical Files", where colleagues provide their clinical experience and opinions, with commentary by PL. In this issue, Drs. Ronald Pies and Manuel Mota-Castillo write about lithium and ADD, respectively.

In the coming year, we expect to extend CEU accreditation to pharmacists and social workers; we will notify you when we have obtained such accreditation. As usual, links to articles are available in the web version of PL. We appreciate your support. Happy new year to you and yours,

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: “Treatment-resistant” depression

A Galenic fallacy

“All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore it is obvious that it fails only in incurable cases.” Galen

“Treatment-resistance” as a concept

It’s well-known that “treatment-resistant” depression (TRD) is a major problem in clinical psychiatry. It’s also widely accepted that there is no illness in which 100.00% of patients respond to appropriate treatments. In other words, even when a disease is correctly diagnosed, and effective treatments are proven to exist, it is never the case that every single person who has that disease will always respond to effective treatments.

In this sense, there always can be treatment-resistance in any illness.

But, in most illnesses, if the disease is correctly diagnosed, and the treatments are proven effective, a minority of cases should be treatment-resistant. By definition, if an effective treatment exists, it will be effective for the majority of cases.

TRD is a different story: One could argue, based on our best studies, that the majority of patients who are diagnosed these days with “major depressive disorder” (MDD), and treated with the class of agents that are proven effective for that treatment (“antidepressants,” or monoamine agonists) are treatment-resistant.

How can that be? If the diagnosis is right, and treatments are proven effective, why are a majority treatment-resistant?

This brings us to the alternative hypothesis: It might not be that the illness is resistant to otherwise correct treatments; it could be that the treating clinician is resistant to changing incorrect treatments for an incorrect diagnosis.

This is where Galen comes in.

Blaming the illness

The quote from Galen that starts this article states the conceptual assumption underlying TRD. The unstated belief, usually completely unconscious to clinicians, is that the MDD diagnosis is correct, and the drugs are just weak. In fact, it could be that the MDD diagnosis is weak, and the drugs are just fine, seeming ineffective because they are being used for the wrong disease.

We’ve always known that misdiagnosis is one possibility in TRD, but this possibility is not taken seriously in most cases. It is listed as one among a dozen reasons for TRD in most cases, and it is given equal emphasis as other reasons, such as medication noncompliance, substance abuse, poor therapeutic alliance, and such.

PL thinks that misdiagnosis should be seen as the most important cause of TRD, and that we should begin by making Galen’s assumption, which many clinicians hold, conscious, and analyzing it, so that we can stop thinking that way.

Galenic assumptions

Galen’s fallacy is obvious: This illness should respond to this kind of treatment; if it doesn’t, then the patients were incurable, or, to use modern terms, “treatment-resistant.” The clear

assumptions are a) the illness is correctly diagnosed and b) the treatments work for that illness.

In TRD, PL holds that both assumptions often are false. Frequently, TRD is present because the “MDD” diagnosis is mistaken. Also, even when MDD is correct using DSM definitions, TRD is present simply because “antidepressants” are less effective than often presumed for MDD. These two points require a discussion of the misdiagnosis literature and a critical analysis of the classic STAR*D study.

Misdiagnosis

In the long list of causes of TRD, misdiagnosis usually is one of many. But some research suggests that one-third to one-half of all cases of TRD reflect misdiagnosis, a frequency that is much greater than the many other individual causes that are raised. Thus, when TRD is observed, misdiagnosis should be examined carefully and seen as the most likely factor far above other possible causes. In other words, other possibilities should not receive the same priority as misdiagnosis, which needs to be ruled out carefully before other possibilities are considered.

Among the other conditions which are misdiagnosed as MDD, the most common is bipolar illness, especially the type II subtype. Hypomanic, and sometimes manic, episodes are missed in clinical histories, often because patients lack insight into those symptoms and do not report them to clinicians, sometimes because clinicians do not ask about or recognize those manic/hypomanic episodes.

When bipolar illness is misdiagnosed as MDD, TRD can result because monoamine agonists have been shown to be ineffective in bipolar

depression, in meta-analyses and multiple randomized clinical trials (RCTs), as opposed to MDD, where monoamine agonists have been shown to be effective over placebo (at least acutely).

Hence TRD is not TRD when it represents misdiagnosis. It is not that the depression is “refractory” to treatments, it is refractory to the wrong treatments. Such patients respond well to a number of dopamine blockers and mood stabilizers, which are proven effective in bipolar depression.

“Antidepressant” efficacy in MDD

The STAR*D study was a NIMH-sponsored study published in the last decade, reviewed in detail in the Classic Article of the Month. As described there, a key finding of that study (although not one accepted by many of the researchers involved with it) was that monoamine agonists are not as effective as often presumed.

Specifically, as noted below, only about 1/3 of patients responded to the whole panoply of monoamine agonists with long-term response. This is much less than the 60-80% efficacy range that many of us often cited before STAR*D. One special observation of concern was that about one-half of patients who responded acutely for a current depressive episode would still relapse within a year, despite staying on the same medication which improved their acute depression. In other words, monoamine agonists seemed much more effective short-term than long-term, acutely than in maintenance prevention.

Hence, the fact that many patients with MDD should get better temporarily, but then relapse despite staying on monoamine agonists, is not an

unusual observation. This happens in about one-half of patients. Another quarter of patients never seem to respond to any monoamine agonist at all, even short-term.

TRD reassessed

Now we can return to the Galenic assumptions. It seems that about one-third of cases of TRD conservatively can be stated to reflect misdiagnosed bipolar illness. Another one-half of cases reflect the inherent low long-term efficacy rate of monoamine agonists in MDD. The remainder of patients, a small group of 20% or so of subjects, may be truly refractory for other reasons, most commonly medication noncompliance or concurrent substance abuse or concurrent borderline personality or concurrent psychotic symptoms.

The two biggest factors, though, which explain the vast majority of cases, are misdiagnosed bipolar illness and the limited long-term efficacy of so-called “antidepressants.”

In the case of misdiagnosis, patients can improve with a change in treatment strategy toward mood stabilizers and/or dopamine blockers.

In the case of low long-term antidepressant efficacy, a larger clinical question is raised about whether and how long such agents should be used. This question has not been asked and answered sufficiently, in the opinion of PL, in the scientific literature on depressive illnesses. It suggests that TRD is the rule rather than the exception in antidepressant treatment of MDD.

The PL Bottom Line

- TRD blames the illness instead of the drugs.
 - The largest class of causes for TRD is misdiagnosis, especially for bipolar depression.
- The second largest class of causes for TRD is an inherent low efficacy of “antidepressants” for long-term maintenance prevention of MDD.
- In the case of misdiagnosis, treatment should shift to mood stabilizers and/or dopamine blockers.
- In the case of low maintenance efficacy in MDD, given STAR*D results, TRD is the rule rather than the exception in antidepressant treatment of MDD.

PL Reflection

The prime object of the physician in the whole art of medicine should be to cure that which is diseased.... Whenever the illness is too strong for the available remedies, the physician surely must not expect that it can be overcome by medicine. To attempt futile treatment is to display an ignorance that is allied to madness.

Hippocrates

Classic study of the month: STAR*D

*Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report.*

A. J. Rush et al, American Journal of Psychiatry. 2006 Nov;163(11):1905-17.

Antidepressant outcomes decline with time in MDD

This study was one of three classic NIMH-sponsored studies at the end of the 21st century, one each in MDD, bipolar illness, and schizophrenia. In the MDD study, called STAR*D, a sequential large randomized clinical trial (RCT) was conducted.

Before STAR*D, there were few RCTs comparing antidepressants to each other, and hardly any looking at outcomes after multiple failed trials.

The STAR*D protocol was as follows: First patients were treated openly with citalopram. If they failed to respond, they were then randomized double-blind to a different monoamine agonist or combination with two monoamine agonists (or other adjunctive agents like buspirone). If they failed this second trial, they were randomized to switching to tricyclic antidepressants (TCAs) or augmentation with lithium or thyroid hormone. If they failed this third trial, they were randomized to a MAOI or the combination of venlafaxine plus mirtazapine.

Response rates are shown in the figure, and further described below in By the Numbers. As can be seen, treatment response was good in the first two episodes, but fell by half thereafter. By the fourth monoamine agonist trial, only 15% of subjects respond to any new treatments, even the most potent agents known, the MAOIs.

Further, even if patients respond, about 40-70% relapsed within one year even if they stayed on the same agents which led to acute response.

Further if intolerable side effects are included, about 20-30% of patients could not remain on their monoamine agonist treatments due to severe side effects (more with the older agents than with newer ones).

In sum: The good news was that about 60-70% of patients responded eventually for the acute depressive episode, if multiple different agents were used.

The bad news was that this response fell off markedly after the first few trials, and, further, only about one-third stayed well for the long-term, defined as just a year of staying well.

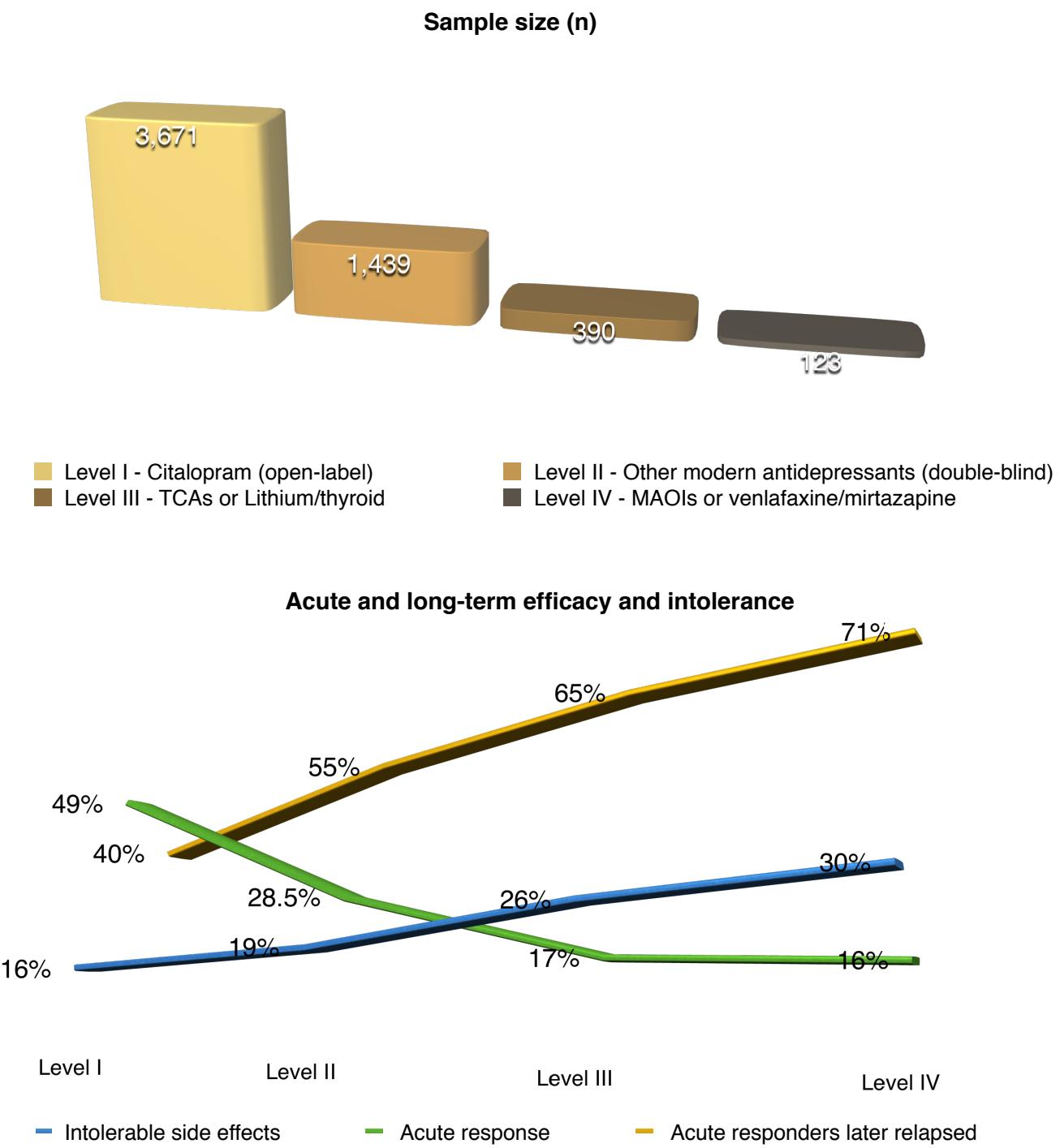
Some researchers and clinicians have interpreted the STAR*D results in a manner similar to what is presented here. The STAR*D researchers themselves adamantly try to interpret their results in as positive a manner as possible.

The case remains, however, that before STAR*D, much higher response rates were cited. After STAR*D, such optimism cannot be supported by this scientific evidence.

The PL Bottom Line

- STAR*D demonstrated good acute response rates in the 60-70% range but low long-term prevention rates in the 1/3 range.
- After multiple failed antidepressant trials, further agents had a very low likelihood of acute treatment response (about 15%)

The STAR*D Protocol: A summary of results



Overall cumulative response without later relapse: 40%

Overall cumulative long-term response without intolerable side effects: 28%

Drug of the Month: Selegiline

An MAOI that isn't more effective than other antidepressants

Biological mechanism

Selegiline is a selective monoamine oxidase-B (MAO-B) inhibitor. In contrast, classic monoamine oxidase inhibitors (MAOIs) block both the A and B enzymes. MAO-A metabolizes serotonin and norepinephrine; MAO-B metabolizes dopamine. By blocking the B enzyme, selegiline is a purely dopaminergic drug. In contrast, classic MAOIs (like phenelzine or tranylcypromine) are also noradrenergic and serotonergic. These differences in neurotransmitter effects may help explain why selegiline should not be seen as a simple MAOI, similar in effect to other agents in this class, and also why selegiline should not be assumed to be as effective as other MAOIs.

MAO-A blockade is associated with greater clinical benefit, but, since norepinephrine activity is robustly increased, it is associated with a risk of hypertensive crisis if a person eats food rich in tyramine. Tyramine is converted to tyrosine and then norepinephrine; in the setting of irreversible MAO-A inhibition, the massive presence of norepinephrine leads to very high blood pressure, which can produce a stroke and be fatal.

Hence the dilemma of MAOIs: If they work robustly, they're dangerous. If they're not dangerous, they don't work robustly.

Acute and long-term efficacy and intolerance

This is the fallacy with selegiline: It is marketed as a "safe" MAOI, but this is because it is not a very effective MAOI.

Clinical efficacy

As is well known, an extensive literature shows that classic MAOIs, like phenelzine and tranylcypromine, are more effective than other antidepressants, like tricyclic antidepressants or serotonin reuptake inhibitors (SRIs). Many clinicians assume this greater efficacy extends to selegiline. This is not the case. No clinical trials ever have proven that selegiline is more effective than other antidepressants.

Since selegiline does not increase norepinephrine or serotonin activity, unlike other MAOIs, it makes sense that it may not have similar clinical effects.

Dosing

The diminished efficacy of selegiline, relative to other MAOIs, is more relevant to the patch form of this medication, as opposed to the oral pill. FDA indication for major depressive disorder (MDD) exists for the patch, but not the pill, mainly because the pill is generic and thus the pharmaceutical industry was able to obtain profits by producing and studying a patch formulation. Biologically, the patch is a selective MAO-B inhibitor at 6-12 mg/d, but at higher doses it blocks MAO-A. This is good if you want more

Fast Facts: Selegiline patch (Emsam)

Typical dose: 6-12 mg/d (range)

Biological mechanism: MAO-B inhibition

Typical side effects: anxiety, insomnia

Less common but important side effects: none

Medically important side effects: hypertensive crisis at high doses (>12 mg/d)

Clinically proven efficacy: Treatment of acute depressive episodes in MDD

antidepressant effect, but it is bad if you want to avoid the restrictive diet needed with classic MAOIs to prevent hypertensive crisis.

MAO-A inhibition begins at 9 mg/d but increases markedly above 12 mg/d, hence the pharmaceutical company's decision to cut off dosing at 12 mg/d. FDA recommendations are that MAOI dietary restrictions begin at 9 mg/d in any case based on the theoretical concern of MAO-A inhibition, although clinical harm through tyramine dietary exposure has not been reported extensively at that dose.

If the oral pill is used, the FDA-approved dose for Parkinson's disease is 5-10 mg/d. At that dose the drug is a selective MAO-B inhibitor, and no dietary restrictions are needed. At 15 mg/d, dietary restrictions often are recommended, and at 20-30 mg/d, some clinical studies find efficacy for acute depressive episodes, although such use of the oral pill would be off-label. At such doses, MAO-A inhibition occurs, and dietary restrictions should be instituted. Some experts think that selegiline may have less risk of hypertensive crisis, even at higher doses than inhibit MAO-A, than other MAOIs, but this clinical hypothesis has neither been proven nor disproven.

The PL Bottom Line

- Selegiline is a mild dopaminergic agent.
- It is a selective MAO-B inhibitor, which is good for avoiding dietary restrictions, but bad for clinical efficacy.
- MAO-A inhibition is required for extensive antidepressant effects.
- Selegiline is not as effective as other MAOIs.
- It is not more effective than other antidepressants.

By the Numbers

Antidepressant efficacy in “major depressive disorder”

Given the above articles, what should you tell your patients regarding the probabilities of responding to “antidepressants” for major depressive disorder (MDD)?

Here are some statistics to remember and to cite with patients based on the STAR*D study. These numbers apply to standard monoamine agonists (antidepressants) used to treat major depressive disorder (MDD):

- Combining two monoamine agonists, or augmenting them (with lithium or thyroid hormone) is similar in efficacy to switching from one monoamine agonist to another.
- With the first monoamine agonist used to treat the first acute depressive episode, the likelihood of clinical response is about 50%.
- With the second monoamine agonist used to treat the first acute depressive episode, the likelihood of clinical response again is about 30%.
- After two failed trials of monoamine agonists for an acute depressive episode, the likelihood of response with a third or fourth agent (even adding lithium or MAOI) is cut in half to about 15%.
- Of those who respond acutely to a monoamine against for an acute depressive episode, the likelihood that they will stay well for a year staying on the same medication is 50% or less.
- Separate from efficacy, about 20-30% of patients will not be able to tolerate side effects in each antidepressant trial.

- In short, using multiple monoamine agonists, about 2/3 of patients will eventually respond for the acute depressive episode.
- However, half of those patients will relapse within a year. Thus using multiple monoamine agonists, only about 1/3 will respond and stay well long-term.

Clinical Files

The Benefits of Low-Dose Lithium: A Personal Reflection

Ronald W. Pies MD

Professor of Psychiatry, Tufts University School of Medicine, Former Editor-in-Chief, Psychiatric Times.

During more than 25 years of clinical practice as a psychopharmacology consultant, many patients were referred to me with so-called "refractory depression." Most, in fact, had been misdiagnosed with recurrent unipolar depression that "failed to respond to antidepressants." With careful assessment and observation over many months, these patients usually proved to have conditions that fell along the spectrum of (for lack of a better term) bipolarity. Most had never experienced a frank manic episode, and, rather than having classic "DSM" hypomanic periods, most had experienced strong dysphoric reactions to antidepressants —a phenomenon I discussed some years ago under the rubric of ARAD (antidepressant-induced agitation and dysphoria). These ARAD patients did not "switch" while taking antidepressants, in the formal sense of meeting DSM-4 criteria for mania or hypomania; rather, they almost always felt "wired", "antsy" and irritable. They typically slept poorly and got into frequent altercations when taking antidepressants. (I discuss ARAD in a podcast on antidepressants and bipolar disorder). My

experience as a consultant eventuated in the development of a scale for detecting the "softer" end of the bipolar spectrum, the BSDS, which Dr. Ghaemi co-developed with me. I also discovered that many of these patients did very well on lithium, either as monotherapy, or—in some cases—in combination with valproate or a low dose of an antipsychotic agent. Once on lithium, many of these patients no longer required antidepressants to ward off serious depressive periods (though it's doubtful that the antidepressants actually did this).

The December 2015 PL issue observed that as little as 300 mg/day of lithium could reduce suicidal tendencies. Indeed, PL added that, with respect to its anti-suicidal properties, "...there is no minimum effective dose" of lithium. While the same cannot be said with respect to lithium's mood stabilizing properties in bipolar disorder, my experience (and some recent research) suggests that quite low doses of lithium may be beneficial in a subset of patients with bipolar spectrum disorders. This was critical in my practice, since many of my ARAD patients had difficulty tolerating the (expectable) side effects of lithium at standard doses and blood levels; e.g., 300 mg tid, with serum Li levels somewhere in the range of 0.6-0.9 mEq/L (as maintenance). To my surprise, however, I found that a subset of these bipolar spectrum patients could maintain relative mood stability on doses of lithium as low as 300-450 mg/day, with blood levels in the range of 0.3-0.5 mEq/L. A few required adjunctive valproate to maintain stability. Of course, these were patients in clinical practice, not research subjects randomized to low-dose lithium in a placebo-controlled study. And so, as PL would no doubt remind us, my observations must be taken with a large grain of lithium salts! Still, after seeing 50 or more such cases, I reached a state of

“provisional belief” in the benefits of low-dose lithium.

Indeed, there is growing interest in the use of very low doses of lithium, not only in the prevention of suicidal behavior, but also in the management of bipolar disorder—and perhaps even in the treatment of some neurodegenerative disorders. Although recent results are mixed, some older data point to the utility of serum lithium levels as low as 0.46 in bipolar patients, with reduction of affective episodes and overall morbidity. One of the unfortunate aspects of psychiatric training in the last 30 years has been the neglect of lithium—with many recent residency graduates having little experience with this remarkable element. Perhaps it's time to re-discover a remedy whose therapeutic uses may date back to ancient Rome!

PL Comment:

Dr. Pies is a prominent psychopharmacologist in the Boston area, widely sought for consultations over three decades. He has seen the transition of psychopharmacology from the lithium era to the advent of the SRIs and newer dopamine blockers. His observations provide a long view of clinical wisdom, based on experience with older drugs like lithium, which, unfortunately, are underappreciated and underused by many clinicians trained in the 21st century. PL would like to underscore Dr. Pies' observations and commends them to younger clinicians, trained in the post-Prozac era, particularly.

PL Reflection

All substances are poisonous; the dose differentiates a remedy from a poison.

Paracelsus

Clinical Files

ADHD: A Clinician's Concerns

Manuel Mota-Castillo, M.D.

Chief Medical Officer, Mesilla Valley Hospital; Chairman of Psychiatry, Burrell College of Osteopathic Medicine, Las Cruces, New Mexico

On January 4th of 2016 the National Public Radio website reported the findings of a renowned pediatrician from the Center for Child Health, Behavior and Development at Children's Hospital in Seattle. Dr. Dimitri Christakis stated that “we should be thinking more about a spectrum of 'attentional capacity' that varies from individual to individual and situation to situation”. He presents this suggestion as a better alternative to the current practice of diagnosing ADHD by looking at list of behaviors and if a child presents with 6 of them the label is attached without ruling other diagnoses that also present with poor attention span and restlessness.

Dr. Christakis' perspective got my attention because it seems to be close to the PL November 2015 special article which presents a new interpretation of the set of symptoms that we currently call ADHD. For that I commend the pediatric researcher but I think that he fell short of presenting the real picture of what is going on in the psychiatric arena regarding ADHD: thousands if not millions of children, their relatives, and classroom peers are hurt by the worsening of the patient' symptoms when they take ADHD medications because their real diagnoses (OCD, PTSD, Social Anxiety Disorder, Bipolar Spectrum Disorders, etc.) are exacerbated by amphetamine-like drugs.

I have heard Ivy League professors of psychiatry and neurology proclaim that in their practice they have dozens of autistic children and “that also

have ADHD and social anxiety disorder". Another famous psychiatrist presented at the 2014 APA Annual Meeting a collection of cases of "comorbid" ADHD and Oppositional-Defiant Disorder (ODD) which sounded like anything else but ADHD. In fact, that renowned professor lost his cool when I asked if he would consider the possibility that maybe the subjects of the study could have different diagnoses because what DSM calls ODD is not a real diagnosis but a symptom of other conditions.

Sadly, clinicians around the world believe in many scientific fallacies and prescribe the most powerful psychotropic substances as if they were harmless candies. Equally wrong is the use of several scales that were designed to measure outcomes of research studies but at some point psychiatrists and psychologists started to disseminate the idea that those instruments had diagnostic power. These days you can hear a mother saying "how can you tell me that my son does not have ADHD when he has been tested multiple times by teachers and other doctors"?

Also hard to understand is the complete disregard for the genetic endowments of patients. A family history of hypertension, diabetes and cancer is considered relevant by every doctor but in psychiatry "it does not apply". I have seen the son of a bipolar mother and a schizophrenic father diagnosed with ADHD, ODD and Conduct Disorder (I call this the "evil triad") and

yet they don't improve "despite adequate treatments".

I think our profession stigmatizes certain illnesses, and celebrates others. Take bipolar illness: 18 years ago, I diagnosed the first preschooler with bipolar disorder (both parents had it), and now such diagnosis would be highly criticized. In contrast, look at ADHD: Two decades ago, ADHD was limited to children in most cases, but now it is diagnosed routinely in adults, and DSM-5 has given its stamp of approval. Why these opposite attitudes? It's not because the scientific evidence supports such contrasts in our professional views. There are reasonable studies to support the diagnosis of bipolar illness in children, and, as reviewed in PL, good reasons to doubt the limited studies which claim validity for adult ADHD.

Hopefully the organizations that represent the psychiatric community will take a responsible role in disseminating the truth about the exaggerated statistics of ADHD. When 90% or more of the patients in a doctor's practice have the same diagnosis the validity of those diagnoses should be questioned.

PL Comment:

PL thanks Dr. Mota-Castillo for these thoughts, bound to provoke some readers to agreement and others to dissent. PL notes that Dr. Mota-Castillo has worked for two decades as a child and adult psychiatrist. What PL would add is that his comments provide a perspective from within child psychiatric practice that is not represented often in professional publications. In his experience, ADHD is increasingly diagnosed within the profession, without much criticism, whereas the slightest increase in bipolar diagnosis, whether in children or adults, is met with strong reaction. He raises the question why this might

PL Reflection

To say the truth, every physician almost hath his favourite disease, to which he ascribes all the victories obtained over human nature.

Henry Fielding, 1749

be the case, from a professional and cultural perspective, and argues that such opinions are not based on purely scientific considerations. PL agrees that these are good questions for further discussion and consideration.

Curbside Consults

Questions and cases from you

Question: Being an addiction psychiatrist, I see a lot of people who come to me for opioid dependence who are also using high doses of benzodiazepines. With buprenorphine, their anxiety generally improves a little but they are frightened by the idea of living without benzodiazepines. Nonetheless, a condition of treatment is tapering off. What I have found repeatedly is that as they decrease the dose and finally get off, their anxiety improves dramatically. I wonder if there is a benzodiazepine-induced hyperanxiety syndrome akin to opioid-induced hyperalgesia.

PL: This is an interesting observation and a good hypothesis. PL has little experience to add but would like to bring this observation to the attention of readers. It makes sense that the brain may adapt to benzodiazepine use in some patients such that the homeostatic mechanisms involved produce more clinical anxiety. In other words, if gabaergic activity is increased with a medication, then the brain's homeostatic mechanism could be to increase compensatory glutamatergic excitation, which can produce anxiety. Once the exogenous gabaergic

stimulation is reduced (i.e., benzodiazepines are stopped), the homeostatic reaction may also decline (i.e., glutamatergic excitation will diminish), producing less clinical anxiety. This is a biological hypothesis to explain your clinical observation, but the important matter is that the clinical observation you describe makes biological sense. It should be kept in mind with some patients in whom long-term benzodiazepine use may be part of the problem, rather than the solution, in managing refractory anxiety.

PL Reflection

I have always worked from the living model. I remember that once in the dissecting room when I was going over my 'part' with the demonstrator, he asked me what some nerve was and I did not know. He told me; whereupon I remonstrated, for it was in the wrong place. Nevertheless he insisted that it was the nerve I had been in vain looking for. I complained of the abnormality and he, smiling, said that in anatomy it was the normal that was uncommon. I was only annoyed at the time, but the remark sank into my mind and since then it has forced upon me that it was true of man as well as of anatomy. The normal is what you find but rarely. The normal is an ideal. It is a picture that one fabricates of the average characteristics of men, and to find them all in a single man is hardly to be expected.

W. Somerset Maugham

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THE PSYCHIATRY LETTER

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Antidepressants in bipolar depression

This issue focuses on the classic question of whether antidepressants are effective or not, and harmful or not, in bipolar depression, my central research interest in psychopharmacology for two decades.

In the CME Special Article, the PL analysis concludes that these medications are ineffective at best and harmful at worst. The vexing question about why they remain used so frequently by clinicians, and why experts continue to support their use despite the evidence against their benefit, is also addressed. The Classic Article of the Month describes results from a major NIMH-sponsored study, STEP-BD, showing inefficacy of two common modern antidepressants institute bipolar depression. The Drug of the Month is paroxetine, a serotonin reuptake inhibitor which has the lowest risk of acute mania induction, but unfortunately is ineffective in bipolar depression.

By the Numbers provides frequencies of risk of acute mania and long-term rapid cycling with various types of antidepressants and subtypes of bipolar illness. The Psychopathology column delves into the phenomenology of bipolar depression, highlighting the importance of mixed, melancholic, and psychotic presentations.

As noted previously, eligible readers can obtain continuing medical education (CME) and continuing education unit (CEU) credits for the special article, by clicking on the link on the website which will lead to post-test questions, after which credits are awarded. We hope you take advantage of this opportunity in current and future issues of PL.

Thank you again for your support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: Antidepressants in bipolar depression

Common practice, poor science

The context

The use of antidepressants in bipolar depression is extremely common and yet it has little scientific evidence to support it. In fact, antidepressants are the most commonly used class of medications in bipolar illness, given to about 50% of patients treated for that diagnosis in the United States. In contrast, the most proven effective treatment in bipolar illness, lithium, is given to only about 10% of patients treated for that diagnosis in the United States.

This common practice occurs despite the fact that there are very few randomized clinical trials (RCTs) that support benefit with antidepressants in bipolar depression. And there are many randomized clinical trials that show that antidepressants are ineffective in bipolar depression. Why is there this disconnect between evidence and practice?

The reluctance to stop using antidepressants in bipolar illness needs to be understood not only in the context of their probable inefficacy but also in the context of the evidence for some harms, such as causing mania, and causing more mood episodes over time.

Let's review the scientific evidence first, and then talk about the clinical reluctance to implement that evidence straightforwardly.

Acute depression

We begin with RCTs of acute bipolar depression. There have been a number of meta-analyses of antidepressants in acute bipolar depression over the last decade. In the most recent such review,

about half a dozen trials met inclusion criteria and overall, antidepressants weren't statistically better than placebo. It's a standard approach in evidence based medicine not to prescribe treatments which are proven ineffective. So we're left with the question why clinicians and many experts still use and recommend antidepressants in acute bipolar depression. Whatever their reasons, they can't base their judgments on these RCTs.

Maintenance prevention

Now we turn to RCTs of maintenance prevention of mood episodes in bipolar illness. The PL editor published a meta-analysis on this topic, which found that antidepressants weren't better than placebo, when used with mood stabilizers, in prevention of mood episodes in bipolar illness.

Most of these studies involved older classes of antidepressants, such as the tricyclic antidepressants (TCAs). There are very few studies of the newer antidepressants, like the serotonin reuptake inhibitors (SRIs), in long-term treatment of bipolar illness. There is in fact only one placebo-controlled maintenance trial of any SRI in bipolar illness. In that study, which has been presented at conferences but not yet published, citalopram was equivalent to placebo. In other words, there are no studies - zero - that show that any modern antidepressant is more effective than placebo in prevention of mood episodes in the maintenance phase of treatment of bipolar illness.

Acute mania

Clinicians often refer to manic induction with antidepressants. Usually the term “manic induction” isn’t well defined. PL recommends that acute mania related to antidepressants be defined as occurring within a few months after starting treatment. It’s important to distinguish between immediate and long-term harms with antidepressants. In the PL view, acute mania isn’t the major problem with antidepressants. Long term worsening of mood episodes, usually depressive rather than manic, is a bigger problem. We’ll turn to that question in the next section of this special article.

Do antidepressants cause acute mania? If we look at the randomized trials, some experts would answer in the negative, because many report equivalent rates of mania in subjects treated with antidepressants versus placebo, and thus a causal connection can’t be established for antidepressants. Yet those RCTs

aren’t set up to identify and test the hypothesis that antidepressants cause mania. Rather they’re designed to test the hypothesis of efficacy with antidepressants over placebo, not worsening with mania. The frequency of antidepressant-induced mania is about 10-30% with SRIs and 25-50% with TCAs, thus only part of the overall sample would experience this outcome. Since these studies are powered for efficacy in the whole sample, not side effects in part of the sample, these RCTs don’t have statistical “power;” this means there aren’t enough patients in the studies to observe enough manic episodes so to make a statistical distinction between antidepressants and placebo. This is the classic statistical fallacy - called false negative bias - of saying that nothing happens when your study is too small to see if

“Rather than acute mania, the PL view is that the most important harm associated with antidepressants in bipolar illness is long-term worsening...”

something happens. Further, in many of those RCTs, patients received antimanic medications, such as neuroleptics or mood stabilizers, which would reduce the frequency of antidepressant-induced mania even more.

Nonetheless, even with these design issues, there are a number of randomized trials - involving TCAs - which show higher rates of mania with antidepressants over placebo. The reason those studies are statistically significant has to do with the larger effect size of frequency of antidepressant induced mania with TCAs (in 25-50% range as opposed to about half that rate with SRIs).

With the above context, PL draws the following conclusions: Antidepressants (like TCAs) have been proven to cause mania in RCTs (in about 25-50% of subjects). SRIs have about half that rate (10-30%). Rates are even lower with concomitant use of mood stabilizers or neuroleptic agents, and also lower in type II (5-10%) than in type I bipolar illness (10-50%). The specific modern antidepressants that have been shown to have the lowest risk of causing acute mania in randomized trials are paroxetine and bupropion.

Long-term worsening

Rather than acute mania, the PL view is that the most important harm associated with antidepressants in bipolar illness is long-term worsening, meaning causing more and more mood episodes over time. These mood episodes tend to be depressive rather than manic, which leads to the paradoxical fact that antidepressants worsen depression long-term in bipolar illness. In some patients, this long-term worsening leads to a rapid-cycling course, meaning four or more mood

episodes yearly. Typically, these patients are labeled as having “treatment refractory” bipolar illness, while in fact they often aren’t treatment refractory. Rather their bipolar illness has been worsened by the mood-destabilizing effects of antidepressants, counteracting the benefits of mood stabilizers. It’s not that these patients have failed to respond to multiple mood stabilizers, as often assumed, but rather that the constant use of long-term antidepressants impedes the mood stabilizers from working. A full and fair trial of a mood stabilizer in this setting must happen in the absence of any antidepressants. Therefore, the PL recommendation would be to stop antidepressants, and then resume mood stabilizers, including those that had been used the past, and frequently a much better response occurs.

The RCT evidence for these observations begins with studies from the 1970s, which used the on-off design to show that when patients with rapid-cycling bipolar illness received TCAs, their cycling worsened, whereas when they were switched to placebo, the cycling improved.

Three decades later, the PL editor conducted two maintenance RCTs of modern antidepressants in bipolar depression, and examined outcomes in rapid cycling versus non-rapid cycling subgroups. In both studies, patients with rapid-cycling bipolar illness had more depressive episodes if they continued antidepressant use long-term, defined as up to one year, as opposed to either not being treated with antidepressants at all, or stopping antidepressants after the acute phase. Thus all three RCTs on this topic have found that antidepressants are associated with rapid cycling bipolar illness. Some experts refer to observational data suggesting otherwise, but a

“...antidepressants worsen rapid-cycling bipolar illness, and thus worsen bipolar illness in about one-quarter of patients with that condition.”

basic principle of evidence-based medicine is that randomized data are more valid than observational data, as we’ll discuss more below, and thus the latter can’t be used to refute the former.

Since rapid cycling occurs in about one-quarter of patients with bipolar illness, it’s reasonable to conclude that antidepressants worsen bipolar illness overall in at least 25% of subjects.

In short, the most valid available scientific evidence indicates that antidepressants cause or worsen rapid-cycling bipolar illness.

The clinical disconnect

Given the above scientific evidence, we’re left with the question why clinicians, and also many bipolar experts, use or recommend these agents. The PL editor has interacted with many clinicians and experts on this topic for two decades. A common view among bipolar experts is that if clinicians continue to use these medications, despite the scientific evidence to the contrary, they must know something. Perhaps clinician

see some real benefit that isn’t captured in the RCTs. This is a possibility. But one would think that after 30 years of research in many RCTs conducted by researchers who generally have been very positively disposed towards antidepressants, some benefit would have shown up. Another hypothesis could be made which is much more consistent with the basic principles of scientific research and clinical medicine. This hypothesis, as discussed the April 2015 PL issue, has to do with the concept of confounding bias. Confounding bias reflects the idea that there are many factors in clinical practice that influence the results seen. Clinicians as well as patients don’t necessarily

know which factors are in play. For instance, it may seem that coffee causes cancer, as repeatedly shown in many huge observational studies. But this association between coffee and cancer is not causal, because of the confounding factor of cigarette smoking. People who drink more coffee also tend to smoke cigarettes, and the latter factor is causal for cancer. Similarly, the fact that clinicians think that antidepressants are associated with improvement in bipolar depression doesn't mean that there is a causal association. The whole point of randomization is to get rid of all the other confounding factors in clinical practice so that a causal scientifically valid judgment can be made. Placebo is a stand-in for natural history, not merely a reflection of psychological wishes, as is commonly assumed. If you have an illness which improves in many people over time, then you have to show that medication does better than the natural course of recovery. Over a century of natural history research, long before any treatments were available, shows that the natural history of bipolar illness is such that episodes last 2 to 4 months for mania and 3 to 6 months for depression. The reason these mood states are called "episodes" is because they have a natural end, as well as a beginning. They will end, even without any treatment, in 3 to 6 months for bipolar depression. Thus, when a clinician gives an antidepressant to a patient with bipolar illness who has been depressed for two months, and then the depression improves two months later, this would be expected even if the clinician had received nothing. The clinician's interpretation of antidepressant benefit is disproven by the randomized trials which show the same benefit with placebo.

"The reason these mood states are called 'episodes' is because they have a natural end, as well as a beginning."

Unfortunately, many bipolar experts tend to ignore the reality confounding bias, in their interpretations of the disconnect between the research studies and clinical practice on this topic. Clinicians haven't been aware enough of the reality of confounding bias in the assumptions they make based on their clinical experience. Both groups would do well to be more cautious in assuming clinical effectiveness when scientific evidence demonstrates the contrary.

Regarding the issue of harm with antidepressants, clinicians tend to be more open to the notion that these drugs cause mania, as opposed to experts who mistakenly ignore the false negative bias of RCTs that are not statistically powered to assess manic induction with antidepressants. Clinicians can't ignore the reality of patients getting markedly manic soon after starting antidepressants. In contrast, the long-term worsening of mood episodes caused by antidepressants can be hard for clinicians to identify, since those episodes occur a year or longer after antidepressant treatment began. A direct association can be hard to confirm in the real world of clinical practice, where medications are changed frequently, and where many stressors and life events occur over years of follow-up. The RCTs of maintenance treatment in bipolar illness come to the rescue by clearing out confounding factors and demonstrating a causal association between antidepressant use and long-term worsening of bipolar illness with a rapid-cycling course.

The English language

Another factor that may be relevant here is that clinicians and patients maybe misled by the English language. As PL has suggested in the past,

the word "antidepressant" is misleading, because it implies, to clinicians and patients alike, that these medications should be useful for any kind of depression, despite the fact that the research literature indicates that they aren't effective for bipolar depression, and as discussed in the last issue of PL, they may not be very effective for many types of major depressive disorder (MDD). PL has recommended the phrase "monoamine agonists" as a more neutral term, leaving open the clinical question of which conditions this class medications can help. For instance, PL suggests that monoamine agonists appear to be more consistently helpful for anxiety rather than depressive symptoms; thus the phrase "antidepressant" rather than "anxiolytic" sends clinicians and patients in the wrong direction.

The PL editor recalls that once, upon giving a lecture on this topic, and reviewing all the above studies, an older clinician left the room and commented to a colleague: The studies may be this way, but I'm still going to use antidepressants. Although clinical practice has its strengths, it also has its limitations. The main limitation of clinical practice involves confounding bias: the many competing and conflicting and often unknown factors that influence outcomes in the real world. If clinical practice is the art of medicine, and randomized trials are the science of medicine, then these two aspects should be seen as complementary. The art of medicine is strengthened by the science, and science needs to be applied with the most effective art possible. The great William Osler put it this way: *Medicine is the lifelong attempt to correlate art with science.* Notice that it isn't the other way around. Science isn't there to correlate with art. It's not the job of research to confirm what clinicians already believe, but rather, more often, to refute clinical

“...preselection of treatment response in a study of treatment response prejudices the matter.”

beliefs. Science is about falsifying our hypotheses, not simply confirming them.

Type II

What about type II bipolar depression? Future PL issues will address this matter in more detail, but a few general comments can be made here. It's commonly believed by many clinicians that type II bipolar depression is more responsive to antidepressants than type I bipolar depression. This impression is based partly on a number of RCTs that report benefit with antidepressants. A key concern about those studies is that they are "enriched", which means that patients are preselected to respond to the antidepressant being studied, before the study even begins. The PL view is that this preselection of treatment response in a study of treatment response prejudices the matter. This research design problem hasn't been appreciated, in the PL view, by the FDA, which accepts enriched studies for indications for treatment.

The same critique holds for maintenance trials of antipsychotics in bipolar illness, some anticonvulsants in bipolar illness, and antidepressants in MDD. This critique has been described in the scientific literature, and future PL issues will return to in more detail. For now, the main point to make here is that the apparent efficacy of antidepressants in some bipolar type II studies may be overstated because of the bias of the enriched research design. Further, when antidepressant efficacy has been examined in RCTs of bipolar depression comparing type I and type II subgroups in the same trial, no differences exist. In other words, antidepressant efficacy in type II bipolar depression was the same as in type I bipolar depression, which means it was equally low in both groups.

Summary

In sum, the PL view is that the scientific literature of randomized trials most simply supports the conclusion that antidepressants are ineffective at best and harmful at worst in bipolar illness. PL is aware that many clinicians will disagree with these judgments and many experts will seek to interpret the data as positively as possible. PL isn't opposed to any class of medications in theory, as many readers will know, since all classes of medications are recommended in PL for whatever use that is scientifically supported. But when randomized trials repeatedly show that a class of medications aren't effective, it's important to draw the simple clinical conclusion that they shouldn't be prescribed routinely. In the case of bipolar depression, it may be that we've been giving a pass to antidepressants because they've been so popular for so long with both clinicians and patients.

The PL Bottom Line

- Antidepressants are proven ineffective in treating the acute depressive episodes of bipolar illness.
- Antidepressants are proven ineffective in treating and preventing future depressive episodes of bipolar illness.
- Antidepressants are proven to cause acute mania in bipolar illness.
- Antidepressants are proven to cause more and more mood episodes, mostly depressive, over time in about one quarter of patients with bipolar illness.
- Antidepressants are ineffective at best and harmful at worst in bipolar illness.

Clinical Tip

Instead of adding antidepressants to a mood stabilizer for a current bipolar depressive episode, add a neuroleptic or combine mood stabilizers.

When a patient is taking a mood stabilizer, like lithium or divalproex or lamotrigine, he or she might still experience a clinical breakthrough depressive episode. Many clinicians then want to add an antidepressant. The above studies show that this decision will be ineffective since antidepressants in that setting are equal to placebo. Instead, RCTs show that adding a proven dopamine blocker can be effective, or combining two mood stabilizers is proven more effective than either agent alone, both acutely and in long-term prevention. Thus, if the patient is taking lithium, add divalproex, or vice versa; or continue lithium or divalproex, and add a dopamine blocker

PL Reflection

No man, however strong, can serve ten years as school-master, priest, or Senator, and remain fit for anything else. All dogmatic stations in life have the effect of fixing a certain stiffness of attitude forever, as though they mesmerized the subject.

Henry Adams

Classic study of the month: STEP-BD

Effectiveness of adjunctive antidepressant treatment for bipolar depression. G. S. Sachs et al,

N Engl J Med. 2007;356(17):1711-22.

A major study demonstrates antidepressant ineffectiveness in bipolar depression

As discussed in the last PL issue, about a decade ago, three classic NIMH-sponsored studies of clinical treatment were conducted, one each in MDD, bipolar illness, and schizophrenia. The MDD study, called STAR*D, was reviewed in the last PL issue. The bipolar study was called STEP-BD (Systematic Treatment Evaluation Program for Bipolar Disorder).

STEP-BD was mostly an observational cohort study, but one large randomized trial was conducted with over 300 subjects to test the hypothesis whether antidepressants are effective for acute bipolar depression. This was a randomized trial of paroxetine or bupropion versus placebo, added to mood stabilizers for the acute depressive episode. The main result was that both antidepressants were equal to placebo for acute efficacy. The two groups also were similar for acute mania induction.

The straightforward interpretation is that paroxetine and bupropion were not effective in the treatment of acute bipolar depression. However, experts often interpret this study by emphasizing the lack of difference in mania induction as well, and thus concluding that antidepressants were neither harmful nor helpful for bipolar depression. The lack of mania induction was unsurprising given the fact that these two antidepressants were specifically chosen

“...paroxetine and bupropion were not effective in the treatment of acute bipolar depression...”

based on prior studies indicating that they had the least risk of acute mania compared to other antidepressants. When given with mood stabilizers or neuroleptics, of course, this risk would be even lower. It would be incorrect to infer from lack of acute mania with those agents which are at least risk of it that no medication in the antidepressant class can cause acute mania.

The larger finding, often underemphasized, is that the antidepressants did not work pharmacologically. Patients improved, but not because of the effects of Paxil or Wellbutrin; they also improved on placebo, which either reflects natural history or the impact of mood stabilizers alone. In any case, in this study, which is the largest and most definitive RCT of this question, antidepressants were found to be ineffective in the treatment of acute bipolar depression.

The PL Bottom Line

- STEP-BD demonstrated that antidepressants were not effective in acute bipolar depression when combined standard mood stabilizers.
- STEP-BD also found that paroxetine and bupropion were not more likely than placebo to cause acute mania, when combined with standard mood stabilizers or neuroleptics.

Drug of the Month: *Paroxetine (Paxil)*

The lowest risk of mania in bipolar depression, but ineffective

Biological mechanism

Paroxetine is a serotonin reuptake inhibitor which, at low doses, is highly selective for serotonin, but at higher doses, also inhibits norepinephrine reuptake. In general, it's often thought that norepinephrine reuptake leads to increased induction of mania. Thus, the observation of low acute mania induction with paroxetine may be due to its selectivity for serotonin at lower doses. However, the flip side is that at higher doses paroxetine probably does not have a low risk of acute mania induction.

This agent also has anticholinergic effects, which has been associated with sedation; some patients also report weight gain.

Other features

When stopped, paroxetine possesses a severe serotonin withdrawal syndrome, though it has a relatively long half-life of 21 hours. Given this long half-life, it need not be dosed more than once daily, and frequently it is best to give it at night due to sedation.

Clinical efficacy

Paroxetine has been shown to be effective for depressive episodes in MDD, but it has been shown to be ineffective in bipolar depression. It also has efficacy for, and is FDA-indicated in, obsessive compulsive disorder, and is probably effective for a range of anxiety symptoms.

Dosing

Paroxetine produces pure serotonin reuptake inhibition at 10-20 mg per day, whereas norepinephrine reuptake inhibition begins to increase at higher doses, and is definitely present with 40 mg per day or more. Low doses, less than 20 mg per day, are less likely to be associated with causing mania. Higher doses, like 40-80 mg/d, tend to be used for obsessive-compulsive disorder.

Fast Facts: Paroxetine

Typical dose: 10-80 mg/d (range)

Biological mechanism: serotonin and norepinephrine inhibition

Typical side effects: sexual dysfunction, sedation

Less common but important side effects: weight gain

Medically important side effects: none

Clinically proven efficacy: Treatment of acute depressive episodes in MDD, treatment of OCD

The PL Bottom Line

- Paroxetine is a pure serotonin reuptake inhibitor at very low doses.
- It is a norepinephrine reuptake inhibitor at higher doses.
- At low doses it is less likely to cause mania, but it is ineffective for acute bipolar depression.
- It has a severe serotonin withdrawal syndrome.

PL Reflection

The central fact of psychology is that each one of us stares forth from an individually shaped and genetically determined nervous system into a world seen from this time and place in a way that will never happen again.

Leston Havens

By the Numbers

Antidepressant risk in bipolar illness

Given the above articles, and the following summary of the psychopathology of bipolar depression, what should you know and tell your patients regarding the probabilities of harms with “antidepressants” for bipolar illness?

Here are some statistics based on a range of research studies. These numbers apply to standard monoamine agonists (antidepressants) used to treat bipolar illness.

- The risk of acute mania with the tricyclic antidepressants is about 50%.
- The risk of acute mania with a serotonin reuptake inhibitors in type I bipolar illness is about 10-30%.
- The risk of acute mania with a serotonin reuptake inhibitors in type II bipolar illness is about 5-10%.
- The risk of long-term worsening of bipolar illness, with rapid cycling course, is about 30% with any antidepressants in type I or type II bipolar illness.
- The above risks are reduced by a factor of about one half for acute mania if concomitant mood stabilizers or neuroleptics are given.
- The above risks for long-term rapid cycling are not reduced if concomitant mood stabilizers or neuroleptics are given.
- About 50% of unipolar depressive episodes are mixed states, which is similar to the rate in bipolar depression.

Psychopathology

Is there something special about bipolar depression?

The prior discussion about bipolar depression is often made in contrast to discussions of unipolar depression. A question often asked is whether depression differs in bipolar versus unipolar illness. Readers of PL will know, as described in detail on the PL website, that this question may not be meaningful if the concept of manic depressive illness (MDI) is correct. The older concept of MDI meant that there was no meaningful distinction to be made between bipolar and unipolar subtypes. If MDI is correct, it may be that depressive episodes of bipolar and unipolar illness will not differ appreciably. The assumption that they differ is based on the assumption that the DSM distinction between bipolar and unipolar illness is valid. As described further on the PL website, this assumption hasn't been proven, and a number of research studies, especially in the last few decades, find otherwise.

That said, the clinical literature in the last few decades, and also in the last century, can be examined to see what differences, if any, have been reported between bipolar and unipolar depression. In the February 2015 PL issue, we discussed the important concept of mixed depression, defined as a clinical depressive episode occurring with multiple manic symptoms. This concept isn't limited to bipolar illness, but also occurs in unipolar depression. It's part and parcel of the MDI concept that most mood states are mixed, involving both depressive and manic symptoms, and not purely one way or the other. If the MDI concept is correct, we wouldn't be surprised to find that most depressive episodes, even for unipolar depression, are mixed. Indeed, Angst and colleagues found that about one half of

the current depressive episodes in so-called MDD involved mixed depression. In bipolar depression, it's reported that about 60% of depressive episodes are mixed. Thus, bipolar and unipolar depression are similar in having mixed states about half the time.

Another distinction involves the concept of melancholic depression, meaning marked psychomotor retardation, anhedonia, and lack of mood lability. Melancholia can be seen as the opposite of mixed depression. Studies find that melancholic depressive episodes are more common in bipolar than unipolar depression, although they also happen in the latter.

Psychotic depression has been consistently found to be much more common in bipolar than unipolar depression.

In sum, there are some differences between bipolar and unipolar depression, with more frequency of melancholic and psychotic depression in bipolar illness. Both of those states are associated with lower response to antidepressants, especially with new generation agents. In contrast, electroconvulsive therapy (ECT) is more effective for those conditions.

One similarity between bipolar and unipolar depression is the frequent occurrence of mixed states, which are probably the most common phenotype in those conditions. Some studies indicate that antidepressants are especially ineffective in the states, and are more likely to worsen those mixed states, with increased suicidality.

Thus, the problem with antidepressants in bipolar depression may not be so much that they are ineffective in bipolar as opposed to unipolar

illness, but rather that they are ineffective for mixed states, melancholia, and psychotic depression. Bipolar depression consists of these specific phenotypes, but so does, to a somewhat lesser extent, unipolar depression.

The PL editor gradually has come to the view that the psychopathology of depressive subtypes (i.e., melancholic versus mixed versus psychotic versus pure) may matter more than the issue of polarity (i.e., bipolar versus unipolar). One way of understanding a century of treatment and psychopathology studies is to conclude that antidepressants are generally less effective in any but the most pure non-psychotic presentations of non-bipolar depression.

“...the psychopathology of depressive subtypes (i.e., melancholic versus mixed versus psychotic versus pure) may matter more than the issue of polarity (i.e., bipolar versus unipolar)...”

PL Reflection

Many persons nowadays seem to think that any conclusion must be very scientific if the arguments in favor of it are all derived from twitching of frogs legs – especially if the frogs are decapitated – and that, on the other hand, any doctrine chiefly vouched from by the feelings of human beings – with heads on their shoulders – must be benighted and superstitious.

William James

Curbside Consults

Questions and cases from you

Question: Does quetiapine have any of the antidepressants' risks (for manic activation or rapid cycling) if used in the context of bipolar disorder, given its serotonin and other receptor profile?

PL: One way of answering this question is to infer that any medication that can elevate mood, i.e. improve depression, should also have some risk of causing mania, or cycling back-and-forth between mood episodes in the long term. It appears that some of the dopamine blockers that treat bipolar depression can cause mania, but less frequently and less severely so than with monoamine agonists. Specific agents that have some evidence in this regard are aripiprazole and ziprasidone. There are hardly any reports of mania being caused by quetiapine. Even though quetiapine is FDA-indicated for bipolar depression, the biochemical rationale for its efficacy is unclear. In contrast to aripiprazole, which is a dopamine agonist, and ziprasidone, which is a powerful serotonin and norepinephrine reuptake inhibitor, quetiapine has very little monoamine agonist properties, with only mild partial agonism at the 5HT1A receptor. It's an extremely sedating medication due to very high anti-histamine potency, though, and some have suggested that the large effect size seen in placebo-controlled trials of acute bipolar depression may be due

partly to the inability to truly blind patients who receive quetiapine versus placebo, because of the immense sedating properties of the former. So the apparent "antidepressant" effects of quetiapine may not be as large as suggested by the RCTs of bipolar depression. If this is the case, the relative absence of apparent manic induction would be consistent with less of an antidepressant effect than is commonly believed.

PL Reflection

What we give to the patient should...be a spontaneous affect, but measured out consciously at all times, to a greater or lesser extent according to need. In certain circumstances a great deal, but never from one's own unconscious. I would look upon that as the formula.

Freud

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THE PSYCHIATRY LETTER

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Are antipsychotics mood stabilizers?

This issue focuses on the classic question of whether antipsychotics (dopamine blockers) are “mood stabilizers.”

In the CME Special Article, the PL analysis concludes that antipsychotics (dopamine blockers) are not mood stabilizers, in terms of prevention of new mood episodes long-term in bipolar illness. This conclusion is based on the inherent invalidity of the research design of “enriched” maintenance trials, which is examined in detail in that article, and applied in detail to the Classic Article of the Month, which describes results from the main maintenance randomized trial that led to FDA indication of olanzapine for bipolar illness. The Drug of the Month is olanzapine, which is seen as mainly effective acutely rather than long-term, and which has major medical harms as risks. By the Numbers provides frequencies of relapse rates by natural history for mood episodes in unipolar depression and bipolar illness.

Eligible readers can continue to obtain continuing medical education (CME) and continuing education unit (CEU) credits for the special article, by clicking on the link on the website which will lead to post-test questions, after which credits are awarded. We hope you continue to take advantage of this opportunity in current and future issues of PL.

Please note the upcoming annual summer course in Cape Cod, directed by me, with the theme this year being: “Becoming a master clinician: Diagnosis, drugs, and existential psychotherapy.” If your schedules allow it, your participation there would be welcome. http://www.neei.org/cape_cod/Becoming_A_Master_Clinician.html

Thank you again for your support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: Are antipsychotics mood stabilizers?

Maintenance “enriched” studies are questionable

Chocolate and vanilla cake

Do you like chocolate cake?

Suppose that a pharmaceutical company decided to market chocolate cake. It wanted a Food and Drug Administration (FDA) indication for maintenance treatment with chocolate cake. It consulted with the FDA and got approval to design the pivotal research study this way: First, a sample of research subjects would eat chocolate cake and vanilla cake. If they liked vanilla cake only they would be excluded from further study. If they liked chocolate cake only, they would now be entered into a research study where they would be randomized to continue eating chocolate cake or eat vanilla cake instead.

“...the sample is preselected for subjects who have already responded to the medication being studied...”

What do you think the results of the “randomized” clinical trial would show? Have we now proven that chocolate cake is better than vanilla cake?

This is how the FDA approves maintenance treatment for antipsychotics for bipolar illness (and also for antidepressants in major depressive disorder).

“Enriched” but not better

The key issue in adjudicating the question of whether antipsychotics are mood stabilizers involves how the research studies test that question. The maintenance studies of dopamine blockers all use a similar basic design: they are “enriched” studies, also called randomized discontinuation trials (RDTs). The term “enriched” refers to the fact that the sample is enhanced in such a way that it is more likely to

show a treatment effect. Put another way, the sample is preselected for subjects who have already responded to the medication being studied. The problem, in the PL viewpoint, is that those studies test treatment response sample already preselected for treatment response. This is obviously a tautology, if true.

As described in the Classic Article of the Month, the basic enriched design of a RDT is as follows: a dopamine blocker is given to a group of patients with acute mania; those who don’t respond or don’t tolerate medication are then excluded; the remaining patients who have responded to the

dopamine blocker for acute mania are then entered into the randomized maintenance trial, in which they either stay on the dopamine blocker or come off it (receive placebo). They are followed for up to one year to see if new mood episode relapse occurs. If they relapse quickly on placebo, it is inferred that the dopamine blocker prevented the mood episode from occurring as quickly. As described in the Article of the Month, the PL critique is that most relapses occur within the first few months of the maintenance trial, meaning usually within 3 months after the dopamine blocker was stopped. These studies aren’t really showing benefit for prevention of mood episodes 6 months to one year or longer after the acute phase, but rather they are showing benefit during and soon after improvement from the acute phase.

All this research design lingo can be translated into clinical experience as follows: Suppose you have an acutely manic patient in hospital. You give that patient a dopamine blocker. The patient improves. You then stop the medication one

month later. The patient relapses two months afterward. Have you just proven that this medication is a long-term preventive agent for mood episodes that would happen years into the future?

In other words, patients are preselected for short term acute efficacy. In the supposed maintenance trial, one is still assessing short term acute efficacy rather than true long-term prophylaxis. This is the main critique made by PL.

The main response from the supporters of the enriched design is that the maintenance trial is capturing a different phase of illness, namely new mood episodes occurring outside of the acute phase of treatment. Let's examine if this is correct.

Another way to answer this question can be found in an analysis conducted by members of the PL editorial board. In that paper, we looked at data from the enriched maintenance trials of lamotrigine in bipolar illness.

The analysis was applied to antipsychotics for their enriched maintenance trials in bipolar illness, because the research design issues were the same. We did not have access to data from dopamine blocker trials, because the pharmaceutical companies who conducted those trials will not make those data publicly accessible to research scholars. However GlaxoSmithKline, the maker of lamotrigine, agreed to give its data to some researchers for analysis after its medication had gone into generic use. Thus we were able to reanalyze their data to address the questions being raised in this special article.

In that analysis, we assessed relapse in the maintenance phase in two ways: a) Did it occur before or after 6 months; b) What was its

“...patients are preselected for short term acute efficacy...[and] one is still assessing short term acute efficacy rather than true long-term prophylaxis.”

polarity? One enriched maintenance trial preselected patients who had acutely responded to lamotrigine for a depressive episode and then they were randomized to either continue or stop it. Another study preselected lamotrigine response for an acute manic episode, and then they were randomized to stay on or come off. Six months or longer was chosen to represent the maintenance phase of relapse, based on natural history research which shows that the untreated average acute manic or depressive episode in bipolar illness lasts about 3 to 6 months (see By the Numbers). Polarity of relapse gave an indication of whether the supposedly new mood episode was indeed different from the acute mood episode. If the polarity of the relapse was the same as the acute episode, and it occurred very quickly after the acute episode was treated,

the apparent relapse was likely to reflect the same recent mood episode, rather than representing a completely new mood episode. Indeed, most relapses occurred in less than six months after the maintenance trial began. Furthermore, all the mood episodes that occurred in the first 6 months were of the exact same polarity as the acute mood episode that had been used for preselection before the study began. In contrast, almost all the mood episodes that occurred after 6 months were of the opposite polarity of the original index mood episode before the study began. This finding is consistent with a century of natural history research indicating that mood episodes in bipolar illness cycle from one phase to the other. In other words, mania typically is followed by depression, and depression is followed by mania. If you don't prevent the opposite phase, it's probably because you aren't preventing the next mood episode.

An example is the aripiprazole maintenance study, which received an FDA indication. Acutely manic patients were preselected for aripiprazole response, and then randomized for up to 6 months to stay on or come off that agent. Aripiprazole only prevented manic, not depressive, episodes. Why? Is it simply because it works well for mania, not depression? This is highly unlikely given that aripiprazole has been proven effective for acute depressive episodes in major depressive disorder. In fact, it was ineffective in one placebo-controlled trial of acute mania. In contrast, the results would make sense if they simply reflect the fact that the study was not long enough, in the PL view, to assess new mood episodes, and that its lack of efficacy in the opposite phase of illness simply indicates that it wasn't preventing new mood episodes.

The PL editor believes that it is a hardly recognized fact that there has never been a negative enriched RDT of any medication in any psychiatric illness. Either all medications are immensely effective for everything, or this design is guaranteed not to fail, which is great for pharmaceutical industry profits, but which directs clinicians and patients into fools' errands.

In sum, these enriched studies aren't preventing new episodes, but simply retesting acute efficacy after already proving acute efficacy.

Definitions

This controversy can be addressed also as a matter of the English language. In a prior issue, PL expressed the view that the term "antipsychotic" is not a scientifically and clinically accurate term. PL prefers the term "dopamine blockers." These agents often are effective in non-psychotic conditions, like depression and mania. The term

"dopamine blocker" was suggested it because it is true, although it is not reflective of all of the biological effects of these agents, and it is neutral as to clinical effect. The term "mood stabilizer" also is meaningless scientifically. These medications do not "stabilize" mood, but rather they treat both acute depressive and manic episodes, and they prevent those mood episodes. What distinguishes these agents clinically to the greatest degree from other classes of medications is the long-term prevention of mood episodes. So the term mood stabilizer really does not capture what these medications do. A more neutral term that reflects their biological mechanism is "second messenger modifier."

"...So the question - 'Are antipsychotics mood stabilizers?' - can be translated...to the question - 'Are dopamine blockers second messenger modifiers?'"

So the question - 'Are antipsychotics mood stabilizers?' - can be translated more neutrally and scientifically to the question - 'Are dopamine blockers second messenger modifiers?' When restated this way, the answer is obvious. Dopamine blockade is not the same thing as second messenger modification. Just to clarify: dopamine blockade happens at the synapse and is associated with improvement in psychotic or manic symptoms primarily. It's an acute effect. Second messenger modification happens postsynaptically and it relates mainly to long-term changes in neurons and their connections with other neurons. Those biological effects would correlate more with long-term clinical effects of prophylaxis of mood episodes. In other words, the basic biological effects of these two different classes of medications differ and correlate with differences in clinical strengths, with acute symptom benefit for dopamine blockers and long-term prophylaxis for second messenger modifiers.

Therefore at one level we can assert that antipsychotics aren't mood stabilizers simply because dopamine blockers aren't second messenger modifiers.

Summary

In sum, the PL view is that antipsychotics are not mood stabilizers because "enriched" maintenance randomized discontinuation trials are inherently invalid based on their preselection of acute treatment efficacy, followed by reassessing acute treatment efficacy. They don't assess new mood episodes in the maintenance treatment of bipolar illness. Because they involve a tautology, they never fail. The FDA approves this design, but doesn't appreciate, in the PL view, the invalidity of how this design is used in psychiatric maintenance studies. This error results in major profits for the pharmaceutical industry, but misleads clinicians and patients into major errors in long-term treatment of bipolar illness.

Given these considerations, PL strongly recommends that clinicians shouldn't consider dopamine blockers as equal to or better than standard second messenger modifiers, like lithium. These maintenance studies don't justify replacing lithium with quetiapine, or replacing valproate with olanzapine. Rather PL recommends that the latter agents be used short term, preferably, and if used long-term, they

should be seen as *adjuncts only* to second messenger modifiers, not as "mood stabilizers" by themselves, that could be effective for bipolar illness *in place of* standard second messenger modifiers like lithium or valproate or lamotrigine or carbamazepine.

The PL Bottom Line

- "Antipsychotics" are not mood stabilizers because they have not been proven to prevent new mood episodes in believable maintenance studies.
- "Enriched" maintenance studies are not valid, preselecting acute treatment response and then assessing the same thing.
- Dopamine blockers are not second messenger modifiers; their different biological mechanisms reflect different clinical effects.
- Dopamine blockers should be used mainly short-term; if used long-term in bipolar illness they should be used as *adjuncts to* second messenger modifiers, *not as replacing* the latter.
- If you like chocolate cake, you're going to like chocolate cake. This doesn't mean that chocolate cake is inherently better than vanilla cake.

Clinical Tip

Instead of replacing lithium or divalproex with olanzapine or quetiapine, use dopamine blockers as adjuncts only in the long-term.

The point of the special article above is not to encourage readers to avoid dopamine blockers altogether in bipolar illness, but rather to understand that they should not replace standard second messenger modifiers, like lithium or divalproex. If used long-term, where they likely are still helpful, dopamine blockers should be given as *adjuncts to* second messenger modifiers, *not as replacements*.

Classic study of the month: *An maintenance randomized trial of olanzapine*

*Randomized, Placebo-Controlled Trial of Olanzapine as Maintenance Therapy in Patients With Bipolar I Disorder
Responding to Acute Treatment With Olanzapine.*

M. Tohen et al, Am J Psychiatry, Volume 163 Issue 2, February 2006, pp. 247-256

A demonstration of the invalidity of the enriched design

The first dopamine blocker to receive a maintenance indication for bipolar illness, which occurred about a decade ago in 2004, was olanzapine. That indication was based on multiple maintenance trials, all of which were enriched. One study involved addition of olanzapine to standard mood stabilizers (lithium or divalproex); another, which is presented here, involved monotherapy with olanzapine versus placebo. Besides these studies, other maintenance RCTs also were conducted in which olanzapine was compared to lithium, in one study, and compared to divalproex, in another study. This analysis focuses on the monotherapy study mainly, which was the basis for the FDA indication.

Background

This study was organized and conducted by Eli Lilly specifically to obtain FDA indication.

Read simply, as presented in the abstract, the results are that 225 patients received olanzapine compared to 136 patients who received placebo, for up to 48 weeks. After recovery from an acute manic episode with olanzapine, those who stayed on it had much more benefit than if they came off. The main outcome was time to a mood episode relapse, which was much shorter with placebo (median of only 22 days) versus olanzapine (median of 174 days). The overall relapse

“...why would all the patients in one arm suddenly relapse within weeks of starting the study?”

frequency was 80% with placebo versus 47% with olanzapine.

This basic description of the study results seems stunning. Olanzapine is incredibly effective. There is twice as much relapse if you don't take it than if you take it.

But even with this simple description, the results should raise a question in the mind of the reader. Note that placebo-treated patients relapse, on average, only 22 days into the study. That means that when the randomized study begins, and patients are given a double-blind pill and they don't know what they are receiving, the placebo patients relapse massively in just 3 weeks. Why is that the case?

If you start a research study designed to assess long-term relapse in one year of follow-up, why would all the patients in one arm suddenly relapse within weeks of starting the study?

Acute withdrawal effects

This brings us to a central demonstration of the invalidity of the enriched design: acute withdrawal effects. In the case of this study, acute withdrawal relapse with placebo is obvious.

Let's set the stage. Before the maintenance study began, patients were recruited with an acute manic episode and they were treated with olanzapine. This was not double-blind or placebo

controlled. It was open-label and unblinded, which means that the patients and doctors were engaged in standard clinical treatment, like you would conduct outside of research. The point was not to show that olanzapine was effective in acute mania; this was already proven. The point was to select out olanzapine responders and make them better so that you could then put them into the maintenance trial to see how long they would stay well. Thus, at the beginning of the maintenance trial, everyone is well. But a few months earlier, they were all in acute manic episodes, and responded to olanzapine.

The preselection process is the central place where the enriched design can become invalid. Let's review who was treated with olanzapine before the maintenance study began, and what happened to them.

In the acute mania phase, before the maintenance trial began, 731 patients were recruited and treated with olanzapine. On average they had two mood episodes in the prior year, one manic and one depressed. They had been in their current manic episode for about one month on average (median 31 days). As noted, 361 patients entered, the study, which means that about one-half of the sample (49.4%, 361/731) did not respond to or tolerate olanzapine for the acute manic episode.

So automatically the maintenance trial of 225 olanzapine and 136 placebo patients is actually a study in which twice as many patients were included originally, but half of them were

"You have only shown an acute discontinuation effect during the manic episode, not a prevention effect for new mood episodes."

excluded because they didn't do well with olanzapine.

So this is a preselected group of olanzapine responders, representing only about one-half of patients who have manic episodes.

Then, if they improved with olanzapine, they were put into the randomized trial after 2-4 weeks of staying well. The average amount of time before entering the maintenance trial was 2 weeks (median 15.9 days for olanzapine, 16.7 days for placebo).

So, to restate it in clinical terms: Suppose you had patients with acute mania, lasting for one month. You then treat them with olanzapine, and some improve and get well. Two weeks later, you stop olanzapine. What do you think would happen?

This fancy expensive randomized trial gives you a definitive answer: They would relapse in 3 weeks (median 22 days).

Have you just proven that olanzapine is effective as a maintenance treatment for prevention of new mood episodes 1 year or longer in the long-term treatment of bipolar illness? Have you proven olanzapine is a "mood stabilizer?"

No. All you have shown is that if you improve with olanzapine for an acute manic episode, you should not stop the dopamine blocker 2 weeks later. That doesn't mean you should stay on it for 2 years or 20 years.

You have only shown an acute discontinuation effect during the manic episode, not a prevention effect for new mood episodes.

PL Reflection

What hits you wakes you up more than what pleases you.
Montaigne

A picture instead of words

The figure tells the story. All patients are well initially, this means that they're in the one-half of the original acutely manic sample that responded to olanzapine. The y-axis represents their relapse rate, starting with 1.0 meaning that 100% are well. The x-axis is days to relapse. Looking at the placebo arm, you'll notice a steep fall as soon as the study begins, with one-half relapsing in 22 days, and about 80% relapsing by about 90 days. From 3 months onward, the placebo line is basically flat, as is the olanzapine line. In other words, all the action is in the first 3 months, namely, massive relapse rates with placebo, and less so with olanzapine. After 3 months, nothing seems to be happening.

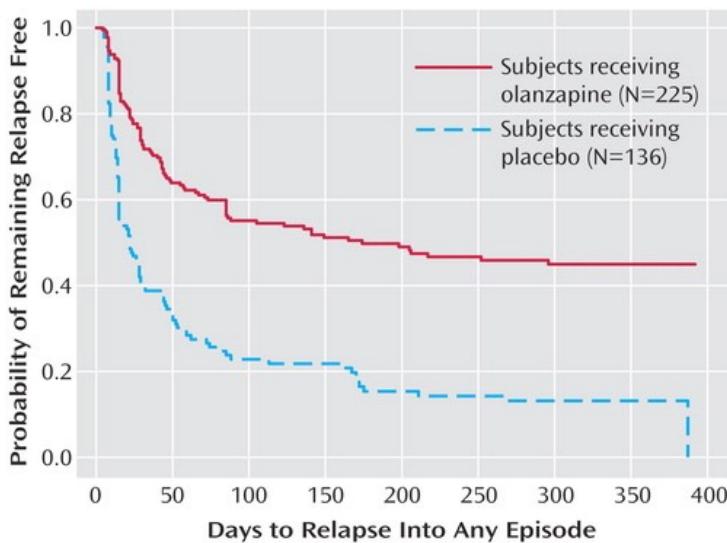
This graph supports visually what is described above conceptually and quantitatively. This study is not really a study of long-term relapse at 6 months to one year of new mood episodes, but rather of short-term discontinuation relapse in 3 months or less back into the acute manic episode that existed only a few weeks before the maintenance study began.

It doesn't, therefore, provide evidence of long-term maintenance prophylaxis of new mood episodes in bipolar illness.

What about the FDA?

If all this is true, readers might be wondering why the FDA didn't figure it out. If this study is so invalid, why did the FDA give a maintenance indication for olanzapine based on this design?

The answer is complex, but we can begin with the fact that the FDA accepts the enriched design as valid; FDA statisticians do not accept the critiques made here about the invalidity of the preselection process. And indeed, there are ways in which the enriched design can be seen as



potentially valid, if conducted in a different way than presented here, but that is a larger story (it relates to other topics, like oncology).

The FDA approved olanzapine with a low threshold of scientific evidence, partly because there were no prior dopamine blockers with indications for maintenance treatment for bipolar illness. When there are no or few proven treatments, the FDA is somewhat more liberal in approving new treatments. But after the approval, and during the peer review process for publication, important questions were raised about this study. The PL editor will disclose here, as he has in public lectures previously, that he was one of the peer reviewers for this study when it was submitted to the Archives of General Psychiatry, the highest ranking general psychiatry journal. In that anonymous peer review, the PL editor made the critiques described above, especially the massive acute withdrawal relapse rates with placebo. Based on that peer review and those of other reviewers, that journal rejected this study for publication. Thus, this study was good enough for FDA indication, and thus approved for general medical practice, but it wasn't good enough for publication in the Archives of General Psychiatry. (Readers will note that it was

eventually published in a different journal two years after the same study passed FDA review for an indication.) The questions that were raised in the scientific community by some researchers influenced the FDA to some extent in that, in October 2005, about a year after giving approval, the FDA held an advisory committee meeting in which it wanted to get advice on the question of whether and how the olanzapine-style trial could be improved to be made more valid. The main focus was on the 2-4 week period of remission from acute mania required before the study began. The FDA wanted to suggest a 6 month or longer period of remission before entry into a maintenance trial. This suggestion was reasonable, in the PL view, because it is consistent with the natural history of bipolar illness, as described in *By the Numbers*. It takes up to 6 months to get out of the acute phase for manic or depressive episodes, so if you want to be certain you are preventing new mood episodes in the maintenance phase, not just relapsing back into the same acute mood episode which you had before the randomized maintenance study started, then 6 months or longer is a wise time frame.

FDA meetings are publicly available, so readers can read, if they like, the minutes of the 2005 meeting online (available here <http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4186MI.pdf>). A few academic experts, who claimed to be present on their “own dime”, joined pharmaceutical industry representatives and some patient advocates, in opposing the FDA suggestion. The opposition from the pharmaceutical industry was obvious: to require 6 months or longer of treatment, even before the maintenance study officially begins, would be very expensive for them, and difficult to complete. Perhaps they knew that if half the patients drop out with just a few weeks of treatment, as happened in this olanzapine study, very few

patients would remain in treatment 6 months later, and thus their maintenance trials would have tiny samples and would fail. The academic experts and patient advocates took the view that the FDA request was an example of “stigma,” putting too high of a standard on psychiatric research, beyond what is the case with other medical conditions. They didn't appear to realize that the enriched design is, in fact, a very low standard of scientific proof, as discussed in this issue of PL. In fact, in the PL editor's review of the medical literature on this topic, there is no other medical discipline in which the FDA approves long-term maintenance treatments based on enriched randomized discontinuation designs. All other medical specialities have a higher standard: you cannot preselect your patients at all for treatment response. Thus, in the PL view, the academic experts in particular were uninformed in their attack on the FDA suggestion, and the upshot, as can be read in the minutes, was that the FDA advisory committee decided against the idea of having a long period of remission before enriched maintenance trials in psychiatry. All agreed, though, that 2-4 weeks was much too short, and a new standard was set of 2-4 months of remission, which has become the way other dopamine blockers have been assessed since that time (like aripiprazole, quetiapine, and lurasidone).

In the PL view 2-4 months is better than 2-4 weeks, but it still isn't long enough to avoid bias against placebo due to acute withdrawal relapse, and it still does not address the basic problem that preselection for drug responses biases the results in favor of the drug.

Who stays well?

Even if you took these results at face value, and believed that they are valid, one still should ask an important question: Not how good was

olanzapine compared to placebo, but how good was olanzapine, period?

The benefits suggested in the olanzapine group may not be as great as they seem, when you switch your focus from the relative effect of comparison to placebo and instead look at the absolute effect of overall benefit.

Recall that these patients were preselected to respond to olanzapine already. Recall also that the natural history of bipolar illness is that the average patient has one episode per year (see "By the Numbers"). In this study, patients were manic just before the study began, and they were required to have had at least 2 other manic episodes in the prior 6 years of treatment, thus their natural history was selected such that they were likely to relapse in 1 year of follow-up, and definitely would relapse within 2 years.

How did olanzapine do in these patients?

About one-half (47%) relapsed during the study, and they did so, on average, by about 6 months (median 174 days).

So, in a patient population selected to relapse by natural history once in 1-2 years, one-half of them relapsed within 6 months, despite being preselected to respond to olanzapine and *staying*

on olanzapine after getting better from an acute manic episode. This relapse rate doesn't bode well. At that pace, everyone would have relapsed in 1-2 years of follow-up, just as would be expected if they were completely untreated.

(Remember the placebo group isn't a valid assessment of non-treatment in this study because of the invalidity of the enriched design, leading to massive placebo relapse just 3 weeks into the study due to acute withdrawal effects, as described above).

The PL Bottom Line

- The olanzapine trial does not show long-term efficacy in prevention of mood episodes in bipolar illness, despite FDA indication.
- It mainly reflects massive and immediate placebo relapse due to an acute withdrawal effect after recovering from acute mania a few weeks earlier with olanzapine.
- Even if taken at face value, half of olanzapine-treated patients relapsed in 6 months, a pace which is consistent with the natural history of recurrence of mood episodes.
- The FDA sought to correct some of the research design problems involving rapid acute withdrawal, but it was resisted.

PL Reflection

Getting acquainted with ourselves is unsettling. There are forbidden thoughts but also commonplace ones. I have often remarked that when the psychotherapist opens us up, he finds what the surgeon finds, all the usual organs. The unique contour of our being only shapes a universal content. It is hard to see ourselves because the individuality we may prize is hardly there. Looking in the mirror we see everyone.

Leston Havens, Coming to Life

Drug of the Month: *Olanzapine (Zyprexa)*

Some benefit, many harms

Biological mechanism

Olanzapine is a dopamine blocker with potent D₂ receptor blockade, along with strong anticholinergic effects. The D₂ blockade is dose dependent, such that at 10-20 mg/d, over 90% of D₂ receptors are blocked. This level of D₂ blockade produces extrapyramidal symptoms (EPS) such as parkinsonian tremor and rigidity, and akathisia. The parkinsonian effects are somewhat mitigated by this agent's anticholinergic properties, but the latter cause their own side effects, especially cognitive impairment, sedation, and constipation.

Like all modern dopamine blockers, it also has serotonin-2 receptor blockade, which likely produces weight gain.

Olanzapine also has strong anti-insulin effects, which produces the dire metabolic syndrome of diabetes, hypertension, and hyperlipidemia, along with marked weight gain and abdominal girth.

Other features

Olanzapine causes notable abnormalities in liver function tests (LFTs), more so than divalproex, and it can cause death by acute diabetic ketoacidosis.

Clinical efficacy

Olanzapine has been shown to be effective for manic episodes and for schizophrenia, and also has FDA indication for maintenance treatment of bipolar illness. It has been proven ineffective in the acute major depressive episode in both bipolar depression and in MDD. However, when combined with fluoxetine (olanzapine-fluoxetine combination, Symbyax), it has been proven effective for the acute bipolar depressive episode.

In the CATIE study, it was shown to be very effective for schizophrenia, but it also had more side effects and was less safe than other antipsychotics.

Dosing

5-10 mg/d are effective for moderate mood states, with higher doses need for severe mania and schizophrenia.

The PL Bottom Line

- Olanzapine is very effective for acute mania and schizophrenia.
- It is much less safe than most other dopamine blockers.
- Its other utility, such as in maintenance treatment in bipolar illness, is questionable for the reasons given in the Special Article.

Fast Facts: Olanzapine

Typical dose: 5-20 mg/d (range)

Biological mechanism: dopamine and serotonin receptor blockade, anti-insulin effects

Typical side effects: marked weight gain, EPS, sedation, constipation

Less common but important side effects: metabolic syndrome

Medically important side effects: metabolic syndrome

Clinically proven efficacy: Acute mania, schizophrenia

By the Numbers

Natural history of mood episodes

For over a hundred years, manic-depressive illness has been defined, but for most of that time, no effective treatments existed. Thus, there is an extensive research literature on the natural course of this condition, especially based on the late 19th and early 20th century work in Germany inspired by Emil Krapelin and his coworkers. Here are some statistics based on those research studies. These time-frames all apply to *the untreated duration of mood episodes, with their spontaneous recovery naturally, without any treatment at all.* (For a review of these sources, see the "Natural History" chapter of Manic-Depressive Illness, 2nd Edition, 2007, Frederick K. Goodwin and Kay R. Jamison).

- The natural duration of an acute depressive episode in unipolar depression is 6-12 months.
- The natural duration of an acute depressive episode in bipolar depression is 3-6 months.
- The natural duration of an acute manic episode in unipolar depression is 2-4 months.
- The typical patient with bipolar illness has an episode per year.
- The typical patient with unipolar depression has an episode every 3-5 years.
- After an acute manic episode, over 90% of patients will have a second mood episode within 5 years.

Curbside Consults

Questions and cases from you

Question: How long would you use Symbax (olanzapine/fluoxetine) for bipolar depression?

PL: That medication is proven effective in an 8 week trial, as with most acute depression studies. Thus it is proven for 2 months, not longer. It has not been studied in maintenance prophylaxis designs, and the olanzapine maintenance studies do not include fluoxetine (besides having the above limitations). Thus, you cannot and should not assume maintenance efficacy based on acute efficacy. Otherwise, everyone who receives penicillin should take it forever. For that reason, PL recommends use of Symbax, if given, for the acute phase only, not long-term.

PL Reflection

Philosophical insight requires that we be content with what is possible for us. We have to operate within limits wherein realization through us is possible. If we want more than we know and are able to do, our thinking becomes deceptive and ruinous at the same time.

Karl Jaspers

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THE PSYCHIATRY LETTER

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The suicide issue

This issue returns to the spring theme of suicide. A year ago, in the April 2015 issue, the Special Article reviewed important aspects of explaining suicide. PL noted that the psychiatric disease that most causes suicide is manic-depressive illness, and that because of the interaction with sunlight, the highest peak of suicide occurs in the spring months, hence the devotion of this month's April issue again to this topic.

In the CME Special Article this year, PL focuses on research on very low doses of lithium in drinking water, and its apparent anti-suicide benefits. The PL analysis concludes that doses as low as 25 mg/d of lithium carbonate could be effective and should be considered in clinical practice. The Current Article of the Month examines a recent Danish study on the natural history of treated major depressive disorder (MDD), which found that most patients don't remain in treatment, even for a short time. The meaning of this result is explored in the Clinical File contribution this month from Dr. Ross Baldessarini. The Drug of the Month is asenapine, a new dopamine blocker with sedating properties that has minimal evidence of metabolic syndrome risk. The Interviewing column explores ways to approach the suicidal patient with a method that employs comments rather than questions.

As with all issues beginning January 2016, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

I invite you again to my upcoming annual summer course in Cape Cod, which has a new theme this year: "Becoming a master clinician: Diagnosis, drugs, and existential psychotherapy." I hope to see some PL readers there for a week of lively discussion and interaction.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: Lithium in drinking water

A tiny dose, about 25 mg /d of Lithium Carbonate, may prevent suicide

Introduction

In the special article and classic article last year, evidence was reviewed regarding antidepressants and suicide, and PL concluded there was little benefit if any with those agents, but there was probably a small amount of harm. Lithium, on the other hand, was shown to have clear and large benefit for suicide prevention. The current article of the April 2015 issue reviewed a meta-analysis of lithium studies which demonstrates that benefit, and readers are encouraged to revisit that article if they want to see that evidence for themselves.

In this special article, we plan to extend that prior discussion by focusing on research on very low doses of lithium in drinking water, and its apparent anti-suicide benefits.

An essential mineral

We think about certain minerals as being essential for life: there's calcium and magnesium, which seem needed for normal heart rhythm. There's sodium and potassium, needed for cell membrane function. These are all basic ions, part of the periodic table of chemical elements. They are essential for life; but we don't think of them as toxic or dangerous. Yet, too much magnesium or potassium causes cardiac arrhythmia leading to immediate death. Too much calcium can cause delirium, and too much sodium causes swelling of the brain.

Lithium also is an essential mineral, needed for viability of life. If you have none, zero, then the organism's ability to live is harmed. We all know too much is toxic, and so it is often seen as dangerous. Yet we don't seem to fear potassium or calcium in the same way.

All drugs are toxic; only the dosing and indication makes them therapeutic. That's the old maxim, dating back to Paracelsus and later William Osler. But the maxim applies not just to "drugs"; it applies to the chemical elements themselves, the basic building blocks of biological life. We should say instead:

All elements of chemistry are toxic; it's only their amount and combinations that make them therapeutic.

First, let's appreciate that lithium is essential for life. Chemists and geologists study such matters by exposing animals to a diet deficient or wholly lacking in a certain element. They then compare those animals to others who are fed a diet rich in the element. If one group dies more quickly than the other, then the element is deemed to be essential for viability of the animal.

With lithium, this research has been conducted with sheep. It turns out that sheep deprived of any lithium have much shorter lifespans than sheep who eat the usual amount of lithium in the diet. These animal studies provide context for studies of effects of lithium in drinking water.

Lithium in water studies

Lithium seeps from rocks into the ground, where it is taken up into water, or into vegetables. It is consumed by animals and humans through eating vegetables or meats of other animals who have eaten vegetables. Eggs, for instance, have a notable amount of lithium. All this depends of course on the source of such food. Since food is shipped to different parts of the world, a better

measure of local lithium supply is the drinking water, which tends to come from local sources.

In the last 50 years, about ten different studies have been conducted of the biological, medical, and social effects of lithium in drinking water. To give a sense of these studies, let's take the first from 1970, which looked at lithium levels in the 100 largest American cities. It found lower overall mortality in areas with higher lithium levels; much of this benefit was related to less death from cardiovascular disease. Another 1972 study compared different counties in Texas. More recently, a 2009 study in Japan looked at over 1 million people, and 4 reports in 2011-2012 came from Japan, England, and Austria, and a new Texas study was published in 2013. These studies mainly focus on suicide, and, rather consistently, they find lower suicide rates in those regions where lithium levels are higher in water compared to those regions with lower lithium levels.

The most obvious question in such population studies is the issue of confounding bias, as discussed in the fourth PL issue. What other factors in these populations could affect suicide rates? Could it be that the lithium association is spurious because of those other factors? As described last year in PL, there are many known risk factors for suicide, such as depression and social isolation, which cannot be assessed in such large national studies. Some proxy measures can be assessed, though, such as living in cities versus rural areas, or measures of poverty and unemployment rates in areas being studied. Some of the recent studies controlled for those social factors. Still, since randomized analysis is impossible in studies of entire countries, we will be left with some uncertainty in such large-scale

“... very low doses of lithium could be sufficient for...suicide prevention....”

analyses. With that caveat, controlling for some social confounding factors, there still is an association between more lithium and less suicide.

The fact that lithium has been proven to prevent suicide in randomized clinical trials, as reviewed in the meta-analysis in last year's April PL issue, is the main scientific rationale for accepting the likely validity of that same association in the multiple studies of lithium in drinking water.

In other words, the water studies don't "prove" that lithium prevents suicide. We already know that is the case with the meta-analysis of RCTs of bipolar illness. What the water studies strongly suggest is that very low doses of lithium could be sufficient for such suicide prevention purposes. We now turn to the meaning of the concept of "very low dose" lithium.

How low is low?

If this association is real, then we can turn to characterizing what it might mean in clinical settings. Clinicians who prescribe lithium are used to thinking of standard doses as around 900 mg/d, which produces blood levels of about 0.6-1.0, which is proven therapeutic for acute mania or prophylaxis of bipolar illness. Lower doses are seen as "low"; thus, for clinicians a dose of 300 mg/d of lithium carbonate would be seen as "low" or "subtherapeutic." Most would consider that dose clinically ineffective.

However, when you start to think about lithium doses from the perspective of the normal diet, rather than prescribing pills for bipolar disease, then the concepts of "low" and "high" begin to change. In the normal diet, we consume about 1 mg/d of elemental lithium. In the water studies, "high" amounts of lithium meant more than that amount. Thus, about 5 mg/d of elemental lithium

would be considered high by dietary standards. This kind of dose produced apparent suicide prevention benefit.

It is important to translate elemental lithium into lithium compounds. For lithium carbonate, 100 mg/d of that compound is equivalent to 18.8 mg/d of elemental lithium. Thus, the “high” dietary amount of 5 mg/d of elemental lithium translates into about 25 mg/d of lithium carbonate. This dose would be considered vanishingly low by clinicians who would think of 300 mg/d as “low”. In fact, 300 mg/d of lithium, which is about 56 mg/d of elemental lithium, is quite high. It is 56 times more than the normal amount consumed in the diet. The “standard” lithium dose of 900 mg/d of lithium carbonate translates to 169 mg/d of elemental lithium, which is extremely high, using the standards of naturally consumed lithium.

In other words, if the suicide prevention studies of lithium are correct, clinicians may be justified in rethinking their conception of lithium dosing, and coming to the conclusion that there is almost no minimum to lithium dosing. Any amount of lithium is better than none, at least for suicide prevention.

This perspective would be justification for giving very low doses of lithium, as discussed in the Clinical Tip below, for suicide prevention.

PL Reflection

The first principle of science is that you must not fool yourself, and you are the easiest person to fool.

Richard Feynman
Physicist

Indications

Another aspect to the water studies is that they showed suicide prevention in the general population, not just people with bipolar illness. Thus, they can provide justification for considering lithium in all suicidal persons, irrespective of diagnosis. Given the risks of toxicity and side effects, if lithium is effective in very low doses for suicide, such dosing could allow for more feasible use in a wide range of populations at risk for suicide, such as military veterans and athletes with chronic traumatic encephalopathy. In other words, don't think of lithium for suicide prevention as only being limited to bipolar illness.

“...there is almost no minimum to lithium dosing...”

A word of caution regarding “parasuicide”, such as self-mutilation and self-cutting.

The meta-analysis of RCTs showed that lithium did NOT reduce parasuicidal behavior. Thus, these considerations apply to serious suicide risk, such as overdoses or hanging or such behavior, and do not apply to persons who only engage in self-mutilation, such as in many cases of borderline personality.

The PL Bottom Line

- Studies of lithium in drinking water show that its anti-suicide effects are present in the general population.
- Lithium should be considered for suicide prevention broadly, not limited to mood conditions.
- It can be given at very low doses, equivalent to about 25 mg/d of lithium carbonate.

Clinical Tip

How do you give very low dose lithium, whether for suicide prevention or for other uses such as dementia prevention?

The PL editor has been asked this question often and has evolved the following approaches to very low dosing of lithium. This issue focuses on suicide prevention, but as mentioned on the PL website, very low dose lithium has been suggested as possibly effective for dementia prevention as well. Thus, these dosing suggestions could apply for both uses.

The above lithium in water studies suggest that more than 1 mg/d of elemental lithium can be effective for suicide prevention. If we take 5 mg/d of elemental lithium as a clearly “high” amount from a dietary perspective, then it translates to about 25 mg/d of lithium carbonate. The smallest pill size of lithium carbonate in the United States is 150 mg/d. Thus a half pill taken every other day should be equivalent to 37.5 mg/d, which would approximate the lithium in water dose of somewhat more than 5 mg/d of elemental lithium.

At least two other approaches exist:

- 1) *Lithium citrate* is available as 300 mg/d in 5 ml liquid form. Thus 1 ml in a dropper would be equivalent to 60 mg/d. Taken every other day, the dose would approximate 30 mg/d of lithium citrate, which is equivalent to about 5 mg/d of elemental lithium.
- 2) *Lithium orotate* is available as an over the counter preparation, with the standard 120 mg/d pill size being equivalent to 5 mg/d of elemental lithium. Its safety is little studied, unlike lithium carbonate, but it is widely used by many in the general population, and it has the advantage of not requiring a prescription or any cutting of pills or small amounts of liquid.

PL Reflection

Insanity is often the logic of an accurate mind outtasked...Stupidity often saves a man going mad. We frequently see persons in insane hospitals, sent there in consequence of what are called religious mental disturbances. I confess that I think better of them than of many who hold the same notions, and keep their wits and enjoy life very well, outside the asylums. Any decent person ought to go mad if he really holds such opinions.

Oliver Wendell Holmes Sr.

Current study of the month: *The natural history of treated depression today*

Heterogeneity in 10-year course trajectories of moderate to severe major depressive disorder: a Danish National Register-based study.

KL Musliner et al, JAMA Psychiatry 2016; 73:346–353.

Few people with “MDD” return for treatment

In Scandinavia, medical treatment is provided and recorded in a national health care system for all people. One of the benefits of this system is that researchers can access data on medical treatment for all people in those countries. This Danish study uses the national medical database to look at the course of treatment for depressive conditions, as diagnosed by clinicians as similar to the DSM-5 definition of “major depressive disorder” (MDD).

The sample identified consisted of 11,640 persons in Denmark who were diagnosed with MDD and for whom researchers had medical data for 10 years in prospective follow-up. They were diagnosed in the 1995–2002 time period. A majority were women (64%) as is typical of depression studies.

The main outcome measure was whether or not they continued to be seen for MDD treatment in each year of follow-up.

Four groups

Four patterns of outcome were observed:

1. In the majority - 77% of the sample - their contact for follow-up treatment was not extensive and was limited to 2 years or less.
2. The next largest group - 13% of the sample - was far smaller, but it was this group that had

“...the vast majority of patients just didn’t need much attention. It isn’t clear whether this is good or bad news.”

extensive contact for up to 5 years, with less contact afterwards.

3. A third small group - 7% of the sample - had continued contact in the second half of the 10 years of follow-up (the second five-year period).
4. The smallest group - only 3% - had consistent and persistent contact for treatment of MDD in the entire 10 year period.

Why did most people not come back?

The first thing to notice is that the vast majority of patients just didn’t need much attention. It isn’t clear whether this is good or bad news.

The rosiest interpretation would be that they all were cured with their prescription of an antidepressant and they didn’t need much further contact for a decade. This optimism is unwarranted, though, with the low one year response rates in the STAR*D study, as reviewed in the January 2016 PL issue. (In that large randomized trial, overall one-year response was present in about 1/3 of the sample).

The less rosy interpretation would be that most patients either didn’t respond to, or didn’t tolerate, treatment, or simply changed their mind for psychological reasons, such as denial or stigma. There is a huge literature supporting the impact of these factors on clinical outcomes.

An important piece of context is that many studies of compliance in outpatient psychiatric treatment of non-psychotic conditions indicate that about one-half of patients drop out of treatment within the first few months to one year. In other words, the baseline for any psychiatric diagnosis (excluding severe psychoses like schizophrenia) is that about one-half of patients will not return for adequate treatment.

So the 75% low-treatment rate in the Danish study should be compared to a 50% baseline. It may not be as terrible as it seems, but it still its worse than what is seen in other settings or other studies. What explained the 25% or so of extra failure to follow-up on treatment?

One idea that PL would like to raise is that this added failure may be due partly to a failure in the concept of “major depressive disorder” (MDD). When many different kinds of depression are mixed into a single broad category, including many persons with “neurotic depression” who have mild constant depressive/anxiety symptoms, it may not be surprising that they don't change much with some SRI treatment, and thus they don't return for more of the same.

Another possibility, as suggested in the Clinical File below by Dr. Ross Baldessarini, is that our drugs may just not work well in real life.

Predictors

In contrast to the above comments, the authors of the paper focused instead not on the majority of patients who didn't come back, but rather on the minority who remained in treatment. They had good medical chart data on some, but not

most, important clinical features of practice. Thus, they had information of family history of other psychiatric conditions, and they had chart data on severity of symptoms.

They found that the 3% group with the most treatment had the most severe symptoms and was more than twice as likely to have family history of schizophrenia. Since “MDD” is not associated with a genetics of schizophrenia, this observation raises some questions about accuracy of MDD diagnosis. Only 4% of the sample had schizophrenia genetics, and only 2% had recorded bipolar family histories. Of course, these assessments also could be inaccurate, with some underreporting, given that this was a national clinical database of real-world treatment, not a research study in which patients were recruited and analyzed with a specific research protocol of interviews.

“Since the course of illness is a diagnostic validator...this study... throws doubt on the scientific validity of the MDD concept”

The authors' main conclusion was that MDD is “heterogeneous” in its outcomes.

Since the course of illness is a diagnostic validator, as discussed in the first PL issue, this study is another new replication that throws doubt on the scientific validity of the MDD concept. This is so despite the fact that the profession has refused to change the basic structure of the MDD concept one iota, including in DSM-5, since its initial formulation in 1980 with DSM-III.

The PL Bottom Line

- The course of MDD in this study was heterogeneous, throwing doubt on the validity of the MDD diagnosis.
- The vast majority of patients appear to have dropped out of treatment, or simply not needed much treatment.

Drug of the Month: Asenapine (*Saphris*)

A new sedating dopamine blocker without metabolic harms

Biological mechanism

Asenapine is a dopamine blocker with potent D₂ receptor blockade, along with strong antiadrenergic effects. The D₂ blockade is dose dependent, such that at 10-20 mg/d, over 90% of D₂ receptors are blocked. This level of D₂ blockade produces extrapyramidal symptoms (EPS) such as akathisia, which appears to be the main clinical problem with this agent, as with the entire dopamine blocker class.

Like all modern dopamine blockers, it also has serotonin-2 receptor blockade, but it seems to have little to no weight gain. Asenapine does not have apparent anti-insulin effects, and thus it does not appear to cause or worsen the metabolic syndrome of diabetes, hypertension, and hyperlipidemia.

It has moderate anti-alpha adrenergic effects, like risperidone. This effect may be a mechanism for notable sedation with asenapine. Clinically this sedation is not as extensive as quetiapine, but it is more than other agents. Some patients cannot tolerate this medication due to oversedation, but for other patients this effect can help insomnia, and it can be a sedating alternative to quetiapine, without the weight gain and metabolic harms of the latter.

Other features

It is given sublingually. Despite flavoring attempts, it can be distasteful for some persons.

Clinical efficacy

Asenapine has been shown to be effective for manic episodes and for schizophrenia. It does not have data or FDA indications for bipolar depression or MDD. However, in its mania studies, asenapine improved depressive symptoms in subjects with mixed manic episodes.

Dosing

5-10 mg/d are effective for moderate mood states, with higher doses need for severe mania and schizophrenia.

The PL Bottom Line

- Asenapine is proven effective for acute mania and schizophrenia.

- It is a good sedating alternative to other dopamine blockers.
- It has minimal weight gain and no apparent risk of metabolic syndrome or worsening diabetes or cardiovascular risks.
- Akathisia remains an important risk, to be managed by keeping the dose as low as feasible and/or using propranolol.

PL Reflection

The world has so lost its sense of humor that it can't laugh - damn it, it can't even cry.

Henry Adams (in a personal letter circa 1910)

Interviewing

Approaches to assessing suicide

Interviewing the suicidal patient is one of the most difficult of clinical tasks. There is an immense amount of secondary gain involved, since patients tend to know that if they are deemed suicidal, they might be hospitalized against their will. Hence they are incentivized to understate or even deny expression of suicidal symptoms. Here PL will describe an approach to the clinical interview, focusing on suicide prevention, that may help compensate for this problem of underreporting of symptoms. This approach is derived from the work of Leston Havens, especially as expressed in his classic paper on "Soundings." Havens' view was that the clinical interviewer should try to become like a tuning fork, the classic medical instrument that would vibrate at different pitches depending on whether it was placed over something solid (like a tumor) or something hollow (like liquid in an organ). We need to vibrate with the patient depending on his/her reactions to our conversation.

The key concept, especially relevant to suicide, is: Do not ask questions. Make comments, and vibrate to the response.

Let's discuss how this can happen through an imagined interview, with initial theoretical context. The basic idea is that the patient's true suicidality can be seen as identifiable on a spectrum of expressions, ranging from complete denial on one end, to straightforward assertion on the other end, with many variations in between of different amounts of suicidality. The interviewer makes comments at the extremes, and depending on the patient's response, tries to move closer and closer to the target somewhere in the rest of the spectrum, which represents the truth.

Consider the following interview, conducted in the setting of some known suicide risk factors, in an outpatient setting. Thus, the interviewer has some concerns about possible suicidality, and the patient wants to avoid involuntary hospitalization. For the purposes of this case, we assume the clinician and patient know each other and have been in treatment for some months:

Clinician: I suppose you must be thinking of killing yourself right now.

Patient: Don't be silly Doc!

C (with some lack of seriousness): Then I suppose you never do.

P: Could be. You tell me.

C: That's hard to believe. Even I feel suicidal sometimes.

P: Ha! Now that's hard to believe.

C (wanting to shift the focus): Let's consider it another way. We both know there are times in the past where you haven't wanted to live.

P: Yes

C: And one of those times could be recent.

P: Maybe

C: It could even have been in the last few weeks.

P: Possibly

C: It might even have been this week, or the last few days.

P: I don't think so.

C: I understand. So you had some of those thoughts last week, but now they're all gone.

P: Well (long pause), mostly.

The clinician knows that the answer is more in the pause than in the denial, which wasn't a complete denial in any case. Notice that the clinician did most of the talking, gently nudging the patient to tell the truth. Notice also that the approach requires some attention to nonviolent aspects of communication, both tone and pausing. In assessing a very serious problem, sometimes an overly serious demeanor can be counterproductive. Even surprising expressions made by the clinician, Havens claimed, can be justified as part of the therapeutic maneuver (called "counterassumptive statements"). Whether the therapist ever truly had been suicidal or not, for instance, is less relevant than whether such a statement, made with some informality, would lead the patient to be more forthcoming about his own mental states, which is the purpose of this kind of interview. Obviously, this approach works when there is some relationship of trust between clinician and client. Even with all this work, the clinician can't be certain because the patient doesn't clearly state the amount of suicidality that is present and exactly when. But direct questioning would not like produce that information either, so this indirect line of conversation can be seen as an approximation to the truth. Combined with other clinical data, not just the interview itself, the clinician then could make some judgments about the extent of the patient's suicidality, and any proposed changes in treatment, including hospitalization.

PL Reflection

All successful medical diagnosis is the precise and intelligent recognition and appreciation of minor differences.

Joseph Bell MD (teacher of Arthur Conan Doyle MD, who created the Sherlock Holmes series)

Clinical Files

On the limits of knowledge in clinical research

Ross J. Baldessarini, MD

Professor of Psychiatry (Neuroscience), Harvard Medical School; Director, International Consortium for Mood & Psychotic Disorder Research; Mailman Research Center, McLean Hospital

We recently reviewed long-term studies of morbidity among clinically treated patients diagnosed with bipolar-I, -II, or major depressive disorder [1]. Levels of morbidity were remarkably high, averaging 40%–50% of time-ill during several years of follow-up. Fully three-quarters of that residual morbidity was depressive among bipolar disorder subjects, and more in major depression. Evidently, standard psychiatric treatments may be quite effective against mania, but much less so for bipolar or unipolar depression. However, important limits on inferences that can be drawn from such data should be considered.

A new report based on Danish federal register data considered nearly 12,000 adult patients with moderate-to-severe major depressive disorder followed over 10 years for interactions with healthcare providers after an index major depressive episode [2]. Strikingly, more than three-quarters of the sample encountered initially were rarely seen thereafter. Far fewer subjects required prolonged initial treatment (13%), experienced apparent recurrences (7%), or were treated more or less continuously (3%).

Such findings indicate that mood-disorder patients who remain in contact with clinical caregivers for several years represent a subgroup—probably a minority not representative of broader, unselected samples. Many persons with mild or transient mood affective illness may not seek help at all. Accordingly, clinical samples are likely to

over-represent those with relatively severe, recurring, or persistent illnesses. Furthermore, most long-term clinical studies of morbidity occur in academic or other institutional settings typically providing tertiary-care services, with further bias toward more severely ill or less treatment-responsive cases.

The point of these considerations is that typical clinical samples are likely to over-represent patients with substantially symptomatic conditions who seek and remain in treatment. That is, our findings [1] of high levels of unresolved depression in such samples may be valid for the kinds of samples that are available, and underscore the challenging nature of mood disorder patients who are encountered in referral and teaching centers. However, such samples probably are not representative of all persons with mood disorders. Such limitations of sampling must surely affect most samples of treated patient-subjects followed over prolonged times.

If clinical samples are as biased as is proposed, it becomes a daunting challenge to consider how better to obtain more broadly representative samples of ill persons of any kind. Given presumably high rates of potential subjects who never seek clinical help or fail to follow-up with initially recommended treatment, short of house-to-house surveys (which have their own limitations and shortcomings), it is very difficult to know how to make sampling more representative of the broad range of affected individuals.

Perhaps some solace can be found in considering that knowledge of the course of illness and response to treatment in even grossly unrepresentative clinical samples may have some value. In particular, they can provide insights of great interest to clinicians and patients in the kinds of clinical settings represented in feasibly

acquired samples. The basic question here may be whether it is better to live with partial and potentially misleading evidence, or to abandon all hope of getting at the *Truth* and to continue to wallow in ignorance.

1. Forte A, Baldessarini RJ, Tondo L, Vázquez GH, Pompili M, Girardi P. Long-term morbidity in bipolar-I, bipolar-II, and major depressive disorders. *J Affect Disord* 2015; 178: 71–78.
2. Musliner KL, Munk-Olsen T, Laursen TM, Eaton WW, Zandi PP, Mortensen PB. Heterogeneity in 10-year course trajectories of moderate to severe major depressive disorder: a Danish National Register-based study. *JAMA Psychiatry* 2016; 73:346–353.

PL Comment:

PL thanks Dr. Baldessarini for his wise commentary on this recent study and his own research on this topic. For PL readers who may not be familiar with his work, Dr. Baldessarini has been an active basic and clinical researcher in psychopharmacology since for over four decades. A lifetime of experience and study goes into his commentary. As discussed in the current study of the month above, the new Danish study raises some important questions. It is set up as a natural history study, but it could equally be seen as a study of the at least two other things: a) the validity of the MDD concept; b) the nature of psychiatric practice. The key finding that Dr. Baldessarini highlights is that the majority, about 75%, of patients initially diagnosed and treated with MDD drop out of treatment. Does this mean that they didn't need treatment to begin with? Or does it mean that they didn't improve, and gave up? Or perhaps they really need treatment, and are simply in denial.

As noted in the Current Article, PL thinks that this kind of heterogeneity should raise some doubts as the scientific validity of the whole MDD concept. Maybe the outcomes are

heterogeneous because the diagnosis really doesn't reflect one condition that can be defined in the single way that DSM-III to 5 assert.

Another possibility, highlighted by Dr. Baldessarini, if PL may be allowed to translate his language into simpler terms that might oversimplify: It could just be that we should just accept that our drugs don't have as much clinical benefit in real-life as we imagine. This idea may seem commonplace, but the Danish study quantifies it in a way that should be jarring to our assumptions: about 75% of our patients with "MDD" don't bother to continue treatment even for a few months. After a half-century of modern psychopharmacology, this kind of observation should make us think. PL suggests Dr. Baldessarini's observations should form the basis for some careful reflection.

CurbSide Consults

Questions and cases from you

Question: What do you think about current practice in use of benzotropine (Cogentin)?

PL: That medication is an anticholinergic drug given by many clinicians to treat or prevent parkinsonian side effects of neuroleptic agents. It has some benefit, and may be useful in some extreme cases of severe schizophrenia. PL is concerned, however, about the extensive use of this medication as a preventive treatment, co-administered along with neuroleptics, even before patients experience any parkinsonian side effects.

This is unnecessary because many patients will not experience parkinsonian side effects with different neuroleptics, or not severe ones. In any case, tremor and rigidity are not life-threatening in almost all cases, and are not usually a major cause for drug discontinuation. Rather, akathisia is the major EPS that both leads to drug discontinuation, and can be life-threatening, by leading to suicide. Yet anticholinergic agents do not have much if any benefit for akathisia, which is best treated or prevented with beta-blockers such as propranolol. Thus, using benzotropine for prevention does not prevent the most important extrapyramidal side effect, akathisia, and may not be necessary for the less important parkinsonian side effects that can occur. One should add that such preventive treatment also adds potentially unnecessary cognitive side effects, which occur routinely with anticholinergic drugs, among other harms (constipation, potential delirium in older persons).

In sum, the PL view is that this medication is overprescribed and should not be given routinely as prophylaxis of EPS.

PL Reflection

Research is the art of finding problems that can be solved.

Otto Warburg

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THE PSYCHIATRY LETTER

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DSM-5: What to think?

This issue examines DSM-5, and in general the question of DSM nosology, and how useful or valid it might, or might not, be. In the CME Special Article, PL examines changes in DSM-5, and what hasn't changed, compared to past DSM revisions. The PL analysis concludes that much of our DSM concepts are not well-based scientifically. Yet clinicians have to learn how to live with it. The Current Article of the Month is replaced in this issue with a book recommendation, the most extensive history of the making of DSM-III.

The Drug of the Month is sertraline, with discussion of some of the lesser-known features of this classic SRI. The case of the month and some of the curbside consults involve depression in medical illness, and other topics such as the use of lithium.

Again, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

We are nearing one month until our annual summer course in Cape Cod, and this will be our final invitation to our readers to attend if they can. The new theme this year is: "Becoming a master clinician: Diagnosis, drugs, and existential psychotherapy." The course promises lively discussion and interaction and exploration of PL themes, such as extensive discussion of the critique of the DSM approach to diagnosis.

Please note our new address on the final page if needed for mailing purposes.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: DSM-5

What's right, what's wrong

Introduction

Only two years ago, the fifth revision of DSM (the Diagnostic and Statistical Manual) was published by the American Psychiatric Association. This diagnostic system has been called the “Bible” of psychiatry. The metaphor suggests some cultural realities. It tends to be worshipped; some view it as the literal truth; it can inspire, but it can be used to suppress dissent. DSM is a Bible that claims to be a science too.

In this analysis, PL examines what the DSM system is and what it isn't. The brief summary is that it has become more like a religion, and less and less scientific.

History

The origins of DSM go back to the first edition in 1952, and the second edition in 1968, but those earlier versions had little impact on the US profession, much less the world. This lack of impact mainly had to do with the fact that American psychiatry mostly was psychoanalytic in orientation. In psychoanalysis, little importance was given to diagnosis, unlike the medical tradition. Diagnoses were “labels,” mere shorthand categories for communication. They weren't “real” and they didn't represent “diseases.” All psychopathology was about unconscious emotional conflicts, mainly dating to childhood; if the conflicts were normal or mild, they produced “neuroses”; if they were severe, they produced “psychoses.” That was the extent of psychoanalytic nosology.

The American Psychiatric Association (APA) organized the first two editions of DSM mainly

“Kraepelin's method was simple: Ignore the myriad symptoms and focus on the course of illness....”

for administrative purposes. Those who ran mental hospitals needed to label the reasons patients were treated. Since psychoanalytic theory mostly ignored diagnostic labels, DSM terms often were taken from the alternative medical approach to psychiatry, popular in parts of Europe, and associated especially with the research of Emil Kraepelin (circa 1900), and other German and French psychiatrists dating back to Philippe Pinel (circa 1800).

Kraepelin's tradition

The French nosologists of the 19th century had produced a descriptive tradition with hundreds of diagnoses. Kraepelin had boiled down those myriad diagnoses to a dozen or two. The three most common psychiatric diagnoses in state hospitals, according to Kraepelin, were general paralysis of the insane (GPI, which soon was found to be neurosyphilis), dementia praecox (soon renamed schizophrenia), and manic-depressive insanity (MDI). He also identified a fourth diagnosis of older age dementia.

Kraepelin's influence was strong for a while because he helped make sense of a mass of patients with similar symptoms. GPI, schizophrenia, and MDI were more or less indistinguishable in symptoms. Most patients were psychotic at some point; many had mood episodes sometimes; some got better; some didn't.

Kraepelin's method was simple: Ignore the myriad symptoms and focus on the *course of illness*. At what age did the symptoms start? How long did they last? Did they persist or go away?

Age of onset. Duration of episodes. Chronicity versus episodicity. Outcome. These are the hallmarks of Kraepelinian diagnosis.

One disease began in adolescence, was chronic, and its eventual outcome was poor in most cases. That's dementia praecox. Another disease began in adolescence, was episodic, and its eventual outcome was good in most cases. That's MDI. Another disease began in middle age, was episodic, and its eventual outcome was poor. That's GPI. A final disease began in old age, was chronic, and its eventual outcome was poor in most cases. That's dementia of old age.

All the above patients were studied carefully in brain anatomy by faculty

Kraepelin had hired for the departments of psychiatry at Heidelberg and in Munich, where he was chairman.

Among those faculty were

Franz Nissl (father of the "Nissl stain") and Alois Alzheimer. In the first two diseases, abnormalities of the brain couldn't be identified. In the third (GPI), brain abnormalities of a diffuse kind were found. In the fourth, specific plaques and tangles were found, with the condition being named after Alzheimer.

Kraepelin had one major weakness: He didn't have any special treatment to offer for his carefully defined diagnoses. He could only give a prognosis - the patient would improve or not - but he couldn't treat any disease. He was a "therapeutic nihilist."

After Kraepelin

The new psychoanalytic movement, in contrast, proposed to be able to treat almost ever everything and everyone - from the sickest psychotic to the healthiest neurotic. Psychoanalysis was therapeutically optimistic.

These promises appealed greatly to the psychiatric profession in the early to mid 20th century, especially in the optimistic culture of the United States.

Kraepelin's influence was strongest in his life, from the 1880s to the 1920s. When he passed away in 1926, his influence began to wane quickly as Freud's star rose. By the 1950s and 1960s, when DSM terms were used, Kraepelin's phrases were mixed with Freud's phrases, but it was the Freudian theory that was seen as important.

A change began to happen in the 1960s and 1970s, though, with the introduction of new psychotropic medications. The "antidepressants" and "antipsychotics" and lithium seemed to have major effects, far beyond what had been available in the era of Freud and Kraepelin. In other words, by the 1970s, there were alternative treatments, which seemed effective in practice, and those treatments seemed to fall in line with Kraepelin's basic diagnostic system of schizophrenia and MDI.

A rebel group within American psychiatry, headquartered at the Washington University in St. Louis (headed by its chair Eli Robins), began to promote and study psychiatric diagnosis using Kraepelin's method of focusing on course of illness, along with using new genetic methods. These psychiatrists were called "neo-Kraepelinian."

At the same time, clinicians were looking for new ways of thinking about diagnoses in their use of the new drugs. The APA planned a 3rd revision of DSM, and it chose a New York psychiatric researcher to head it, Robert Spitzer. New York was the mecca of world psychoanalysis, and Spitzer had been steeped in it, but was also

sympathetic to neo-Kraepelinian ideas. He decided to invite the Washington University crowd to help prepare DSM-III. The APA leadership, headed by psychoanalytic leaders, didn't care, because, following Freudian ideology, it didn't think diagnosis mattered.

By the late 1970s, the APA leadership realized that the DSM-III task force was moving from Freud back to Kraepelin's methods. The majority of American psychiatrists were Freudian in orientation. The DSM-III changes needed to be approved by a vote of the APA General Assembly, and by the APA Board of Trustees, all overwhelmingly controlled by Freudian clinicians.

In the final year or two of the DSM-III process, before its ratification by the APA in 1980, Spitzer negotiated hundreds of changes to make the final document acceptable to the Freudian rank-and-file and leadership of the APA. By that time, most of the Washington University neo-Kraepelinian members of the task force were disgusted and dropped out of the process. One of them even committed suicide.

DSM-III

In the end, DSM-III was seen as a radical change from its predecessors, and it was in some ways. It defined schizophrenia as Kraepelin had, based on the course of illness being chronic and worse, as opposed to the Freudian definition which ignored outcome. It introduced the term "bipolar" and "major depressive disorder", which was not how Kraepelin thought of it, but which was derived from the MDI concept. It introduced many other categories which weren't part of the psychoanalytic jargon but were purely descriptive. It also introduced many categories that were

psychoanalytic in concept - such as the dozen "personality disorders."

In short, DSM-III began as a scientific research project, along the lines of Kraepelin's tradition, and it ended up becoming a compromise with psychoanalytic theory and with the beliefs and labels used by clinicians in practice.

"Pragmatism"

In other words, from the very beginning, science and scientific research was not the primary motivator or method of DSM-III. It had been the ideal for the neo-Kraepelinian group at Washington University, but they were soon excluded and marginalized in the DSM-III process by Spitzer and the Freudian majority of the APA. Spitzer was explicit about the process: science couldn't be the main method partly because there was much that wasn't known or studied scientifically, and partly because DSM-III was meant to be useful to clinicians, so it should reflect clinicians' beliefs.

The head of the next revision, DSM-IV, has called this process "pragmatism." This is the main method of DSM revisions. What is best for the profession? This decision is made by the APA leaders and by the activists of the APA. Sociologists call this kind of activity a "social construction." It's a cultural creation based on social, economic, and political currents. It's not science, by the usual definition of hypotheses and experiments and objectivity.

The DSM-III process was justified by Spitzer and his supporters as representing progress but being limited by its era. We can't make a completely scientific document, the DSM-III leaders said, but we can at least take our best science now and combine it with a consensus of the clinical

community. We'll achieve "reliability": everyone will agree on how we define our labels, like a dictionary. Then with future research, we can change those definitions to make them closer and closer to reality: "validity". Reliability was supposed to lead to validity eventually.

DSM-III leaders either didn't realize or didn't care to worry about the fact that DSM-III definitions would become so reliable that no one would ever dare change them. They'd become so reified that every year forever would remain 1980.

DSM-IV

This is what happened with DSM-IV, in 1994, under the leadership of Allen Frances. The dictionary became an object of worship, transformed into a Bible. DSM-IV leaders made it explicit that changes should be as few and as minor as possible. The radical changes of DSM-III could barely be altered. Some small changes were made based on research, but larger changes were rejected on "pragmatic" grounds: DSM definitions were fine as they were, meeting the needs of clinicians.

It went unrecognized that the promise that reliability would lead to validity had been thrown aside. What mattered wasn't what was true, based on scientific research, but what was useful, based on the pragmatic beliefs of DSM-IV leaders and APA activists.

DSM-5

14 years elapsed between the third and fourth revisions of DSM. 19 years would pass before the 5th revision was published in 2013. A whole generation. Psychiatry spent two generations, almost 40 years, with the basic structure and content of DSM-III in 1980. The pragmatic

ideology had prevented major changes in 1994, and the same approach became the rationale for little to no change in 2013.

Initially, there was interest in some major changes in DSM-5. In particular, over half a century of personality research had supported the concept of personality "traits" or dimensions, rather than "disorders" or categories. The DSM-5 personality disorders task force carefully documented and supported that large amount of scientific evidence. It recommended dropping the long-used psychoanalytically-based "personality disorder" categories, and replacing them with personality traits (like neuroticism, extraversion, and openness to experience, among others). The DSM-5 leaders and scientific review committee approved this radical change. In the final weeks of the DSM-5 process, before the vote of the APA general assembly, the Board of Trustees of the

APA vetoed the explicit recommendations of the personality task force, and kept the personality disorders categories mostly unchanged from the initial definitions of

1980. Traits and dimensions were placed in "Section 3", which represents alternative definitions that aren't part of the official categories of DSM-5.

In other words, pragmatism again took precedence over science. Though personality is the clearest example, there are other examples. Sometimes, a notable amount of scientific research was deemed inadequate, on "pragmatic" grounds, to make small changes (such as the duration of hypomania; it was feared bipolar illness would be overdiagnosed). Other times, despite less scientific research than the above example, major changes were made because of pragmatic beliefs (such as the addition of

"...the promise that reliability would lead to validity had been thrown aside."

“disruptive mood dysregulation disorder” in kids, again aimed at discouraging bipolar diagnosis).

To their credit, DSM-5 leaders took some steps in the direction of accepting science as their main criterion. One example is the removal of the antidepressant exclusion for the diagnosis of acute mania or hypomania. Previously, based solely on the “pragmatic” preferences of DSM-IV leaders, bipolar disorder couldn’t be diagnosed if manic/hypomanic episodes happened solely in the presence of antidepressant treatment. Research shows that this observation is common in bipolar disorder (10-50% of cases) but very rare in major depressive disorder (MDD, <1% of cases). In other words, antidepressant-induced mania happens almost exclusively in people who have bipolar illness.

Other examples of mostly science-based changes included the acceptance of an autism spectrum, and the reconceptualization of mixed states as occurring in both MDD and bipolar disorder. Other examples of mostly “pragmatic” changes include: the broadening of the ADHD diagnosis to extend the age of onset to 13 and to define it into adulthood; the rejection of a bipolar spectrum; ignoring the concept of affective temperaments; and the rejection of the concept of prodromal schizophrenia.

Controversy

While these DSM-5 changes and non-changes were developing, many commented from the sidelines. Much attention was given to the leaders of DSM-III and IV, Spitzer and Frances, who often criticized DSM-5 leaders no matter what the latter did. If they changed something, like the antidepressant-induced mania exclusion, the prior DSM leaders would criticize the change on

“...pragmatism again took precedence over science.”

“pragmatic” grounds. Oh no, they’d say, now everyone will get diagnosed bipolar. In the case of this issue, DSM-5 leaders made a change despite the pragmatic criticism.

In many other cases, DSM-5 and/or APA leaders caved to the external criticism led by the “pragmatic” crowd: most importantly, the personality trait/dimension concept was vetoed at the last second; the prodromal schizophrenia concept was dropped despite extensive scientific evidence in its favor; the ADD concept was broadened; the “disruptive mood dysregulation” concept was invented to discourage bipolar diagnosis. Ideas like the bipolar spectrum concept were never even briefly considered in any serious way.

In short, DSM-5 was mostly pragmatic, not scientific, like its predecessors.

An obstacle to knowledge

Where does this leave us? We have to accept DSM-5 definitions from a legal and practical perspective. We have to use them for insurance forms, and to protect ourselves against lawsuits. But we don’t have to believe in them.

The same week as the official publication of DSM-5 in May 2013, the head of the NIMH, Thomas Insel, announced that DSM diagnoses would no longer be used for scientific research funded by the NIMH. Despite political pressure and a later joint press release from the NIMH and APA, Insel had told the truth: Science isn’t the primary basis for DSM definitions, and hence it isn’t useful for scientific research.

If we want to know what genes cause a disease, or the biological processes of an illness, we will not find such genes or biological markers using DSM

diagnoses. This statement is based on 40 years of failed research in psychiatry, but is also based on simple logic:

Why would nature structure its genes and biology based on the “pragmatic” preferences of DSM leaders or APA committees?

In fact, DSM definitions have been an obstacle to scientific progress, because, since they aren't based on our best science, they will steer scientific studies in the wrong direction, with both false positive and false negative findings in genetics, biology, and pharmacology.

The admission of the NIMH has undercut the scientific legitimacy of the DSM system, and it leaves clinicians in a quandary: Can we use a diagnostic system that isn't scientifically-based and scientifically-sound?

If DSM isn't good enough for research, why should we accept it as good enough for practice?

A Solution?

The PL approach is simple: Focus on the science. Where DSM-5 agrees with the scientific evidence, accept DSM-5 definitions. Where DSM-5 disagrees with our best scientific evidence, so much the worse for DSM-5.

We can accept the DSM system as a dictionary, in the PL view, but not as a Bible. There are no Bibles in science, only hypotheses, which we need to be willing to refute, not just accept.

Even as a dictionary, though, DSM-5 is weak. Its field trials found poor reliability of major categories, like MDD. (The latter had a “kappa” value of 0.31, which is worse than prior field trials in DSM-IV and DSM-III). In other words we

“Why would nature structure its genes and biology based on the “pragmatic” preferences of DSM leaders or APA committees?”

have given up on validity, and explicitly placed science below “pragmatism”, and even so, the same DSM definitions invented in 1980, largely unchanged (as with MDD) after nearly four decades of use, aren't even as reliable as in 1980.

The DSM-5 leadership sometimes boasts about a million copies sold in a year, and the fact that the DSM system is used all over the world. This is the case: a large part of the APA budget is based on sales of DSM. And the world has taken DSM at face value, as if it's the truth. But clinicians should know, all over the world, that the DSM system is a reflection of the “pragmatic” beliefs of mainstream American psychiatry. DSM is not, first and foremost, a reflection of our best science.

Clinicians would then be free, with this recognition, to accept or reject or modify DSM definitions based on the best research and based on their own experience and their own best judgment. This is the PL view.

In each patient case, state the DSM-5 diagnosis. And then state your best provisional clinical diagnosis, based on your own clinical judgment and scientific research of which you might be aware. In other words, make two diagnoses in each case: what the mainstream profession tells you (DSM-5) and what the scientific literature and your own clinical judgment tell you. Don't let the former preclude or define the latter. Use the former for legal and administrative purposes. Use the latter to provide the best clinical care.

The PL Bottom Line

- DSM is a social construction, based on “pragmatism” much more so than science.
- Use DSM administratively, not necessarily for best clinical practice.

Current book of the month: *The history of DSM-III*

The Making of DSM-III: A diagnostic manual's conquest of American Psychiatry

Hannah Decker, 2013, Oxford University Press.

The documents tell the story

This month, PL replaces the current article with a book recommendation. In keeping with the special article, PL recommends Professor Decker's book as the best documented resource about the DSM-III process. A professor of history who specializes in history of psychiatry, Decker is well-positioned to report this history. She interviewed the main protagonists and she studied the APA archives to examine the content of the committee discussions in DSM-III. The result is the best single source for understanding the history of DSM-III.

PL encourage readers to make their own judgments about this history when reading this book. Decker is at her strongest in reporting the facts: What was said. When. By whom. She proves with excellent documentation that DSM-III was a "social construction," the invention of a profession, not a simple compilation of scientific data.

In her interpretations of those facts, Decker has one perspective, but others could also be taken. She is sympathetic to Spitzer in particular, whom

"...the vast majority of patients just didn't need much attention. It isn't clear whether this is good or bad news."

she appears to like personally. But likability shouldn't cloud historical judgment. What is missing from this book is an awareness of the harmful scientific legacy of DSM-III. Decker documents the jettisoning of scientific research as the primary standard of DSM-III, but she doesn't identify the many harmful effects that have ensued. She describes in detail the many "pragmatic" compromises made by Spitzer, such as removing the term "neurotic depression" and replacing it with three less scientifically solid terms ("major depressive disorder", "generalized anxiety disorder", "dysthymia"). But she doesn't appreciate the scientific weakness of that change. Informed readers can draw those conclusions from the facts she provides.

The PL Bottom Line

- This book is the best documentary history of modern psychiatric diagnosis.
- It demonstrates that the DSM system is a social construction, not primarily based on scientific research.

PL Reflection

People in the world can be classified by the maximum length of time their thoughts are diverted from themselves.

John Kenneth Galbraith, economist

Drug of the Month: Sertraline (*Zoloft*)

Dopaminergic, safest in heart disease

Biological mechanism

Sertraline is a classic serotonin reuptake inhibitor (SRI), well-known to most clinicians. It's easy to dose and has a wide range of uses.

What few know is that it isn't a pure SRI. It has notable dopamine reuptake inhibition. In some animal studies, its dopamine reuptake blockade is similar to methylphenidate. It's hard to know whether this mechanism has important clinical effects in humans though. One would expect weight loss and enhanced sexual function with such dopaminergic effects, yet these clinical outcomes don't tend to occur in humans.

Sertraline is the best studied antidepressant in persons with heart disease, and it's the most proven safest agent in the setting of cardiovascular diseases. The SADHART study didn't find that sertraline improved cardiac outcomes, though some analyses suggest some such benefits. But at least it can be stated that it doesn't worsen cardiac outcomes and has no known cardiac risks. (The same cannot be said of many other antidepressants, such as bupropion, which has an amphetamine-related structure and can cause cardiac arrhythmias; or venlafaxine, which has some association with increased risk of sudden cardiac death, which is also the case with methylphenidate).

Clinical efficacy

It often isn't appreciated that the randomized trial literature of sertraline in MDD, conducted in the 1990s, was almost entirely outpatient, not conducted in hospitalized patients. Thus, there is no appreciable scientific evidence that sertraline is effective in hospitalized or severe depression.

It has few drug interactions and can be used without much concern about liver interactions, unlike some other SRIs.

Dosing

At low doses (25-50 mg/d) sertraline is more purely serotonergic and has anxiolytic effects. Its mean effective dose in the MDD studies was about 75 mg/d (with a range of 50-100 mg/d). Though it can be

dosed higher, it hasn't been proven to be more effective for MDD above 100 mg/d than below that dose.

The PL Bottom Line

- Sertraline is a versatile agent, but not proven effective in severe depression
- It has dopaminergic mechanisms, but clinical implications are unclear.
- It is the most proven safest antidepressant in persons with cardiovascular disease.

Case of the Month

Depression in heart disease

A 65 year-old man with coronary artery disease s/p bypass grafts 3 years ago presents with marked depression along with new-onset nonspecific homicidal ideation. He had been taking SRIs for years, most recently paroxetine 40 mg/d, which had been stopped three months earlier and switched to bupropion. His depressive periods had begun 30 years previously, and responded partially to SRIs, but had worsened in the past three years in association with worsening heart disease. He and his wife deny past manic/hypomanic episodes, and he denied any known psychiatric illness in first or second degree relatives. He had long standing diabetes since his early twenties, but not hypertension.

The PL recommendation was to begin sertraline in place of bupropion, since the former is more proven safe in cardiovascular disease than the latter. Further, the patient's new and unusual homicidal ideas likely reflect serotonin withdrawal syndrome since stopping paroxetine abruptly three months earlier. PL also recommends brain MRI to assess possible white matter infarcts, associated with diabetes, which may explain recent worsening of unipolar depressive illness.

The prognosis of the patient's depressive illness is not good, but at least sertraline will be safer than other options and will mitigate serotonin withdrawal symptoms.

PL Reflection

Could a greater miracle take place than for us to look through each other's eyes for an instant?

Henry David Thoreau

Curbside consults

Questions and cases from you

Question: I use lithium on a regular basis not only for manic or hypomanic conditions but also at lower doses in treating depression. Over the years that I have used it, side effects have been rare. I regularly monitor kidney and thyroid function. Rarely have I had to discontinue because of decreased kidney function. Fairly recently, a male patient of mine on both topiramate and lithium started developing increased creatinine and decreased GFR. Both can have adverse effects on kidney and I decided to stop both. Kidney function is now normal. The decision to stop was based on several serial kidney panels. He is doing fairly well but did better on lithium. Levels were about 0.6. I am wondering whether or not to restart the lithium and closely monitor kidney function.

PL: It's common to note that when lithium is stopped for renal reasons, many patients don't do as well with other agents, such as valproate or lamotrigine, as they did with lithium. After trying other agents, you could have a full informed consent discussion with the patient about the merits of resuming lithium, despite the renal side effects that the patient has experienced. Perhaps it could be used at slightly lower levels, and/or with nephrology consultation as well. All of medicine is about weighing risks and benefits; and even if the risks are more than mild, if the benefits are equally higher than other options, the tradeoff may be acceptable to the patient. In the end, it's the patient's decision though, with the clinician's role being to provide the information the patient needs for a fully informed decision.

Question: How neuroprotective is lithium? And if this is the case, should it be given in low doses as in your discussion in PL to other individuals or in general?

PL: There's no definitive answer to this question yet, but the PL opinion is that it is reasonable to consider giving very low-dose lithium (equivalent to about 5 mg/d elemental lithium) to individuals who are not diagnosed with mood conditions, if they have other risk factors for dementia, such as a strong family history. Lithium is strongly neuroprotective, much more so than any other psychotropic agent, as was detailed in the PL special article last month. Unlike other agents, the neuroprotective effect of lithium is repeatedly proven in many different animal species and in humans. This effect is very robust neurobiologically in vitro and in vivo, including in the clinical human studies described last month.

Question: A type of depressive syndrome that I don't think you mention is chronic, low grade depression that in my opinion is related to chronic systemic inflammation caused by multiple medical problems. I work with a lot of patients who have several chronic conditions such as diabetes, hypertension, or heart disease. They tend to present with a low grade type of depression characterized by low energy and motivation, fatigue, anhedonia, low mood, poor sleep, and isolation. They don't seem to have anything in their presentation or history that would trigger me to think of bipolar, melancholia, or neurotic depression. There is some evidence looking at the role of chronic inflammation in mood issues. I haven't found them to respond very well to "traditional" depression treatments such as SRIs or cognitive behavioral therapy. Often they come to me already on duloxetine (Cymbalta) for chronic pain issues or may have been started on citalopram, sertraline, or other SRIs by primary care. If the mechanism is more inflammatory, it may not be a surprise that their depressive symptoms aren't responding to these medications. Sometimes I use bupropion for the stimulant like effects, but I haven't found a good

solution for most of them. What are your thoughts in these patients?

PL: The question of depression and inflammation is interesting. As you note, there may be kinds of depressive syndromes that are based in medical causes that are unrelated to manic-depressive illness (bipolar or unipolar depression), and unrelated to specific subtypes of depression such as mixed depression, melancholia, or neurotic depression. All the above depressive presentations are part of what might be called "primary" depressive illnesses, or, for want of a better word, "psychiatric" causes of depression. Medical illnesses can cause "secondary" depression in persons who do not have the "primary" psychiatric causation of family genetics. In those medical cases, the depressive syndromes are caused by various factors. Perhaps the most common is so-called "vascular" depression, which involves brain micro-infarcts leading to white matter abnormalities. This condition is associated highly with diabetes and/or hypertension, and monoamine agonists (antidepressants) are less effective in these vascular depressive conditions, as opposed to primary depressive conditions.

You raise another major medical cause of depression, which is known inflammatory disease. Some would argue that all depression involves inflammation, which is present in the pathophysiology of depressive states. Cytokine activity is increased, natural killer cell activity is decreased, and various changes are present in the kynurene system which many think relate to the link between inflammation and depression. Many monoamine agonists have anti-inflammatory effects in persons with depressive syndromes; in other words, when their depression improves, their inflammatory states normalize with monoamine agonists.

However, the reverse doesn't seem to be the case: anti-inflammatory agents that are not monoamine agonists (like NSAIDs) have been studied in acute depressive episodes and generally are found to be ineffective. Steroids, which are potent anti-inflammatory agents, actually cause or worsen depression in many persons (and cause mania in others). So the relationship between depression and inflammation is complex.

Your observation that monoamine agonists are less effective in depressive conditions related to medical or inflammatory diseases would be consistent with the general observation that this is the case with most medically caused secondary depressive conditions. Traditionally, as in post-stroke depression, mainstream psychiatry has recommended amphetamine stimulants, like bupropion. Of course those agents have some risk of sudden cardiac death and/or arrhythmias which should give us pause in using them, in addition to the animal studies indicating neurotoxicity of the more potent amphetamines such as methylphenidate.

The PL viewpoint is that one should use those monoamine agonists that are available in such cases, but the risks of amphetamine stimulants lead us to avoid those agents. Perhaps bupropion is the least risky of that class.

One idea to consider is minocycline, an antibiotic that has been studied and found to be effective in some randomized trials both for depressive syndromes as well as for psychotic symptoms of

schizophrenia. Typically dosed at 150 mg/d, the proposed mechanism of benefit is inflammatory, involving the kynurene system. We agree, though, that the general prognosis of these patients is likely to remain worse than primary depressive syndromes.

PL Reflection

Meetings are held because men seek companionship, or, at a minimum, wish to escape the tedium of solitary duties. They yearn for the prestige which accrues to the man who presides over meetings, and this leads them to convoke assemblages over which they can preside. Finally, there is the meeting which is called not because there is business to be done, but because it is necessary to create the impression that business is being done. Such meetings are more than a substitute for action. They are widely regarded as action.

John Kenneth Galbraith
Economist

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THE PSYCHIATRY LETTER

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Mood Temperaments

This issue examines the concept of mood temperaments in detail. Allusions have been made in prior PL issues to the mood temperaments and what they mean beyond their standard DSM-based usage. In the CME Special Article this month, PL describes the basic mood temperaments in some detail: dysthymia, cyclothymia, and hyperthymia. Their relationship to personality traits and to the DSM-based concept of personality disorders is discussed. The Current Article of the Month examines a recent prospective study which found that young adults who met ADD criteria did not have that condition since they did not have that condition as a child. A New Drug Update column examines two new antipsychotics that have just come to the US market, a dopamine agonist/antagonist and a new agent that has, for the first time with proven efficacy for psychosis, no dopamine blockade at all. By the Numbers examines the frequencies of mood temperaments in clinical practice. The Case of the Month examines a case of hyperthymic temperament previously misdiagnosed as anxiety and depression.

As with all issues beginning January 2016, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

Our second summer course is upcoming, on August 1-5, and is focused on psychopharmacology intended for the advanced clinician. If you missed our earlier July course, we hope you consider attending this Harvard CME course.

If PL readers are able to attend, we can continue in person some of the discussions conducted in writing here.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: Mood temperaments

An alternative to personality disorders

Introduction

You've heard of dysthymia, but it's not just a mild type of depression. You've heard of cyclothymia, but how frequently do you diagnose it? You've probably never heard of hyperthymia. These are the mood temperaments, a class definition which in itself is an important point, unlike the DSM vague term of "disorders", which doesn't identify what kind of condition is present. In DSM-III and IV, dysthymia and cyclothymia were placed on "axis I", not on axis II with the personality conditions, and thus most people do not make the connection that these are temperaments, i.e., part of personality. They are not separate "disorders" unrelated to personality. This always was the concept of dysthymia and cyclothymia dating back at least a century.

In this article, we'll review what these conditions mean, historically and scientifically.

Definitions

Let's look in some more detail into the clinical psychopathology of mood temperaments, for they are more complex than presented in DSM. A useful resource is the TEMPS (Temperament Evaluation scale from Memphis, Pisa, and San Diego) scale, which is the most validated research scale to assess mood temperaments. As an aid to clinical diagnosis, a short self-report TEMPS scale (37 or 50 item) can be invaluable.

At one level, the temperaments can be defined as mild versions of mood states, but they go beyond that initial concept to include basic differences in personality traits and in energy levels, as expressed in sleep patterns and behaviors, such as

"...temperaments can be defined as mild versions of mood states..."

sexual and social or work-related activities. Hence, the following brief descriptions apply:

Hyperthymia involves a mild manic state as part of one's basic temperament. Such persons are high in energy, need less sleep than most people (often 4-6 hours nightly), have high sex drives, are highly social, extroverted, often workaholics, and often humorous. They are described as the life of the party, as fun-loving, and can engage in risk-taking behaviors that others avoid, such as skydiving or bungee-jumping or motorcycle or airplane flying. They dislike routine, and are spontaneous. They can be quite anxious and inattentive.

Dysthymia is the reverse, a mild depressive state as part of one's basic temperament. Such persons are low in energy, need more sleep than most people (often 9-11 hours nightly), have low sex drives, are socially anxious, introverted, low in work productivity, and not humorous. They avoid risk-taking behaviors, are devoted to routine, and can be obsessive. They can be quite anxious but not usually inattentive.

Cyclothymia involves constant alternation between mild manic and depressive states on a day-to-day, or a few days at time, basis. Such persons go up and down in mood and energy and activity levels, though they can be generally mostly extroverted and productive and social. They tend to be risk-takers at times, and are unpredictable, and spontaneous. They can be quite anxious and inattentive.

The original concept

The concept of mood temperaments was best systematized about a century ago by the German

psychiatrist Ernst Kretschmer. These ideas predate Kretschmer, with descriptions in Kraepelin's work and earlier writers. In Kraepelin's texts, we read about "manic temperaments" and "depressive temperaments". Kretschmer developed these concepts, which eventually led to the concepts of hyperthymia and dysthymia respectively. Dysthymia is an old term, found in ancient Greek Hippocratic texts, referring to depressive moods. "Thymia" mean emotion, and "dys" mean low or sad. In 19th century literature in France and Germany, the word "cyclothymia" was used to reflect temperaments that were up and down. Kraepelin's concept of manic-depressive insanity wasn't developed by him until 1898. At the same time, he incorporated the old concepts of dysthymia and cyclothymia as depressive and manic temperaments. A few decades later, Kretschmer expanded on the idea of a "hypomanic" personality (hyperthymia) to capture the three main mood temperaments.

... They are not separate or independent diseases..."

In the original view of Kraepelin and Kretschmer, these temperaments are mild variations of manic-depressive illness. They are not separate or independent diseases or disorders, as the DSM system sets them up. They are part of the same condition, just mild versions, "formes frustes", as in the French term.

This is no different than saying that mild adrenal insufficiency is related to but not the same as Addison's disease; or that mild hypothyroidism is related to but not the same as Grave's disease. Mood temperaments are different in severity but not in kind from severe depressive or manic illness.

This concept was lost in the mid to late 20th century, as psychoanalytic concepts rose in

prominence, and Kretschmer's views were lost. The concept of personality was seen through a psychological, rather than biological, lens, and related to psychoanalytic concepts of emotional development. As DSM-III evolved in the 1970s, these psychoanalytic approaches were codified into the definitions of the "personality disorders," which mainly use psychoanalytic constructs. The terms "dysthymia" and cyclothymia also were resuscitated, but not as mild versions of unipolar depression or bipolar illness, but rather as separate labels. Dysthymia in particular was added to allow for a different term to replace "neurotic depression," which was thought of in psychoanalytic terms. This use of the concept of dysthymia had nothing to do with the traditional concept of this condition as a mood temperament.

Cyclothymia was included for descriptive reasons, it seems, and the term "hyperthymia" was never included in DSM-III or its follow-up revisions, for unclear reasons.

Post-DSM-III

Hence after DSM-III, if these terms were used, they were never understood in their original context. Dysthymia was used frequently as a comorbidity, added to generalized anxiety disorder, to capture that same concept of "neurotic depression" which DSM-III sought to rename. Cyclothymia was used infrequently. Hyperthymia was forgotten completely.

Instead personality was conceived solely in psychoanalytic ways, with special popularity of borderline and narcissistic constructs.

At the same time, a huge literature on dimensional personality traits was completely ignored by DSM-III and its follow-up revisions. Yet, the experimental psychology research world continued to conduct that research and validated

a number of classic personality traits, such as neuroticism, extroversion, and openness to experience (NEO).

At the same time, beginning in the 1980s, some researchers began to return to the original concept of mood temperaments, and began to study dysthymia, cyclothymia, and hyperthymia - not in their DSM descriptions - but as mild versions of depressive or bipolar illness.

They found that indeed the ideas of Kraepelin and Kretschmer could be confirmed with newer research. Often, patients with bipolar illness, for instance, had baseline dysthymia in between their depressive and manic episodes. Or patients with unipolar depression had baseline hyperthymia in between their depressive episodes.

Further, they found that the relatives of those patients often had just mood temperaments; in other words, while some relatives had full-blown unipolar depression or bipolar illness, others only had dysthymia all the time, or cyclothymia all the time, without any intervening full depressive or manic episodes.

These observations confirmed the perspective of Kretschmer and Kraepelin that these mood temperaments are biologically and genetically related mild variants of manic-depressive illness.

Clinical Implications

The rediscovery of mood temperaments in recent years has allowed for a new perspective on personality. Instead of only using DSM-based psychoanalytic concepts of personality disorders, we can take a more dimensional perspective, using mood temperaments. Mood temperaments are dimensional because they simply are milder

versions of mood illnesses, as opposed to being categorically different conditions. Thus, a patient can have both unipolar depression and cyclothymic temperament, or both bipolar illness and hyperthymic temperament. The conditions are not mutually exclusive.

Further, much of the mood lability and impulsivity that is diagnosed using the DSM system only through the lens of personality disorders can be reconceived through the lens of mood temperaments as mild versions of manic-depressive illness.

For instance, patients with cyclothymia have constant mood lability and impulsive sexuality, just as is defined as part of borderline personality. Those traits do not distinguish the two conditions; other traits would need to be considered instead (such as sexual trauma and self-cutting in borderline personality, versus bipolar genetics in cyclothymia).

Further mood temperaments provide some clinical implications, if used, that go beyond many common assumptions in clinical practice.

For example, if a patient presents with a first depressive episode at age 50, without any prior depressive or manic episodes, it often is assumed that this presentation is unusual, since mood episodes should begin by age 30 or earlier in unipolar or bipolar illness. If that patient had hyperthymic temperament at baseline, though, then the age of onset is not unusual. Mood temperaments are present throughout life; in other words, they are present in childhood and adolescence and then persist. Thus the age of onset of abnormal mood in that patient is not 50,

"... mood lability and impulsivity... diagnosed only through the lens of personality disorders can be reconceived..."

with the first depression, but 15, with onset of definable hyperthymia.

Indeed this presentation is typical: Many persons have hyperthymia or cyclothymia for decades, before their first depressive, or even manic, episode in middle-age or later life. This late-life onset depression and mania has been reported in the past. But few researchers have assessed a link with baseline abnormal mood temperaments.

“Adult ADD”

Often persons with hyperthymia or cyclothymia will have problems with attention, due to constant or frequent manic states. Since these mood temperaments are not diagnosed commonly in current clinical practice, clinicians instead notice the attentional symptoms mainly. With current pharmaceutical marketing and DSM-based support, many such persons get diagnosed with “adult ADD.” Since amphetamines improve attention symptomatically in all persons, including normal controls, clinicians and patients often make the mistaken judgment that such adult ADD exists and is improved by those amphetamine stimulants. In fact, underlying manic symptoms can worsen with amphetamines, and partial improvement of attentional symptoms often comes at the expense of worsening of other aspects of hyperthymia, such as sexual impulsivity. Sometimes full manic episodes can be caused. Other times, full depressive episodes can be caused, as the manic state switches into its opposite pole.

Instead, treatment of manic temperaments with low-dose mood stabilizers can produce similar attentional benefits as seen with amphetamines, without worsening, or risk of worsening, of mood symptoms as described above.

“... The treatment of mood temperaments...should involve low dose mood stabilizer medications...”

Treatment

The treatment of mood temperaments, if undertaken, should involve low dose mood stabilizer medications, based on the PL experience. For cyclothymia or hyperthymia, this would involve low-dose lithium (300-600 mg/d) or valproate (250-500 mg/d) or possibly standard dose lamotrigine (50-100 mg/d). For dysthymia, it would involve low dose standard monoamine agonists (antidepressants). When full clinical depressive episodes are present, along with mood temperaments, then the above medication classes may be needed in full doses, either by themselves, or with standard monoamine agonists.

The research literature is limited because mood temperaments have either not been included in DSM systems, or not identified as temperaments.

Hence researchers and pharmaceutical companies have not conducted much research on their treatment. Further research is needed to clarify and revise the above recommendations. For now, PL recommends clinicians start with these ideas and be flexible in their practice, revising their treatment patterns based on their own clinical observations.

The PL Bottom Line

- Mood temperaments are mild variations of manic-depressive illness.
- They can be mistaken for other conditions like adult ADD.
- They can be present along with recurrent depressive episodes, and if observed in hyperthymia or cyclothymia forms, would entail some mood stabilizer use, with or without antidepressant medications.

Current study of the month: *Adult ADD which isn't ADD?*

Attention-Deficit/Hyperactivity Disorder Trajectories From Childhood to Young Adulthood

A Cayet et al, JAMA Psychiatry 2016; 73:705-712.

It's not the same people

In Brazil, a birth cohort study was started in 1993 of 5249 persons who were followed from birth throughout childhood into adulthood up to age 18. About 80% of the total cohort was successfully followed. At age 11, they received an ADD screen which was repeated at age 18.

Overall 8.9% of the sample met ADD criteria at age 11. This prevalence increased to 12.2% at age 18. This observation would seem to support the view that ADD persists into adulthood in all patients; in fact some new cases are picked up.

This study used the concept of a diagnostic hierarchy, however, unlike almost all prior studies of adult ADD. It didn't ignore other diagnoses. Thus, it assessed whether ADD was present in adulthood only in the setting of other diagnoses which can cause inattention, specifically mood (bipolar and MDD) and anxiety (GAD and social anxiety) conditions. When those other diagnoses were ruled out, and researchers assessed the presence of only ADD itself, without any other potential diagnostic causes, the adult prevalence rate fell by about one-half, from 12.2% to 6.3%.

Thus, to review, about 9% of children met ADD criteria. This rose to 12% of young adults at age 18. But this fell again to about 6% if ADD is defined as meeting ADD criteria and not having other psychiatric diagnoses that can cause inattention.

At first glance, even with this complex analysis, it would still seem that about 2/3 of children who

had ADD persisted into adulthood: 9% at age 11 versus 6% at age 18.

However, this wasn't the case, because they weren't the same people.

Of children at age 11 who met ADD criteria, only 17% continued to meet those criteria at age 18. In other words, ADD went away in 83% of children by adulthood. This finding is consistent with over half a dozen course studies conducted prior to the introduction of medications for adult ADD. In that literature up to about the year 2000, the overall finding was that about 90% of children with ADD no longer met criteria by around age 20. This Brazilian study confirms that earlier literature.

"...ADD went away in 83% of children by adulthood...."

It also throws some light on current debates about adult ADD, however, in that it still found a good number of young adults met ADD criteria, even though they didn't have ADD as a child.

Thus, the second important observation here was that only 12.6% of the adult ADD cohort also had been identified as having ADD as a child in this prospective study where they had been assessed previously for ADD. In other words, 87.4% of adults who met DSM criteria for ADD as adults had not experienced it as a child.

Interpretation

How believable are these results and what do they mean? The authors refer to a recent meta-analysis

of adult persistence of childhood ADD which fully agreed with their findings: adult persistence was less than 20% overall. They also refer to another large recent study which found only 5% persistence of childhood ADD when followed further into middle age adulthood.

The observation that about 5% of adults have impaired attention, which cannot be attributed to ADD or to other psychiatric conditions like mood and anxiety syndromes, is important.

It's important to emphasize that these persons do not have "ADD" because this study proves that their inattention is not persistence of childhood ADD.

So what do they have?

One possibility is that they experience "normal" inattention, in the sense that they are at the extreme of a normal curve for inattention. Since selective attention is a normal psychological trait, what we might appreciate is that attention exists on a normal curve, with most of us at the middle, near the 50th percentile. But two standard deviations to either side will represent about 5% of the general population, who are either overly-focused (which is consistent with obsessional or manic thinking) or under-focused (which is labeled "ADD" frequently).

This perspective, about normal variations in attention, has been described in a prior PL issue,

“...about 5% of adults have impaired attention, which cannot be attributed to ADD or to other psychiatric conditions...

and this study result can be interpreted as supportive of that interpretation.

It should be noted that these persons did have some clinical consequences of their inattention, such as increased criminal behavior, incarceration, and suicide attempts.

Importantly, personality conditions were not assessed, so the possibility that some of them had mood temperaments, as discussed in this issue, would also be present.

Further, prior research suggests that a subgroup of patients with childhood ADD later are diagnosable with antisocial personality, which could correlate with some of the findings in this study.

The PL Bottom Line

- ADD does not persist into adulthood in about 80% or more of children.
- About one-half of apparent adult ADD may be caused by mood and anxiety conditions.
- About 5% of adults in this sample met ADD criteria but did not have adult ADD, since they did not have prior childhood ADD.
- The presence of inattention in 5% or less of the general population is due to causes other than ADD, which could include mood temperaments or normal variation on the psychological trait of attention.

PL Reflection

It's easier to fool people than to convince them that they've been fooled.

attributed to Mark Twain

New Drug Update: Brexpiprazole (*Rexulti*) and Pimavanserin (*Nuplazid*)

New antipsychotics with novel mechanisms

This month PL highlights two new antipsychotics recently on the market in the US. The first, brexpiprazole, is a partial dopamine agonist, like aripiprazole, but with some differences. The second, pimavanserin, is an “inverse serotonin agonist,” without any dopamine blockade at all, just approved for treatment of psychosis in Parkinson’s disease.

Brexipiprazole

Biological mechanism

This agent is a dopamine blocker but it also has dopamine agonism. This basic mechanism is similar to aripiprazole. The difference is a matter of potency. As usual, the D₂ blockade is dose dependent, such that eventually, over 90% of D₂ receptors are blocked. This level of D₂ blockade produces extrapyramidal symptoms (EPS) such as akathisia, which may remain the main clinical problem with this agent, as with the entire dopamine blocker class.

The dopamine agonism of this agent is somewhat less than occurs with aripiprazole. In animal studies, there was 43% agonism for brexpiprazole compared to 61% for aripiprazole. The relevance of this distinction may be that brexpiprazole may have less of some of the dopamine stimulation effects that are seen with aripiprazole, which may be observed clinically in terms of mania induction or possibly reduced antipsychotic potency.

Like aripiprazole and other new antipsychotics, brexpiprazole does not appear to cause or worsen the metabolic syndrome of diabetes, hypertension, and hyperlipidemia.

Clinical efficacy

Unlike most other antipsychotics, brexpiprazole was not initially indicated for the classic antipsychotic indications of schizophrenia and mania. Instead, it was developed to be indicated by the FDA indications for schizophrenia and for MDD as an adjunct to SRIs. It has not yet been studied for mania or bipolar depression.

Dosing

2-4 mg/d are proven effective for the above indications.

Pimavanserin

Biological mechanism

This agent is the first proven antipsychotic that does not cause dopamine blockade. A number of prior putative antipsychotics, which were not dopamine blockers, have been studied over the years; most of those agents were pure serotonin blockers. When studied in clinical trials, though, those agents didn’t work. This agent appears to be the first to have proven some clinical efficacy, in this case for psychotic symptoms in Parkinson’s disease. The purported mechanism of pimavanserin is “inverse agonism” of the serotonin 1A receptor. This mechanism is thought to result in complete blockade of serotonin activity at that receptor, as opposed to other prior serotonin blockers, which still allowed for a small amount of activity at that receptor. Whether this mechanism truly explains the antipsychotic efficacy of this agent remains to be seen.

Clinical efficacy

For now, this medication is only FDA indicated for psychosis in Parkinson’s disease. However, a randomized trial in schizophrenia has shown

efficacy over placebo. We'll need to see if that efficacy is replicated and then followed by FDA indication. If this occurs, this would be a major shift in treatment of severe psychosis in schizophrenia, as well as possibly for mania or bipolar illness, since this agent would be the first non-dopamine blocker that would be effective for classic psychosis.

Dosing and other features

The effective dose is 34 mg/d for Parkinson's psychosis, with pill sizes of 17 mg per pill. This agent has a very long half life of 2 1/2 days. Thus it would take 1-2 weeks to achieve a steady state, if not longer in older persons with Parkinson's disease. This feature of this medication should be kept in mind.

Side effects

The main observed side effect in the clinical trials in Parkinson's disease was peripheral edema. There was no weight gain or metabolic syndrome.

The PL Bottom Line

- Brexpiprazole is proven effective for schizophrenia and as an adjunct for MDD. It has somewhat less dopamine agonism than aripiprazole.
- Brexpiprazole has minimal weight gain and no apparent risk of metabolic syndrome or worsening diabetes or cardiovascular risks. Akathisia remains a potential important risk.
- Pimavanserin is a pure serotonin blocker which is proven effective for psychosis in Parkinson's disease. It does not cause extrapyramidal side effects.
- Pimavanserin has a very long half-life of 2-3 days.

By the Numbers

Mood temperaments

How frequent are mood temperaments?

It depends partly on how they are defined. In one study, they were defined as 75% or more items being endorsed on the TEMPS scale. Using that definition, about 40% of patients in a mood disorder clinic met the definition of cyclothymia. About 15% met the definition of hyperthymia, and 10% were definable with dysthymia.

About 50% of patients did not have any full mood temperament. If they endorsed mood temperament criteria, they did so only in less than 50% of items. Thus, they might have some mood temperament features, but not enough to meet the full definition of any one.

If the cut off is put at a lower threshold of 50% of items, then the majority of persons with mood conditions - about 80% - meet the definition of a mood temperament.

Population prevalence studies are limited, but genetic studies which have looked at mood temperaments have noted that they are the most frequent diagnoses in family members of persons with mood illnesses. These family members don't have full-blown depressive or manic episodes. Thus, since mood conditions occur in about 5-10% of the general population in the US (about 5-10% for MDD and 1-2% for bipolar illness), one could infer that mood temperaments occur in about 10-20% of the general population, at least in the US. In many cases, they occur by themselves, meaning that no other diagnoses are present. In other cases, they occur as the baseline temperament in between full depressive or manic episodes in persons with mood illnesses.

Case of the Month

A 50-year-old woman presented with refractory anxiety and depression that had failed multiple antidepressants and dopamine blocker trials. She had experienced decades of anxiety and depressive symptoms, which were more or less constant. Brief periods of worsened depression likely met full criteria for a clinical depressive episode many times in the past, with durations of weeks to months. Her anxiety was generalized, with occasional panic attacks. Benzodiazepines had limited benefit, as did six different SRIs.

In consultation, her family history was unknown mostly, and medical history was uninformative. She had no prior trauma or self-cutting or suicide attempts or psychiatric hospitalizations or psychosis, and no past manic/hypomanic episodes. She was an active lawyer, with a family of three adult children, and marriage of 24 years duration. Despite being functional, she was very distressed and felt unable to function as well as she could with less anxiety and depression.

In review of her basic personality traits, she described herself as highly extroverted, sociable, fun-loving, and energetic. She normally slept about 6 hours nightly and was not tired most of the time. The NEO scale confirmed the above description, with high scores on neuroticism, extroversion, and openness to experience. She met criteria for over 75% of items of hyperthymia on the TEMPS scale.

The PL diagnosis was hyperthymic temperament. The treatment recommended was low-dose divalproex, since it has anxiolytic effects directly, unlike lithium or other anticonvulsants. In one month, with 500 mg/d of divalproex, she reported marked improvement, sustained for over one year of follow-up, without notable weight gain or other side effects.

Curbside Consults

Questions and cases from you

Question: I have been treating a now 49-year-old patient for years diagnosed with schizophrenia. The medications that have best stabilized him are fluphenazine 40 mg/d and risperidone 4 mg twice daily. He also takes escitalopram 5 mg/d for depression. All trials thus far to alter this combination have led to decompensation. He and family are aware that using two antipsychotics is polypharmacy and they have approved this combination. Within the last six weeks I decided to try one agent, risperidone, and started to carefully cross titrate medications. Prior to any changes a serum risperidone level was taken and results indicated that his risperidone dose was similar to a 16mg dose. I was at first perplexed by this and then realized that fluphenazine is a potent inhibitor of 2D6 and read recently that patients with elevated C-reactive protein (CRP) can have elevated serum levels of antipsychotics. His CRP was tested as normal. He is unwilling to use a depot medication which in itself might not offer any advantages. He is unwilling to do a trial of clozapine because of the initial weekly CBC for the first six months. He is closely monitored by a cardiologist and has a pacemaker. His lipids and hemoglobin A1C are normal. He has a trifascicular bundle branch block. QTc is mildly prolonged. The family and the patient don't want to change the current combination because "this is the most stable he has been in years". I welcome any suggestions on continued treatment.

PL: The treatment of schizophrenia is symptomatic. Patients don't recover completely in most cases, but rather the goal is improved quality of life. Thus, the benefit-risk calculation in schizophrenia should pay special attention to harm given limited benefits. One reason why polypharmacy with dopamine blockers in this

disease is not recommended is that benefits are limited when adding more dopamine blockers, but harms rise greatly. Put another way, once you block more than 90% of dopamine receptors with one neuroleptic, you won't get much more benefit with trying to block a few more percent. On the other hand, extrapyramidal harms increase notably.

That said, this case brings up an important aspect of clinical common sense. It can be very hard to get patients off neuroleptics which they have taken for a long time, even if those agents aren't helpful. In other words, they might not help, but they can still harm when taken off. This scenario may reflect a withdrawal syndrome of some variety, or simply adaptation of body and brain to long-term exposure to a drug's effects.

In this case, the main potential problem with fluphenazine (Stelazine) is tardive dyskinesia (TD), which happens in about 20-50% of persons with traditional neuroleptics in 5 years or more of treatment, as opposed to less than 1% of persons with newer generation neuroleptics. However, if he has been on fluphenazine now for a number of years (more than 5) then future risk of TD is lower. In other words, he has passed through the highest risk period for TD, which is the first 5 years of treatment.

The observation of high risperidone levels is interesting, and may reflect the pharmacokinetic effect you describe. In that case, one wonders whether the combination really is helping him, or whether it's simply the effect of high dose risperidone.

The low dose of escitalopram probably is not helping him pharmacologically or biologically, partly because the dose is low, partly because randomized trials also show repeatedly that

antidepressant benefit in schizophrenia is minimal to none.

Of course, the idea also can be kept in mind that the diagnosis may not be pure schizophrenia. If there is an affective component, such as repeated depressive episodes, which would be consistent with a schizoaffective picture, then some benefit with low dose antidepressants might make sense.

Other harms of concern include cardiac arrhythmia as you mention, with some potential risk given QTc prolongation, as well as, longer term, possible hypertriglyceridemia with risperidone.

In all, PL would be supportive of the overall goal of tapering down and potentially coming off fluphenazine, and continuing only risperidone. However, the longer this patient has taken fluphenazine, PL would expect that it would be difficult to get off that agent. If that is the case, as long as TD and other harms are not present, it may be that the risk-benefit calculation for this patient would be consistent with continuation of the current regimen which his family feels has helped him. The family's opinion should be given a good deal of weight.

These considerations are meant to provide food for thought, for discussion with the patient and his family. In the PL approach, this is not a straightforward scenario where a definitively correct perspective exists.

Question: What is the PL viewpoint on the adjunctive use of buspirone for obsessive compulsive disorder (OCD)?

PL: Buspirone has a reputation for having mild benefits in whatever use, whether anxiety or depression. There was some surprise that it showed more benefit than expected for refractory depression in the Sequenced Treatment

Alternatives for Depression (STAR*D) study. In that study, it was similar in benefit, when added to citalopram, to switching to a different antidepressant, such as venlafaxine. Its use in generalized anxiety has been limited, with mild benefit in general. In the experience of PL clinicians, it also has had limited benefit if any in OCD. Buspirone is a complex drug, with

essentially mild 5HT1A agonistic properties. The mild clinical benefits are consistent with its limited biological effects. On the other hand, it also has few side effects. Thus, in general, PL doesn't see buspirone as a particularly effective treatment for any condition, including OCD.

PL Reflection

Do you realize how strangely a human being is constructed, that his virtues are often the seed of his downfall and his faults the source of his happiness?....For a long time I have known that I am not a genius...I am not even very gifted; my whole capacity for work probably springs from my character and from the absence of outstanding intellectual weaknesses. But I know that this combination is very conducive to slow success....I wanted to explain the reason for my inaccessibility to and gruffness with strangers, which you mentioned....I always comfort myself with the fact that people subordinate to or on a par with me have never considered me unpleasant, only superiors or people otherwise above me.....Even at school I was always the bold oppositionist, always on hand when an extreme had to be defended and usually ready to atone for it....You know what Breuer told me one evening?...He told me that hidden under the surface of timidity there lay in me an extremely daring and fearless human being. I had always thought so, but never dared tell anyone.

Sigmund Freud

In a private 1886 letter to Martha Bernays, his fiancee, written as a young man

PL Reflection

Delusion is the literal interpretation of metaphor.

Otto Dorr MD
Contemporary Chilean psychiatrist

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THE PSYCHIATRY LETTER

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**Please send your
questions and
comments to**
info@psychiatryletter.org

Summer symposium topic: The diagnostic interview

This issue discusses a topic that was raised in this year's Cape Cod summer symposia: how to conduct a diagnostic interview. The CME special article goes into some detail about one way to conduct a diagnostic interview, focused on mood conditions. The general overview would apply to other diagnostic settings as well. This summer issue provides more space for that aspect of the many topics discussed in the summer symposia. Next month we will resume our monthly column of articles and drugs of the month.

This month we also provide a Psychopathology article on alcohol abuse/dependence, written by PL Board member Dr. Derick Vergne, in which he discusses the kinds of questions to ask in an office interview to differentiate different types of alcohol abuse/addiction.

The Case of the Month examines a woman with panic attacks from whom benzodiazepines were withheld, but in whom those agents would appear to be reasonable to use.

We discuss the topic of medical marijuana, which came up in the summer symposia, in the Curbside Consults section.

As with all issues beginning January 2016, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

We appreciate your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: The diagnostic interview

A guideline from the summer symposia

Introduction

This year's Cape Cod summer symposia were the occasion for much discussion about important aspects of clinical practice. In this issue, we will describe and summarize some highlights of that discussion. One symposium was broad, and aimed at discussing diagnosis in detail, as well as the existential approach to psychiatry ("Becoming a master clinician: Drugs, diagnosis, and existential psychotherapy"). The second symposium was more focused on psychopharmacology, but aimed at the advanced clinician ("Psychopharmacology: A master class"). In this review, we'll focus on a question that arose about how to conduct a diagnostic interview. The discussion on that question touches on important aspects of existential approaches to psychiatry as well.

Psychopathology first, then diagnosis

The basic order in which one should assess a case is psychopathology, then diagnosis, then treatment. One cannot know the diagnoses until the symptoms are established; that's why psychopathology goes first. So don't begin with diagnoses in mind; begin with a search for symptoms. Then later begin to organize your understanding of those symptoms into potential diagnostic groupings. If a diagnosis then fits the psychopathology, you can begin to think about and discuss treatment options. These days, the psychopathology step is skipped usually, as clinicians immediately seek to apply DSM diagnostic groups. The existential tradition always begins with trying to understand the patient's experiences, to see if they represent psychopathological symptoms, and only then, in some cases, to proceed to a diagnosis.

"...Don't begin with a diagnosis in mind; begin with a search for symptoms..."

This diagnostic interview discussion will focus on assessment of mood symptoms, but a similar approach would apply to anxiety or delusional or other symptom groups.

Before the interview: Ask for family and friends to be present

Usually, when you go to the waiting room to find your patient, someone else is there, a family member and friend. About half the time, that other person remains seated. Most clinicians don't invite that person to join the interview. They should. Not only that, it is wise to inform patients before their first interview that they should seek to bring a family member or friend along with them.

This is for two reasons: first, family members and friends can corroborate the history or, in the case of mania, actually provide accurate history whereas patients, due to lack of insight, often invalidly deny the presence of some features of their personal history, especially manic or hypomanic episodes. Second, when discussing treatment options, the presence of others in the office improves the likelihood that the treatment plan will be understood and implemented; frequently, patients are depressed and cannot clearly understand the complex treatment options being described – family members can hear and repeat what was said later to the patient. Further, if family members aren't present, the patient will later have to explain what is said to them; it is better for the family to hear

what I have to say directly from the clinician, rather than secondhand.

If there are concerns about certain confidential topics (which usually do not directly impact on the diagnostic interview anyway), family can be asked to leave the room for a few minutes in the middle of the interview, and then invited to return toward the end when clinicians provide diagnostic impressions and treatment recommendations.

Begin with depression

Usually, the presenting complaint is depression. As the psychotherapeutic saying goes, it is best to meet patients where they are; so clinicians should start by the non-controversial and straightforward determination of the presence of clinical depression.

“...depression is not a diagnosis, but only a constellation of signs and symptoms...”

At one level, one simply identifies depression to get beyond it. In other words, it often is relatively easy to know that a patient has a current clinical depression – it may only take five minutes to quickly review current neurovegetative symptoms – but that is not the end of the evaluation, only the beginning. This is because depression is not a diagnosis, but only a constellation of signs and symptoms. Diagnoses are bipolar depression, or secondary depression, or unipolar depression – with unipolar depression signifying that the bipolar and secondary diagnoses have been ruled out. So, as soon as a clinical depressive episode is identified, especially currently, the clinician

should stop talking about depression, and shift the focus to identifying past mania or hypomania and assessing possible secondary causes (mainly medical).

It is irrelevant, for instance, to spend much time assessing how depressed the patient is, whether she is hopeless or helpless, whether her symptoms are atypical or typical, and so on. All those features are important perhaps prognostically and therapeutically, but they are unimportant diagnostically. They do not differentially diagnose bipolar as opposed to secondary or unipolar depression.

Obviously an assessment of concurrent psychotic symptoms can be diagnostically and therapeutically relevant, and an evaluation of suicidality is clinically necessary; but soon after identifying depression, the clinician should shift the focus to the more onerous task of looking for past mania or hypomania, and possible secondary causes.

Assess the course of depressive illness

Before doing so, however, PL would emphasize something that is rarely done: *evaluate the course of the depressive illness*. The reader will recall that the course of depression, unlike the details of current depressive symptoms, *can* differentiate between bipolar and unipolar conditions, as well as help identify secondary depression. Too often clinicians simply say: “The patient has major depression,” as if that is enough to make a diagnosis. They have no idea when the

depressive episodes began, how many there have been, how long they have lasted, precipitating factors, interepisode symptoms, and so on.

Here is what is diagnostically important: age of onset, number of episodes, duration of major depressive episodes, and interepisode status. Ask patients how far back they can remember depression for the first time, refreshing their memory as to the definition of a major depressive episode (daily depressed mood or anhedonia with multiple neurovegetative symptoms, day in and day out, most of the day nearly every day, for weeks on end or more).

Then ask how long their depressive episodes have lasted in the past. Here patients usually throw up their hands and claim

ignorance. The clinician can reply, "I could make it up, but your guess is better than mine." Patients need to know that this is important; force them to think about it. Usually they can give an average duration; it need not be precise – if they are especially exasperated, give them options: more than a month, less than a month, about six months, over a year. These are the time-frames that are diagnostically relevant, since unipolar depression lasts 6 months to a year or longer while bipolar depression is shorter, usually 3–6 months or less. Also assess the durations ideally in untreated periods to understand the natural unmedicated history, but if a patient has been non-responsive to medications, then

"...Usually they can give an average duration; it need not be precise..."

treated periods should reflect the natural history of the illness.

Then ask how many episodes the patient has had: "How many times in your life have you felt very depressed like that?" Usually, if currently depressed, patients overestimate their past depression: "Forever" is the common desperate answer. "Really?" one could reply, "All your life, every day, day in and day out, without ever having one day of being different, forever?" Usually, they back off at that point. "So how many times?" "I don't know, doc." Again one can offer multiple choice answers: "Just once? A few times? More than five times? More than 10 or 20 times?" Sometimes it is obvious in the

history that the patient has had many episodes, more than 10 or 20; in that case the exact number matters little. What does matter diagnostically is that if a patient has one or two or three episodes, this is common in unipolar depression and uncommon in bipolar disorder. Many episodes is more common in bipolar illness, especially if they are brief (less than 3 months in duration).

Finally, once you have identified the ballpark number of episodes, determine if there are periods of wellness between episodes. This is usually not difficult; either patients will claim they are always depressed, which may reflect interepisode dysthymia or subclinical depression, or they have periods of euthymia, which they or their family can clearly describe: "Were there ever times when you

were not depressed and were your normal self, or normal like everyone else, in your mood energy, for weeks or months on end or longer?"

Spend more time assessing past mania or hypomania

In the typical interview, it might have taken five minutes to establish that the patient has a current major depressive. Another 5-10 minutes should establish the depressive course of illness. Next, one should take as much time as needed (up to 15 minutes or more) to examine the ins and outs of possible past mania or hypomania. Unfortunately this part of the interview, the most important clinical aspect diagnostically and therapeutically, is often

conducted with only a single question or hurriedly. The clinician should take his or her time, and come at the question slowly and in a roundabout fashion, so as to avoid patients' natural defensiveness about the stigma of bipolar disorder.

PL suggests beginning by an open-ended question, especially if you have established a period of normal or euthymic mood in the past in the assessment of the course of depressive illness: "Did you ever feel the opposite of depressed, where you were not sad and down and depressed, but you also weren't just your normal self?" With equivocal responses, one might get more specific: "Did you ever have times where you were more energetic than normal, compared to when you were not depressed, or more

energetic than most people around you, so that you were doing lots of things or not sleeping much and not feeling tired?" Or perhaps: "Did you ever have periods where you were angry and irritable but not depressed, and full of energy, doing lots of things?"

If a somewhat positive response is elicited, or if the patient comes to the appointment with possible past mania as a clinical question, clinicians can ask an open-ended question, so as not to direct the patient toward manic criteria, but seeking to get their own words about it: "Tell me about how you felt, and how you behaved, or what people told you about how you were, during that time (when you felt hyper or more energetic than usual or where you or your doctor or others said you might be manic or hypomanic)?"

"...write down what the patient says verbatim..."

Then, importantly, clinicians should *write down what the patient says verbatim*. It is very important to do this. Bipolar disorder is such a controversial topic, with patients getting different opinions from different doctors, that it is important to avoid miscommunication by letting the patients speak for themselves. Consider if you write: "The patient had elevated mood, with decreased need for sleeping, flight of ideas, distractibility, and increased goal-directed activity for five days." The patient may disagree and go to another clinician, who is skeptical about the bipolar diagnosis, and that clinician might simply disbelieve my

interpretation of what the patient had said. But no one could deny mania if you write: "The patient stated that he would feel 'hyped up and like I could do anything, I was a tyrant, felt I was smarter than everyone else, like there was nothing I couldn't do, I didn't need to sleep for days on end yet I was full of energy, I was giddy at times, my thoughts were all over the place, I couldn't keep up with them, I would wake up in the middle of the night and clean the house five times over, then the next day I would paint the house inside and outside even though it was perfectly fine, and a week later I would do it again with a different paint color."

Once a manic or hypomanic episode is identified, the diagnostic process is over:

the diagnosis of bipolar disorder has been made. If mania or hypomania cannot be identified, the interview is still not over; then the absence of mania/hypomania needs to be confirmed by third parties. This is done most efficiently if family or friends are present at the interview; if not present, the clinician should call, or ask the family to call, to quickly review mania criteria over the phone. Sometimes you can make this phone call during the patient interview, sometimes later.

Examine causes of secondary depression

These causes are most often medical, though they can also be psychosocial. It is important to distinguish between a trigger and a cause. A trigger is the final event that leads to the episode, but it is not the sole or even the

main cause of the episode. This is similar to what Aristotle called the efficient cause. Sometimes there is a certain trigger, sometimes another trigger, and sometimes no trigger. Don't focus on triggers, though they may be somewhat relevant later especially in psychotherapy; they are diagnostically irrelevant.

Unfortunately most patients, and many clinicians, focus on the most recent psychosocial triggers as if they were absolute causes of episodes. This is a big mistake. The best way to think about this problem, in the

"...If mania or hypomania are not identified...the absence...needs to be confirmed by third parties...."

PL viewpoint, is to recognize that the brain is a rationalizing machine. The classic split brain experiments in epilepsy show us how: In patients with intractable seizures requiring corpus callosotomy (severing the two hemispheres of the brain from each other), one creates a circumstance where the right hemisphere might note something and yet not be able to transfer that information to the left hemisphere, where verbal control is located. Since the left visual field is transmitted to the right hemisphere, researchers can place the right visual field behind a blindfold, and show pictures in the left visual field, such as violent and anxiety-provoking images. The right hemisphere sees these pictures, and the patient feels scared and nervous. When asked why, the patient says: "Well, my neighbor had a car accident last week and I was thinking about that?" or "I was thinking about the recent war in the Middle East." In other

words, the patient cannot verbalize why he suddenly feels anxious or scared, yet he comes up with an explanation, any explanation, as long as it is plausible, even though it is wrong. We do this all the time: so when patients say there are depressed because of x, y, and z happening in their lives – they may be right, and they may be wrong: we cannot take those explanations as true at face value.

True psychosocial causation, secondary depression due to a psychosocial cause, should be relatively obvious and should be placed in the context of a non-recurrent course of illness: The patient may have one episode after a horrible psychosocial trauma; or maybe two episodes after two horrible psychosocial traumas; but most people, fortunately, do not have many isolated psychosocial traumas (or if they are the victim of recurrent abuse, they usually experience prominent post-traumatic symptoms rather than simply major depressive episodes alternating with euthymia). If recurrent major depressive episodes occur, the psychosocial factors should be seen as triggers, not causes.

The role of substance abuse should be seen in the same way as psychosocial stressors. If a patient never had mania, then takes cocaine for the first time in her life, and then has a manic episode, one can call that condition cocaine-induced mania. But, if she has experienced many manic episodes and many periods of cocaine use, it would seem difficult

“...True psychosocial causation ...should be placed in the context of a non-recurrent course of illness...”

to demonstrate a one-to-one correlation so as to justify the diagnosis of mood disorder secondary to cocaine use. Often the situation is the reverse: cocaine use frequently occurs in those settings as the result, rather than the cause, of manic episodes.

The same is the case with medical factors. One might have no past depression, then have a stroke, and then experience a major depressive episode. That is post-stroke depression. Most individuals do not experience repeated strokes (since most persons get treated) followed by

depressive episodes after every stroke. On the other hand, mild hypothyroidism may be a factor in contributing to recurrent depressive episodes.

Unlike the above scenarios, there is a kind of secondary depression which, when present, is *sui generis*. Perhaps the most important secondary cause of clinical depression is “vascular” depression. As discussed on the PL website, this condition consists of small microvascular cerebral infarcts, visible on MRI, usually the consequence of hypertension and/or diabetes. This type of depression is common in middle and older age, and has a poor prognosis.

Treatment history

The rest of the history involves obtaining treatment history, family history, and other aspects of a standard medical evaluation. In the interests of space, PL will not examine these topics in detail except to say that

treatment history and family history should be examined in more detail than is commonly the case. For treatment history, for instance, the relevant factors needed are not only the names of the medications, but the durations of treatment, doses if available, and concomitant medications used. For each medication, one should assess efficacy and side effects and the reason for discontinuation. Whatever the patient can recall should be documented as well as possible.

At times, patients claim they cannot remember details are often overconcerned with being exact. For instance, when you ask how long they took a certain drug, they become exasperated because they cannot remember if it was 2 months or 3.5 months or 4.25 months. Since they can't be precise, they will just say they don't remember. Clinicians can then give them multiple-choice options: "Was it less than one month, more than one month, more than one year, more than ten years?" Obviously this forces them to say something and we can get some valuable data, such as the idea that they took the drug somewhere between 1 to 6 months.

However long it was used, clinicians should ask about whether other medications were taken with it. Often patients can say that other medications were taken, but they do not remember which ones. It is just as important to know that they did *not* have monotherapy trials, especially with mood

"...treatment history and family history should be examined in more detail than is commonly the case..."

stabilizers in bipolar disorder, than to know the details of the other medications they received. Clinicians can then ask whether they thought the medication trial was effective or not, and whether they had side effects. People usually remember side effects more clearly than efficacy, though sometimes they can be clear when a drug was either definitely not effective or definitely extremely effective. It is still clinically very useful to see if one can elicit either extreme response marked efficacy or marked inefficacy, or the absence of ever having such clear good or bad effects. Sometimes, if a patient has taken many drugs from the same class (such as ten different antidepressants), clinician can simplify the efficacy assessment by asking, "Was there any one of these that worked very well for you, that stands out as especially effective?" Also, if efficacy is reported, one should ask about whether the drug maintained its benefits if used long-term (to assess tolerance or "poop out").

Final steps

When a diagnosis is made, clinicians should describe their rationale for that diagnosis, based on symptoms, course, genetics, and treatment response - the four classic validators of diagnosis. Then treatment options can be discussed. It is important, respectful, and humane to explicitly state the diagnosis to the patient before discussing treatments in any way, and

further to elicit a two-way dialogue about the patient's feelings about the diagnosis.

The clinician should keep in mind, and the patient should be told, that working diagnoses are just that – working; so they are liable to change, and in fact should not uncommonly change, in the course of months to years of follow-up. In psychiatry, the course of the illness is the final arbiter of diagnosis: “Time will tell whether this diagnosis is right, or whether another one turns out to be the case,” I tell my patients. Time will tell; both clinicians and patients need to be open-minded and revisit the diagnosis over time. A major mistake, often seen in public mental health settings, is that a diagnosis (often schizophrenia or “depression”) is parroted over years, often from clinician to clinician, without ever being re-evaluated, even though the course of illness often clearly proves it wrong.

Steps in the diagnostic interview of mood condition

Identify a current clinical depressive episode (5 minutes)
Assess the course of depressive illness (5 minutes)
Spend more time assessing past mania/hypomania (10-15 minutes)
Examine causes of secondary depression (5 minutes)
Obtain past treatment history (5-15 minutes)
Discuss the rationale for the diagnosis (5-10 minutes)
Discuss treatment options (5-10 minutes)

Suggested times will vary based on complexity of a patient's history. In a newly diagnosed patient, no time is needed for past treatment history, and more time can be spent on course of illness, secondary triggers, and discussion of diagnostic rationale. In a patient with extensive past treatment, the other sections might be somewhat briefer to allow for more extensive examination of past treatment history.

The PL Bottom Line

- In the diagnostic interview, don't forget to assess course of illness.
- Assess manic symptoms more extensively and more indirectly than depressive symptoms.
- Obtain past treatment history in detail.
- Always discuss the rationale for diagnosis.

PL Reflection

The past does not repeat itself; but it rhymes.

Mark Twain

Psychopathology

Asking the right questions about alcohol abuse/dependence

*Derick Vergne MD, Harvard Medical School,
McLean Hospital*

Addictive disorders are not categorical states but dimensional ones. There is no "state" whereby a clinician can say that a patient is, or is not, addicted.

Many would try a beer, some would try cocaine, many won't get hooked, but some will. Most of us would conclude that we didn't get hooked on alcohol after drinking just one beer because we have self-control; we know better. We are unaware that our genetic makeup might dictate, under the right circumstances, whether we are one of the unlucky ones to become dependent after one beer. For instance, individuals with an alternative version of the opioid receptor mu (OPRM)

will be more responsive to the euphoric effects of alcohol; their brains will create the pleasurable intensity to a higher degree when compared to the average OPRM version (which would provide the "average" pleasurable experience). There is therefore some degree of "luck" to whether your brain is, or isn't, more responsive to the effects of drugs of abuse; in this case, alcohol. In the case of alcohol dependence, evidence points to a higher positive response by alcoholics to naltrexone if they have the OPRM genetic version that promotes the higher brain pleasurable response to alcohol. In other words, the higher the pleasurable experience to alcohol intake, the more likelihood of response to an agent (naltrexone) that "blocks" (albeit not 100%) its pleasurable effects.

"...How does drinking alcohol make you feel?..."

In the office, when evaluating a patient, it is unlikely that we are going to be able to test for the OPRM genetic polymorphism (it's still only done in clinical research). In order to shed some light into the neurobiological background (at least indirectly) of our patient, two important questions to ask in the initial evaluation of, say, an alcoholic patient are: "How does drinking alcohol make you feel?", and "What does it do for you?" Responses vary and the clinician also has to make sure that those questions are asked going back to different points in the natural history of the illness, for instance, how did it make you feel the first time you had alcohol at age 14?, then How did it progress from there?. In the case of alcohol abuse/dependence, some patients might mention that it relaxes them, that it makes them feel "good" and disinhibited so they can "socialize more". These responses are in contrast to the general worrier, agoraphobic, who drinks alcohol in order to feel "less anxious" in order to go to the grocery store. This type of response can also be observed in trauma-related disorders, like PTSD. With the latter response to alcohol it is less likely that naltrexone will be of help. Rather, mounting evidence points to a role for gabapentin (an anticonvulsant many times used as an adjunctive anxiolytic) for the treatment of alcohol withdrawal and relapse prevention (see review for gabapentin on the September issue of PL). In this case alcohol is used as an "anxiolytic"; there is no effect on the brain's reward (pleasure) system.

In sum, the right kinds of questions can help determine why a patient might be addicted to alcohol.

Case of the Month

When it's okay to prescribe benzodiazepines

A 29-year-old woman presented with a diagnosis of panic disorder and generalized anxiety disorder (GAD), for which she is treated with paroxetine for 6 months. She seeks consultation because she reports "not feeling myself" in recent months. She saw her primary care doctor a year ago for panic attacks, which occurred about once monthly. The primary care doctor was reluctant to give her benzodiazepines, and prescribed paroxetine 20 mg/d. This dose produced tremor, which improved at 15 mg/d. Her panic symptoms completely resolved for 6 months, and her function at work improved. However, about 3 months ago, she began to feel less interested in social activities and less interested in her work. She denied low energy or other depressive symptoms. She had one depressive episode 4 years ago, after a break-up, which improved a year later without medication treatment. She has no other mood episodes in the past, and denies any manic or hypomanic episodes. Manic symptom denial was confirmed in a phone call by the consultant to the patient's mother. She denies any other past psychiatric symptoms, has no medical illnesses, no drug allergies, and no past trauma. She is single and in a long-standing relationship, and has been productive and functioning well at her work in a publishing company for 5 years. She has no current or past history of alcohol or drug abuse of any kind.

The PL impression was that she was experiencing the side effect of apathy syndrome from serotonin reuptake inhibitors. The use of benzodiazepines, like lorazepam, initially on an as needed basis, and if needed on a regular basis, was recommended. Specifically, it was recommended that paroxetine be stopped and replaced with a benzodiazepine. Since she has no substance abuse history, her risk

of benzodiazepine abuse or addiction is very low, probably less than 5% based on some research. She has a troublesome SRI side effect, and long-term SRI treatment itself will be associated with tolerance and major withdrawal symptoms. Her panic symptoms are not very frequent, only once monthly, and she has no need for SRI treatment for any other recurrent mood condition. Thus, the PL consultant was impressed by the limited nature of her panic symptoms, and the troublesome nature of her SRI side effects, along with absence of a need for constant, long-term treatment of any medication. This clinical picture, along with absence of substance abuse, would support the prescription of benzodiazepines instead of SRI agents.

Curbside Consults

Questions and cases from you

Question: What do you think of medical marijuana?

PL: This topic will gain in importance as we see more states legalizing marijuana in the near future. In the states in which it has been legalized, PL has heard from colleagues that some problems have arisen. The potency of THC in the legalized marijuana appears to be much higher than the potency in the illegal plant used in past decades. This high-potency marijuana appears to be causing some cases of paranoia or even possibly onset of depressive or delusional states. Further, its addictiveness is heightened if used in high potency form.

One observation that is important is that some younger people in particular appear to be confusing legalization with safety. Alcohol is a legal substance, but it is not safe. Amphetamines are legal substances, with a prescription, but are

not safe in many settings, or at certain doses. The PL viewpoint is that it is important to discuss with patients the there is a difference between legalization and safety. There are known risks of marijuana in animal studies in terms of harmful effects on the brain, just as is the case with alcohol. This in itself is not a reason to criminalize it, but it also remains a fact, even if the substance is legalized.

As with all substances, harms should be understood well and consented if used recreationally or medically. As with alcohol and amphetamines, whether in recreational or medical use, harms should never be ignored.

The history of amphetamines suggests a possible repetition. Those agents were available freely without prescription in post World War II Japan, and a huge addiction problem arose. They were available in post World War II United States with a prescription but there was no FDA control upon them. Most prescribed amphetamines were

diverted to illegal use. Both in Japan and the US, those agents remained legal, but only in medical use, and with strict controlled substance regulation.

In contrast, alcohol was widely used recreationally, then prohibited disastrously, and then returned to recreational use. It has never been given for medical purposes primarily. And it remains the most widely abused class of substance in the United States, leading to attention primarily by law enforcement, as with strict drunk driving punishments in most states.

We will see what the future of marijuana use holds in the United States, whether it follows the pattern of amphetamines or alcohol or a mixture of both. One thing is clear: it is a substance of abuse, and legalization does not imply safety.

PL realizes that this topic is in flux, and these perspectives are presented tentatively and provisionally, and could be in error in many ways. PL is open to other perspectives from readers.

PL Reflection

William Osler's Three Rules for Medical Practice

1. Consume your own smoke. Don't complain about the inevitable trifles of the day's routine. Things cannot always go your way.
2. The practice of medicine is an art, not a trade; a calling, not a business. We are not here to get all we can out of life for ourselves, but to help others become happier.
3. The hardest of all – Love, charity, requires not only beneficent acts, but an end to hard thoughts.

William Osler

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**Please send your
questions and
comments to**
info@psychiatryletter.org

Schizoaffective illness

This issue examines the clinical conundrum of schizoaffective illness. Is it a legitimate diagnosis? Does it reflect a real illness? How does it relate to schizophrenia and affective illness?

Clinicians frequently face patients with the clinical picture of schizoaffective illness. In this issue, PL examines what it means. The main conclusion drawn is that schizoaffective illness, when truly present, reflects the chance comorbidity of schizophrenia and affective illness.

As an extension of last month's issue on the diagnostic interview, Dr. Tammas Kelly provides his insights into how he approaches the diagnostic interview, with a special emphasis on the benefit of an initial self-report questionnaire.

The classic study of the month examines the Roscommon family study and its implications for the diagnostic validity of schizoaffective illness.

The drug of the month is venlafaxine and its active metabolite desvenlafaxine. The many risks and harms of this agent are discussed in detail.

As with all issues beginning January 2016, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

We appreciate your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: Schizoaffective illness

The chance comorbidity of schizophrenia and affective illness?

Introduction

Our understanding of schizoaffective disorder can be organized in five different theories. One approach holds that schizoaffective disorder is its own illness, separate from others, as appears to be the case superficially by its separate diagnostic criteria in DSM-IV. A second model holds that schizoaffective disorder represents a middle clinical picture on a psychotic continuum that extends from bipolar disorder to schizophrenia; in other words, this model rejects the Kraepelinian dichotomy of bipolar disorder and schizophrenia. A third model argues that schizoaffective disorder represents the comorbidity of affective disorders and schizophrenia, thereby maintaining the Kraepelinian dichotomy and explaining overlap

symptoms as chance co-occurrence. A fourth theory views schizoaffective disorder as basically a variant of bipolar disorder, and a fifth sees schizoaffective disorder as a variant of schizophrenia.

Many clinicians unconsciously take the first approach. They assume that since "schizoaffective disorder" represents two words, and they exist on a page of paper, especially in the DSM criteria, then those two words must represent a "real" thing, a real illness in the real world, separate and apart from other illnesses. This common human conclusion flows from the assumption that once you name something, it exists. Of course we name many things that don't exist, sometimes fantasies, sometimes mere falsehoods.

"[There is an] assumption that once you name something, it exists."

In the May PL issue, we reviewed the rationale for why many DSM labels do not correspond to "real" diseases or illnesses, but rather represent social constructs of the American psychiatric profession. Separate from this fact, we should keep in mind that any diagnostic label represents only a clinical picture, first and foremost. Whether that clinical picture is a different disease or illness from another clinical picture - that's a different question.

So as we get into the discussion of schizoaffective illness, PL would like to remind readers that we are talking about a "clinical picture": we see patients who have mixtures of delusions/ hallucinations along with mood. What this clinical picture means - is it a separate illness or not? - is another question.

Phenomenology

At the level of observation, the term "schizoaffective" simply applies to those individuals with continuous psychotic and mood symptoms. Unlike mood disorders, psychotic symptoms are not brief. And unlike schizophrenia, mood symptoms are not absent. Clinically, many patients seem to fall into this overlap region. In fact, the original paper describing the occurrence of such patients with such overlap was published in 1933. Indeed, Kraepelin himself observed that a good number of patients had such overlap of manic-depressive and dementia praecox symptoms. Hence, the fact that such overlap occurs is almost universally

accepted, even by Kraepelin, who originated the idea that mood and psychotic disorders differ.

By itself, the presence of overlap doesn't invalidate the diagnoses of schizophrenia and manic-depressive illness (MDI). This is partly because phenomenology is only one of four diagnostic validators (along with genetics, course of illness, and treatment effects/biological markers). This is also partly because a difference in symptoms is not an all-or-nothing phenomenon. In other words, to say that schizophrenia and mood disorders differ in symptoms is not to say that they *never* overlap. It only means that they *usually* don't overlap. And indeed, some well-done symptom prevalence studies have shown that patients with mood and psychotic symptoms tend to differentiate into two big groups, one with mainly mood symptoms and one with mainly psychotic symptoms, although there is some overlap (Figure 1).

It is sometimes argued that the mere existence of schizoaffective disorder is a counterexample to the Kraepelinian dichotomy of schizophrenia and affective illness. As should be clear from the above considerations, this is not the case. Some overlap is expected; and symptoms are only one aspect of diagnostic validation. To refute the Kraepelinian diagnostic schema, one would also need to look at genetic, course, and treatment response data.

Genetics

If schizoaffective disorder is a separate illness in its own right, one would expect that it would breed true in families. However, almost all genetic studies are consistent in demonstrating that it doesn't breed true. Schizoaffective disorder isn't found mainly in families of persons with schizoaffective disorder. Rather, various studies suggest a unique pattern. In some studies of families of persons with bipolar disorder, there is an increased prevalence of schizoaffective disorder, bipolar type. In some studies of families of persons with schizophrenia, there is an increased prevalence of schizoaffective disorder, depressed type. And in a number of well-executed studies comparing both major groups, schizoaffective disorder is more prevalent in families of persons with schizophrenia or bipolar disorder than in control populations or than in families of persons with schizoaffective disorder.

These results are consistent with a number of possibilities. In some persons, schizoaffective disorder, bipolar type appears to be a more severe variant of bipolar disorder. In others, schizoaffective disorder, depressed type appears to be a less severe variant of schizophrenia. And in still others, since it seems to run in both families of persons with both schizophrenia and bipolar disorder, only two explanations seem possible: (1) either schizoaffective illness may indeed be the counterexample to the Kraepelinian there is no dichotomy between bipolar disorder and schizophrenia; no distinction between any psychotic disorders can be made and they should all be seen as one continuum; or (2) schizoaffective disorder may simply represents the

comorbidity of having, by chance, schizophrenia and bipolar disorder (or unipolar depression) *at the same time*, just as one might have diabetes and asthma at the same time.

The genetics of schizoaffective disorder argues against the concept of a separate illness, but the four other possibilities remain open.

Course

Studies of the course of schizoaffective disorder tend to be rather consistent: the course of the illness is more severe than in bipolar disorder but less severe than in schizophrenia. Further, schizoaffective disorder, depressed type appears to demonstrate less recovery than schizoaffective disorder, bipolar type.

These findings again are consistent with the four remaining models.

If there is only one continuum of psychotic illness, bipolar disorder may lie at the less extreme end, schizophrenia at the more extreme end, and schizoaffective disorder in between. Hence schizoaffective disorder might have an intermediate course. On the other hand, if it represents a comorbidity, it may be that the more severe outcome of schizophrenia is leavened by the coexistence of bipolar disorder so that an intermediate outcome would be observed in schizoaffective disorder. Further, if the bipolar type of schizoaffective disorder is a variant of bipolar disorder, it would be expected to have a worse outcome than bipolar disorder but better than schizophrenia. Also, if the unipolar depressed type of schizoaffective disorder is a variant of schizophrenia, one would expect a better outcome than schizophrenia given the more responsive affective illness factor.

“....there is no evidence that schizoaffective disorder represents a separate illness distinct from schizophrenia and bipolar disorder...”

In sum, the course studies are similar to the genetic studies in supporting all of the models except the concept of a separate illness.

Treatment Response

This is the least specific diagnostic validator, but it still can be useful. There are few studies of treatment of schizoaffective disorder, but it is generally thought that these patients require long-term treatment with antipsychotic agents, as in schizophrenia, and long-term treatment with either mood stabilizers (bipolar type) or antidepressants (unipolar depressed type) as in the corresponding affective disorders. Again, this treatment response pattern is consistent with all four models except the separate illness model.

And the answer is....

What are we to conclude? What appears most clear is that, its appearance in DSM-III through 5 notwithstanding, there is no evidence that schizoaffective disorder represents a separate illness distinct from schizophrenia and bipolar disorder. Studies of symptomatology vary, but some important and well-done studies tend to find a difference in symptoms in psychotic and affective populations that more or less falls along the lines of Kraepelin's dichotomy of schizophrenia and affective disorders. While there are overlap areas, such overlap is empirically expected in a real-world population of persons (or animals or any other grouping). Therefore, studies of phenomenology can be interpreted as leaning against the single psychosis continuum model.

If schizoaffective disorder represents a comorbidity of schizophrenia and bipolar disorder, one would expect an epidemiological prevalence that is significantly lower than the other two. In other words, schizoaffective disorder should be very infrequent, since comorbidity should not be overly frequent by chance. Clinical impressions to the contrary notwithstanding, epidemiological prevalence studies indeed demonstrate that schizoaffective disorder appears to be very infrequently diagnosable in the general community, at a level of less than 0.5%, which is much lower than accepted prevalence rates for schizophrenia (1%) and bipolar disorder (2-4%).

Three final models

These considerations suggest that the remaining three models are consistent with the available diagnostic research (Figure 2):

1. Some persons experience mainly bipolar mood symptoms, with only some excess of psychosis. These persons are diagnosable with schizoaffective disorder, bipolar type, seen as a severe variant of bipolar disorder. By and large, they need aggressive mood stabilizer treatment and perhaps somewhat less aggressive antipsychotic treatment. They have a relatively good prognosis.
2. Some persons experience mainly psychotic symptoms, with only some excess of unipolar depressive symptoms. These persons are diagnosable with schizoaffective disorder, depressed type, seen as a somewhat less severe variant of schizophrenia. By and large, they

“....schizoaffective disorder appears to be very infrequently diagnosable in the general community...”

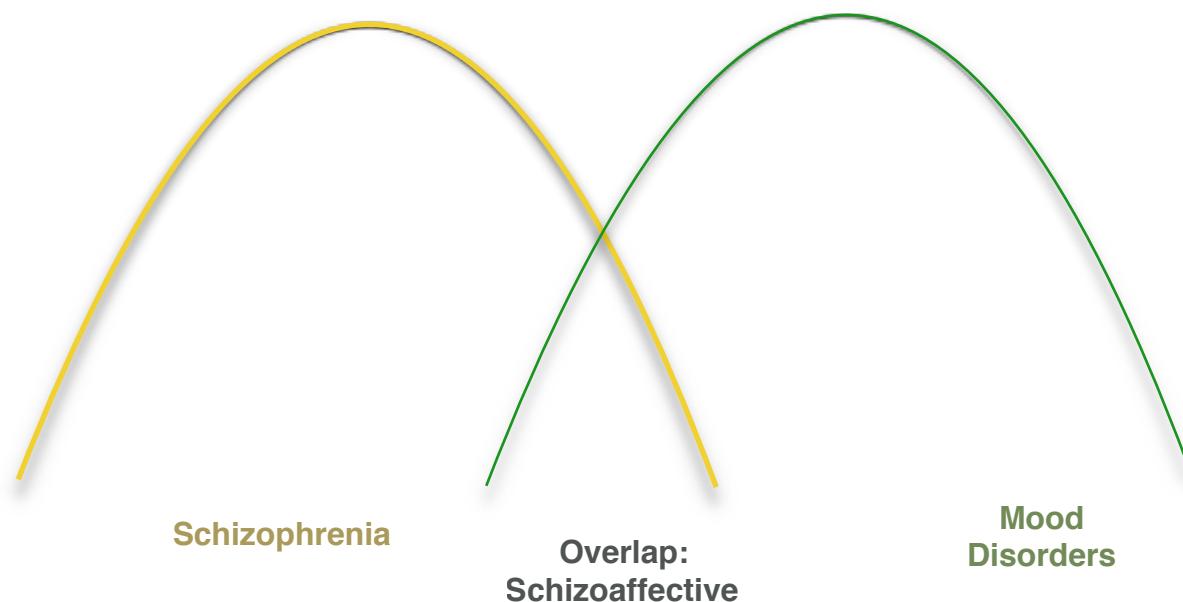
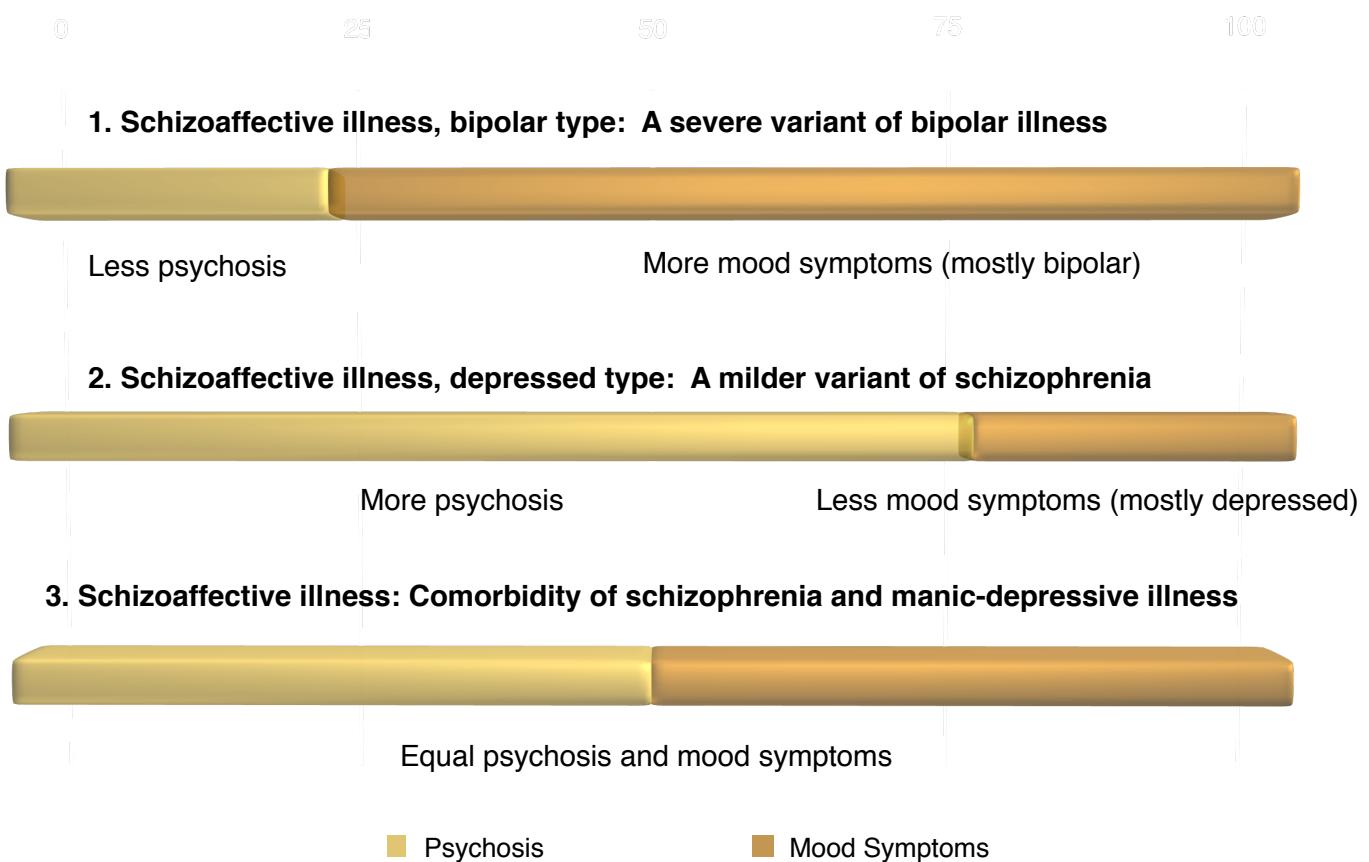
need aggressive antipsychotic treatment, and perhaps somewhat less aggressive antidepressant treatment. Their prognosis, though better than in schizophrenia, is usually only fair.

3. Some persons appear to be truly schizoaffective: they experience psychotic and affective symptoms in more or less equal amounts. This group represents the true comorbidity of schizophrenia and affective disorders, has an intermediate outcome, and requires aggressive, persistent, long-term treatment with both antipsychotic agents and either mood stabilizers or antidepressants.

If clinicians try to differentiate apparently schizoaffective patients in this manner, they will encounter these three groupings.

The PL Bottom Line

- Schizoaffective disorder isn't a valid separate illness.
- When defined strictly, it likely represents the chance comorbidity of schizophrenia and manic-depressive illness in the same person.
- When mood symptoms predominate, it represents a more severe version of manic-depressive illness.
- When delusional/hallucinatory symptoms predominate, it represents a less severe version of schizophrenia.
- Treatments should target mainly the mood, or mainly delusions/hallucinations, depending on which of the last two above variants are present.

Figure 1. Symptom overlap does not invalidate two separate illnesses**Figure 2. Three varieties of schizoaffective illness**

Clinical Corner

Diagnostic interviews: Work smarter not harder

Tammas Kelly MD, Colorado

Consider how the rest of medicine makes a diagnosis: there is an initial interview followed by a physical exam. The physician will order blood tests, x-rays or some other type of diagnostic procedure. Each of these steps generates data, the latter two objective data. Unfortunately, in psychiatry we have no x-rays and it's extremely rare that a physical exam will help us make a diagnosis.

The three most important factors in real estate are location, location and location. Similarly, in making a diagnosis the three most important factors are data, data and data. The 50-minute initial interview has dominated the diagnostic process of psychiatrists since long before I became a psychiatrist 31 years ago. Historically when our biggest treatment weapon was psychotherapy, and making the correct diagnosis was less important, 50 minutes was sufficient.

When we are unsure of the diagnosis, we are supposed to schedule another appointment. If need be, we collect ancillary information from family and friends. Today the average patient acuity dictates that we make a diagnosis and start treatment by the end of the first interview. If we are to take a frank appraisal of our profession, the majority of psychiatrists will make up their mind about diagnosis in less than 50 minutes, and rarely collect ancillary information and seldom reevaluate the diagnosis even in the face of treatment failure. Economic and administrative factors (such as working for mental health clinics or hospitals) push us into limiting ourselves to 50 minutes. Sometimes it's our own arrogance.

The problem is 50 minutes is simply not long enough. Even if the patient is a good historian, it

isn't long enough. For those of us who remember oral boards I don't think there was any one of us who didn't complain that 30 minutes was enough time to collect a sufficient amount of information to rule in or out the 13 most common psychiatric diagnoses, formulate a treatment plan and present and discuss the treatment plan. Oh yes we were also supposed to build rapport, collect a social history, find out about past medications, suicide attempts and hospitalizations. It just couldn't be done. If we are realistic it can't be done in 50 minutes either.

If we are unsure of the diagnosis, we are supposed to collect ancillary information from family and friends preferably at the initial appointment which just narrows that 50 minutes further.

We should have sufficient information to rule out or suspect all 13 most common psychiatric diagnoses. When was the last time you saw a "review of symptoms" in a psychiatric workup?

How then are we to compensate for this "data deficit"? We could simply lengthen the interview process and indeed psychiatrists do an 80-minute assessment. We could take two hours. However, there are many patients that can barely tolerate 50 minutes. The business maxim comes to mind. Work smarter not harder. We could borrow a page from our psychological brothers and sisters. They long ago concluded that oral interviews were insufficient to make an assessment. They collect data through a written test. In my clinic, the Depression & Bipolar Clinic of Colorado, every patient must fill out a 36-page questionnaire before they can be seen.

There are large advantages to the 36-page questionnaire. Patients have time to sit and contemplate the answers instead of dealing with the social pressure of trying to remember history, discerning the vocabulary used by psychiatrists

and answering questions while trying not to look like a loser in front of a “authority” figure. Transference is alive and well. It often interferes with the gathering of good data. Filling out the questionnaire before the initial interview decreases the transference issues. The upshot is people are generally more truthful on the questionnaire. Both because patient had to fill out the questionnaire before most transference issues start, and because the patient has committed to answers, it becomes difficult to gloss over an issue.

Diagnosing bipolar disorder has become the subject of much debate. The questionnaire has become an invaluable tool in ruling in and ruling out bipolar disorders. Verbally most previously undiagnosed bipolar patients will deny highs.

The 36 page questionnaire collects data on: demographics, current medications, current vitamins and nutraceuticals, current medical diagnoses, and ask for past medications, naming each one, its brand and generic names, its length of use, side effects, and it was stopped. The questionnaire contains screening questions for the 13 most common psychiatric diagnoses. In addition it has questions about caffeine intake, sleep history, history of head injuries, sleep apnea, hospitalizations both medical and psychiatric, suicide attempts, PMDD, demographic information, employment history and family history. Family history means addresses each relative, names most psychiatric diagnoses, and asks about the presence of psychiatric symptoms.

Patients have a hard time remembering all the medications they have had in the past. I present them ahead of time a full list of psychiatric medications, both brand and generic, and the patient at leisure (without the social pressure of trying to remember names in front of a doctor) can, with the visual clue of the name of the

medication, remember much more about their experience of past treatments. In an interview are you going to go through 40+ medications one by one? There are important clues that you can miss.

There are many more advantages to the questionnaire that I won’t go into here. I will say that patients’ reactions to the questionnaire is telling. Most are impressed saying no other psychiatrist has been as thorough. Patients who complain almost never stay in treatment. There also is a family version to gather information from loved ones.

PL Commentary:

Dr. Kelly makes some important points in his commentary on last month’s PL issue and its approach to the diagnostic interview. His main recommendation is to use a written questionnaire before beginning the diagnostic interview. This way, clinicians are not starting from nothing but actually have some material to use in the course of their interview. His questionnaire is rather lengthy, and clinicians might also consider brief self-report scales as other options, such as the Mood Disorders Questionnaire, the Bipolar Spectrum Diagnostic Scale, or the Beck Depression Inventory. Many clinicians like to use the Patient Health Questionnaire (PHQ-9) as an initial screening tool. The PL view is that all these scales can be useful as screening tools if they are followed up in the diagnostic interview. The common mistake is that the scales are used in place of the diagnostic interview. In the medical setting, if the PHQ-9 is negative, then no further psychiatric evaluation is made. This is a huge mistake for many reasons, including lack of insight on the part of patients as well as stigma, which lead to false negative self-report, not to mention the panoply of possible psychiatric problems that are not captured on these scales.

Classic study of the month: *Is schizoaffective disorder valid?*

Examining the validity of DSM-III-R schizoaffective disorder and its putative subtypes in the Roscommon Family Study. Kendler KS¹, McGuire M, Gruenberg AM, Walsh D. Am J Psychiatry. 1995 May;152:755-64.

There are very few such patients in the general population

In the 1990s, a classic genetic study was conducted in Roscommon County, Ireland. That area was reported to have a somewhat high prevalence of schizophrenia, so the thought was that a genetic study might have a good chance of finding familial relationships to schizophrenia and other psychotic diseases.

One analysis that was done involved the relationship between DSM-IIIR schizoaffective disorder and schizophrenia and affective illness.

Methods

This was a family study, not a family history study. It's important to recognize the difference. Most clinicians obtain family history: this means asking the patient (proband) about psychiatric diagnoses in family members. Or it might involve asking family members of the patient about psychiatric diagnoses in other family members. Rarely is the reported presence or absence of psychiatric diagnosis in other family members investigated, much less confirmed or refuted. Everything is secondhand, sometimes hearsay.

A family study involves actually identifying and interviewing the family members to establish the presence or absence of psychiatric diagnoses. It is not done in clinical practice, only in research.

In the Roscommon study, after initial identification of probands with schizophrenia or affective illness, 86% of their traceable living first-degree relatives were interviewed using gold-

standard DSMIIIR research diagnostic interviews.

Results

In probands with schizoaffective illness, 55% had relatives with affective illness. In contrast, probands with schizophrenia only had 28% of relatives with affective illness. So it was twice as much for the schizoaffective group.

In probands with schizoaffective illness, 6% had relatives with schizophrenia. In contrast, probands with affective illness only had 2% of relatives with schizophrenia. So it was thrice as much for the schizoaffective group.

In probands with schizoaffective illness, only 2% had relatives with schizoaffective illness. Similarly, probands with schizophrenia had 3% of relatives with schizoaffective illness, and probands with affective illness had 4% of relatives with schizoaffective illness. So it was similar in all groups, and certainly not more in the schizoaffective group.

In short, schizoaffective illness did not breed true. It is not genetically specific. Instead, it reflects the presence of genetics for both schizophrenia and affective illness at the same time.

Interpretation

What does this mean? It means that the DSM schizoaffective label, although it is a word that is spelled differently than schizophrenia or affective illness, does not reflect a reality in the natural

"...schizoaffective illness did not breed
true..."

world that is independent of schizophrenia or affective illness. It isn't a real independent illness.

That doesn't mean it isn't a clinical picture. It doesn't mean you don't see patients with mixtures of delusional and affective symptoms. It means that clinical picture does not reflect an independent disease. You can have pneumonia with a cough and high fever; you can have pneumonia without a cough and high fever. Two different clinical pictures, but not two different diseases.

Instead, the shared genetics of schizophrenia and affective illness allows for only two possibilities. One option is that schizoaffective illness proves that the claimed diagnoses of schizophrenia and affective illness are in fact only one illness. The problem here is that the Roscommon family study showed that, unlike schizoaffective illness, schizophrenia and affective illness bred true separately. Affective illness was somewhat more common in relatives of affective than schizophrenic probands (34% vs 28%), and schizophrenia was much more common in relatives of schizophrenia than affective probands (8% vs 2%, a four-fold relative risk). Thus, the genetic studies supported the view that schizophrenia was a different disease than affective illness.

That leaves one other option: that schizoaffective illness reflects the chance occurrence of getting the genes for both schizophrenia and affective illness in one's family.

A good line of evidence to support this chance comorbidity model is the epidemiological prevalence of schizoaffective illness.

“...Two different clinical pictures, but not two different diseases...”

Prevalence

It is a widely underappreciated fact that, contrary to popular clinical opinion, schizoaffective illness is rare. It is well-known that schizophrenia occurs in about 1% of the general population, and that affective illness occurs in about 10% of the general population using standard DSM definitions. In contrast, in most studies, the frequency of schizoaffective disorder is consistently lower than schizophrenia or affective illness.

If schizoaffective illness represents the chance comorbidity of affective illness and schizophrenia, one would expect that the prevalence of schizoaffective illness would be equal to the multiplied prevalence of the other two conditions. So 1% for schizophrenia multiplied by 10% for affective illness would give an expected chance prevalence of both at the same time of 0.1%. This is close to what is calculable from the available epidemiological data.

The PL Bottom Line

- The Roscommon study found that schizoaffective illness did not breed true.
- Schizoaffective patients had genetic loading for both schizophrenia and affective illness.
- General population prevalence of schizoaffective illness is lower than either schizophrenia or affective illness.
- The most defensible interpretation is that schizoaffective illness represents the comorbidity of schizophrenia and affective illness.

Drug of the Month: Venlafaxine (*Effexor*) and Desvenlafaxine (*Pristiq*)

Don't prescribe it for someone with heart disease

Biological mechanism

Venlafaxine has been marketed as a serotonin-norepinephrine reuptake inhibitor (SNRI), as a way to try to differentiate it from other serotonin reuptake inhibitors (SRIs). But in fact, venlafaxine is just another potent SRI, with some noradrenergic reuptake blockade at higher doses. It isn't the reverse: it isn't a potent noradrenergic reuptake blocker, with some serotonin reuptake blockade. In this sense, it is much more like fluoxetine (Prozac) than it is like duloxetine (Cymbalta). Fluoxetine is the classic SRI prototype, but many clinicians don't realize that it also has some norepinephrine reuptake blockade, similar in potency in fact, in animal studies, to venlafaxine. In contrast, duloxetine is a much more potent norepinephrine reuptake blocker than venlafaxine, while still having some serotonin reuptake blockade (unlike the purely potent norepinephrine reuptake blocker, desipramine).

In other words, venlafaxine is much more like other SRIs than being like classic noradrenergic agents like desipramine.

Clinical efficacy

Like other SRIs venlafaxine has proven efficacy in MDD, mostly in moderate to severe cases, not mild MDD. There are some data of more benefit with venlafaxine in hospitalized depression compared to other SRIs. However, specific randomized studies of venlafaxine in patients who

failed SRIs found that venlafaxine is NOT more effective than other SRIs in that setting of treatment-resistant depression (unlike the adjunctive efficacy proven with aripiprazole and brexpiprazole).

It has few drug interactions and can be used without much concern about liver interactions, unlike some other SRIs.

Dosing

At low doses (37.5-75 mg/d) venlafaxine is more purely serotonergic and has anxiolytic effects. Its mean effective dose in the MDD studies was about 225 mg/d (with a range of 150-300 mg/d). Though it can be dosed higher, it hasn't been proven

to be more effective for MDD above 300 mg/d than below that dose.

Cardiac Harms

Most US clinicians don't realize that venlafaxine is one of the most dangerous antidepressants to use in the setting of cardiovascular disease (in contrast to other agents, like sertraline, proven relatively safe in that setting). There were some cases of sudden cardiac death with venlafaxine, which were not known until some years after its introduction to the marketplace in the 1990s. Awareness of these cases led the UK regulatory body to contraindicate it in 2004 in all persons with hypertension or heart disease. After some protest from clinicians and the relevant

pharmaceutical company, the UK regulatory body revised its restriction in 2006 to restrict venlafaxine use only in persons with uncontrolled hypertension or in persons at high risk of ventricular arrhythmia.

It's well known that venlafaxine raises blood pressure. The amount of increase has been downplayed by its manufacturer, by giving a mean increase of only up to 3 mm Hg. But this average downplays the important minority of patients who have notable increases in blood pressure. In persons with hypertension, it doesn't make sense to use an antidepressant that worsens hypertension, when many other safer options are available.

Other Risks

Venlafaxine is among the worst agents for causing serotonin withdrawal syndrome, presumably due to its short half-life, which is still the case with the XR formulation. This agent also causes mania at least twice as much as is the case with other SRIs, according to randomized trials. Thus, it shouldn't be prescribed at all in bipolar depression.

Desvenlafaxine

This agent is the active metabolite of venlafaxine. Sometimes, active metabolites can have different effects than the parent drug, but this does not seem to be the case with desvenlafaxine. Except for some differences in dosing, all of the above benefits and harms apply to this agent as well.

The PL Bottom Line

- Venlafaxine is more of a standard SRI than anything else.
- It has many harms, especially major cardiac risks, and PL recommends that it not be used in patients with cardiac disease or hypertension.
- It has severe serotonin withdrawal syndrome and high risk of mania, and thus should not be used in bipolar illness.

PL Reflection

In psychiatry, you can do biology in the morning and theology in the afternoon.

Robert Daly MD
courtesy of Ronald Pies MD

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Please send your questions and comments to
info@psychiatryletter.org

Psychotherapies in practice

This issue examines the general role of psychotherapies in practice, which kinds to use, and how to use them. The overall concept of recovery is emphasized, and overuse of medications in an attempt to “treat to remission” is analyzed.

The classic study of the month examines an FDA review of all available data on prevention of depression with monoamine agonists (antidepressants). The FDA analysis is critiqued from the perspective of inherent bias in the “enriched” maintenance clinical trial design, which preselects only drug responders to assess further drug response. In the PL view, this design is biased, and could explain why drugs studied in this way never fail. The FDA’s acceptance of this design is noted, as PL seeks to help clinicians better appreciate the limitations of the available long-term evidence on efficacy with antidepressants in depressive conditions.

The drug of the month is lurasidone, a new dopamine blocker, which is used increasingly in bipolar illness. Its benefits and limitations are examined. The case of the month assesses a diagnosis of bipolar illness in the setting of acute sexual trauma. The limitations of making such a diagnosis in that setting are discussed. Multiple questions and comments are addressed in Curbside Consults.

As with all issues this year, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

We appreciate your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: Psychotherapies in practice

When and what kind?

The problem of functioning

Our medications produce symptomatic benefit, but often not functional recovery. Patients' symptoms may improve, but they often don't return to normal lives in the sense of returning to their previous level of work or study, or in the sense of resuming or maintaining their previous level of interpersonal relationships. For instance, despite almost complete symptomatic recovery from a manic episode, only about 40% of patients recover functionally two years later. The majority have continued problems at home with their spouses and family, and aren't able to be employed full-time. Partial remission of symptoms, with some residual depression or cycling, generally leads to incomplete functional recovery as well.

Sometimes we can't do better, but we shouldn't be complacent. Patients want to be completely well, and many of them can be. But more and more medications, partly due to worsened quality of life from side effects and partly due to limited efficacy, may not be the means to reaching that goal. It's not unreasonable to hope that psychotherapies and psychosocial interventions may help fill this gap, and lead to better functional recovery.

What kind of psychotherapy?

You might be tempted to conclude that therefore all patients should receive medications and psychotherapy, especially of the psychoanalytically-derived approach. But matters are more complex.

Psychotherapies can be, and are, studied empirically. Which have the most evidence of efficacy? In mood conditions, for example, the most common varieties, the supportive and psychoanalytically-oriented types, have the least amount of empirical support. Instead, as clinicians know, cognitive-behavioral therapy (CBT) has been proven effective in treatment of acute depressive episodes. Prevention of depressive episodes has been shown in unipolar depression and bipolar illness with CBT, and also in bipolar illness with family-focused therapy and psychoeducation. Unfortunately most psychotherapists are mainly trained in the least-proven approaches: supportive and psychoanalytically-oriented therapies.

"Unfortunately most psychotherapists are mainly trained in the least-proven approaches..."

Outside of mood illnesses, these therapies may be more relevant. For instance, in PTSD and trauma-based scenarios, psychoanalytically-based therapies have a long tradition, and have some evidence of proven benefit. In contrast, CBT seems less effective in those setting, as well as in settings where symptoms are chronic, as in borderline personality. In the latter conditions, variants on psychoanalytically-oriented approaches have been shown to be beneficial.

A forgotten psychotherapy

There is another type of psychotherapy that often is forgotten in such discussions: the existential approach. One definition of existential methods involves the systematic effort of "being there" for patients. This means not only providing an ongoing empathic connection, but constantly

valuing and promoting the therapeutic alliance as a key ingredient to any treatment. As Ronald Pies has suggested, one might even view the therapeutic alliance as a mood stabilizer. The constant presence of the psychopharmacologist, being available for quick appointments during periods of instability, or perhaps the short phone call with a medication change at times – these are the features of the therapeutic alliance that help stabilize patients. In the case of bipolar illness, one can conceive of pharmacological mood stabilizers as providing a kind of coarse mood stabilization, reducing the severity and frequency of full mood episodes. The patient is often left with residual, less severe mood instability, and psychotherapeutic interventions that may be able to act as fine-grained mood stabilizers.

Residual symptoms

To some extent, the problem of functional impairment may be a problem of residual symptoms (often depressive), which might improve with psychotherapeutic interventions. But sometimes functional impairment even persists with almost no symptom impairment. In those cases, other factors, such as long-term cognitive impairment as a result of mood episodes, need to be examined. Also, in the case of mood conditions, patients sometimes become so used to being ill that, once their mood symptoms are improved pharmacologically, they are unable to cope with the demands and needs of a non-depressed, non-manic lifestyle.

These are the types of issues that require the careful assistance of well-trained psychotherapists. Pills aren't enough in these circumstances.

"Our medications are like sledgehammers but sometimes all we need are tuning forks."

The problem of despair

When we speak of “residual” symptoms, the term assumes that those symptoms reflect leftover illness. Another possibility exists: what appears to be residual may actually be new. Those symptoms could reflect a psychological reaction to years of suffering: a kind of existential despair. Even after biologically-based symptoms or episodes are controlled or reduced with medications, many people appear to suffer from a sense of despair at having lost so much for so long. In such cases an existentially-oriented psychotherapy can be useful; even the therapeutic alliance between doctor and patient can be seen as an existential treatment in that setting. More medication isn't necessarily the answer.

Here's a metaphor to get this idea across, in the example of mood conditions:

Our medications are like sledgehammers, but sometimes all we need are tuning forks. Sledgehammers help when patients are severely ill with acute depression or mania; medications can improve those severe mood swings. However, when patients have only mild depressive symptoms, antidepressants either fail to work or just cause mania or more mood cycling. We need tuning-forks in such circumstances, not sledgehammers, and sometimes a strong therapeutic alliance, or psychotherapies, can be those tuning forks that can make all the difference between more, as opposed to less, remission and recovery.

Other psychosocial interventions

Psychotherapy can be provided by psychiatrists, but also by social workers, psychologists, and nurse practitioners. Social workers and psychologists may be particularly well-placed to

provide psychotherapy because, increasingly, they often have more formal training in psychotherapies than do psychiatrists and nurses. Other psychosocial interventions are also relevant, however, many of which are related most closely to the field of social work. These include residential assistance, such as half-way house living or structured day treatment programs. These settings lead to better medication compliance as well as improved functioning. Vocational rehabilitation is important to begin the process of retraining patients for work settings appropriate to their state of symptomatic recovery. Vocational counseling is relevant in teaching patients how to go about the basics of advancing a career. Family therapy is quite important in terms of assessing and maximizing support networks for patients.

Support groups

Perhaps the newest psychosocial support network involves patient and family-run organizations, like the National Alliance for Mental Illness (NAMI), and the Depression and Bipolar Support Alliance (DBSA), among others. People can learn more about their conditions, and get the most help, from peers who have those conditions, rather than from authority figures like health professionals. Family members find these support groups helpful as they cope with loved ones with these serious illnesses. Persons who are involved in these support groups have better outcomes. It's unclear what is cause and effect, but the association is important.

PL recommends that clinicians inform patients about these support groups, and that clinicians work closely with these groups wherever possible. In the long run, more alliances between patients, clinicians, and families produce better outcomes.

“...symptom reduction should not be the sole and primary focus of treatment.”

The concept of recovery

Now we come to the concept of recovery, which relates to functional improvement, but goes further.

Clinicians tend to focus on symptoms. But patients care about side effects and function and overall quality of life. Recovery captures these other aspects of treatment outcomes, along with the subjective aspect of being able to have subjective meaning in one's life. In short, recovery is about getting back to having a "normal" life, like other people without psychiatric conditions.

This desire can be misinterpreted as rejecting the whole concept of psychiatric disease, and in a way, pretending that no illness exists. There has been a great deal of debate in the recovery community on this topic. The PL view is that psychiatric diseases exist, and that some of them need the right treatments. But

PL agrees that symptom reduction should not be the sole and primary focus of treatment.

“Treat to remission”

These considerations are important when faced with the commonly repeated mantra: “Treat to remission.” In practice, this attitude can result in drug after drug being added, leading to side effect after side effect, with limited symptom improvement.

By caring about recovery, clinicians would balance symptom remission with attention to side effects, function, and quality of life. Obviously patient preferences would be important, as opposed to an abstract commitment to achieving symptom remission.

This perspective relates to the observation that symptoms are not purely negative. There are positive aspects to some mood symptoms in particular, with depression being associated with realism and empathy, and mania being associated with creativity and resilience. These positive benefits of mood symptoms appear to be pronounced when those symptoms are mild.

Thus, treating to remission, so as to remove all mood symptoms, even mild ones, may actually harm a patient's quality of life, and impair recovery. This may be one reason so many people in the recovery movement have developed negative attitudes towards medications, as well as negative attitudes towards the prescribers of medications. As mentioned, these attitudes can be extreme and incorrect, but they can be understood in the context of overzealous prescribing in service of the ideology of treating to remission.

Who provides the psychotherapy?

These days, most psychotherapies are provided by non-MD mental health clinicians. Although some psychiatrists bemoan this fact, non-MD mental health clinicians can respond justifiably that the presumption that psychotherapy is not provided well by non-psychiatrists is unproven.

The reverse might be claimed as follows:

Readers of PL know that the clinical practice of psychopharmacology is quite complex. It isn't simple. It takes a great deal of effort. Thus, to be an excellent practitioner of psychopharmacology, most clinicians would need to put most, if not all, of their efforts into that goal.

Similarly, mental health clinicians of all stripes likely would agree that psychotherapy is quite complex. It isn't simple. It takes a great deal of effort. Thus, to be an excellent practitioner of psychotherapy, most clinicians would need to put most, if not all, of their efforts into that goal.

How can one person truly be excellent at both? This isn't to say there aren't exceptional cases, but as a rule, it is very difficult to be excellent at either psychopharmacology or psychotherapy, much less both.

Hence the PL viewpoint is that psychotherapies are very important in the practice of psychiatry and mental health, and that multiple treaters with as much expertise as possible in separate disciplines of psychopharmacology and psychotherapy, who work together, can provide excellent care. In fact, such an approach may be the way to provide the best overall care.

The PL Bottom Line

- Psychotherapies are important in the overall management of many conditions.
- They especially can help with functional impairment and overall recovery.
- Treatment to remission may produce worse outcomes than a focus on overall recovery.

PL Reflection

If you come out early to practice on the morning of the championship game, in case you have to take the last shot, it's too late. You practice all year to take the last shot.

*Larry Bird,
basketball star (paraphrased)*

Classic study of the month: *Do antidepressants prevent depression?*

Review of maintenance trials for major depressive disorder: A 25 year perspective from the Food and Drug Administration. A Borges et al. J Clin Psychiatry. 2014;75:205-214.

An FDA review of all its available data

There has been a great deal of controversy in recent years regarding the efficacy of antidepressants in acute depression. As a result of some of that public debate, the FDA conducted an internal review of a related but different question: the long-term maintenance efficacy of antidepressants.

The issue of long-term efficacy has been discussed in research circles for some years in relation to a question of methodological bias. The FDA review sought to address some of those concerns.

“...the study of prevention is conducted in patients who have responded already to the drug being studied...”

In this summary, PL will examine the debate, and what the FDA concluded, and what PL thinks.

Are the studies biased?

The research design question for maintenance studies is important to understand. These studies are called “enriched” because patients are preselected to respond to the drug being studied.

Think of it this way: To do a maintenance trial, a study to prove long-term prevention, patients have to be well, not ill, when they enter the study. Then one sees whether new episodes of illness happen in the future.

So patients needed to be recruited into the maintenance studies who are well. But most well persons aren't motivated to go into randomized placebo-controlled trials. Usually, instead, they come for treatment or research when they are ill or symptomatic. In the case of depression,

patients would be recruited when depressed, and treated with an antidepressant until they become well, and then they would enter the randomized maintenance trial to see if they stay well.

In other words, in these studies, patients are treated before they enter the research study, so that prevention can be tested. But what should they be treated with? Any antidepressant? Or the antidepressant being studied for prevention?

Since these studies usually are designed by pharmaceutical companies, they tend to use their own medication for the initial acute treatment, to get patients well, before they enter the maintenance prevention trial.

Thus, the study of prevention is conducted in patients who have responded already to the drug being studied. Does this bias the study?

Outcomes

The claim could be made that since acute treatment efficacy may not be the same as maintenance or prevention efficacy, then the design isn't biased necessarily. Two different kinds of outcomes are being assessed.

In unipolar depression, there is consensus that the acute phase of depression lasts 6-12 months, and that the maintenance phase of prevention of new episodes begins 12 months or longer after the acute phase.

Thus, the question of whether new episodes are being prevented has to do with whether outcomes are being assessed one year or longer after the acute depressive episode.

Do the maintenance randomized trials of antidepressants show such benefit?

The FDA review

The FDA decided to review its data to help answer this question. Pharmaceutical companies are required by law to give all their data to the FDA when they seek indications for marketing. These data are patent protected, so they remain confidential within the control

of the FDA. Pharmaceutical companies are under no obligation to publish those data, and the FDA is under an obligation to keep them confidential. But the FDA can analyze and publish those data without identifying features and researchers can access deidentified data using the Freedom of Information act.

This paper represents an internal FDA review of all the data it possessed for the past 25 years on this topic, which consisted of 15 studies.

Results

The FDA found that all 15 studies showed antidepressant efficacy for maintenance prevention. That's 100% success!

In contrast, the FDA database has been studied repeatedly and it has been found that about 50% of acute depression studies in MDD show efficacy of antidepressants, but about 50% show inefficacy.

So what is the case? Are antidepressants incredibly effective in long-term prevention, but only so-so for acute treatment?

Or is there something wrong with the "enriched" design for long-term prevention?

The FDA addressed a main concern regarding the enriched design, which is that there can be withdrawal effects. This means that since patients are being treated with the antidepressant being studied, before the study begins, and then the responders enter the maintenance study, those who get switched to placebo have a rapid withdrawal relapse. The FDA defined withdrawal as 2 weeks or less after randomization, but only 6% of patients had such relapse. Thus, the FDA concluded that there was not much withdrawal relapse.

"Are antidepressants incredibly effective in long-term prevention, but only so-so for acute treatment?"

The FDA was very impressed that the studies were consistently positive and concluded that antidepressants are very effective in prevention of MDD.

Interpretation

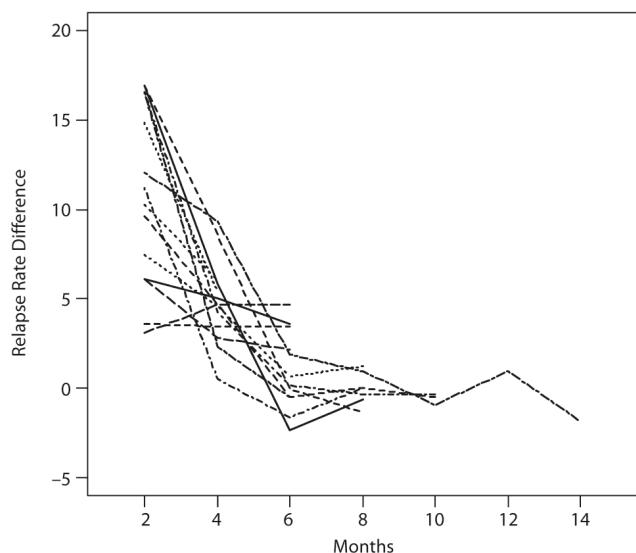
PL has some concerns regarding the FDA's rosy interpretation.

The concept of withdrawal relapse isn't limited to 2 weeks. The idea is that if only drug responders are included in a study, the study is inherently biased because it is testing what was already proven. The only way it could work would be if the maintenance drug response was a different outcome than the acute drug response. Maintenance is defined as 1 year or longer, not 2 weeks. The FDA review didn't assess outcomes after 1 year versus before 1 year, or even after 6 months versus before 6 months.

In fact the FDA review included a figure, shown on the next page, which depicts how almost all the benefit seen with antidepressant over placebo in the "maintenance" trials occurred in the first 6

months of follow-up, which is not the maintenance phase of treatment, but still part of what is called the “continuation” phase, meaning that the acute episode has not yet resolved naturally. Any relapses seen in that time frame are back into the same episode which was active a few months earlier, and cannot be assumed to represent new and different mood episodes.

Figure 3. Relapse Rate Differences Between Drug and Placebo Arms at Each Double-Blind Phase Time Point in Antidepressant Maintenance Studies^{a,b}



^aEach curve represents a study.

^bOnly 14 studies are presented. The Kaplan-Meier curve for study B could not be reproduced due to incompleteness of the dataset for this older study.

After 6 months, there was no further benefit with antidepressants over placebo. The FDA review shows this figure, but it doesn't acknowledge its relevance to the question of whether the enriched maintenance study design is biased.

Thus, in the PL viewpoint, because it doesn't assess or prove benefit 6 months or longer after the acute phase ended, the FDA review doesn't

really answer the question of whether there was inherent bias in the design.

There is another sign that the FDA review didn't solve the problem of bias of the enriched maintenance design: the absolute 100% success rate. It doesn't make sense that the same drug class would fail to be effective half the time in acute 2-month studies, and then succeed 100% of the time in 1-year maintenance studies. At the very least, the question can be raised that the enriched maintenance design may succeed 100% of the time because it is biased; that's the whole point. It never fails because it isn't fairly testing anything.

Even if this critique of the enriched design is granted, it doesn't prove that antidepressants are ineffective in prevention of depressive episodes in unipolar depression. It only means that they aren't proven effective, despite the apparent efficacy of these 15 studies.

The same concern regarding this enriched design applies to other drugs and other maintenance studies, such as dopamine blockers in bipolar illness, as discussed in the PL website (to be discussed further in future PL issues).

The PL Bottom Line

- Antidepressants are proven effective for maintenance prevention of depressive episodes in 15/15 MDD studies in the possession of the FDA.
- Either antidepressants are incredibly effective agents in long-term prevention of depressive episodes, or the enriched maintenance design is too biased to prove or disprove such efficacy. PL leans toward the latter interpretation.

Drug of the Month: Lurasidone (*Latuda*)

A new dopamine blocker for bipolar depression

Biological mechanism

Lurasidone is a dopamine D₂ receptor blocker without other major neurotransmitter effects. Like other new dopamine blockers, it does not cause or worsen metabolic syndrome or have appreciable weight gain.

Clinical efficacy

Lurasidone is somewhat unusual in that it was never studied and proven for acute mania, as is the case with almost all other dopamine blockers. Instead, after its initial proof of efficacy in schizophrenia, it was studied and proven effective in acute bipolar depression. Those are its two FDA indications.

Further research has been conducted in maintenance treatment of bipolar

illness for prevention of mood episodes as well as for major depressive disorder with mixed features (MDD-MF). Those latter uses have not been given FDA indications yet though. A maintenance indication may come in the future, but it appears that the MDD-MF indication will not occur, apparently because this new DSM-5 indication has not been seen by FDA reviewers as worthy of specific drug treatment indication yet. For what it is worth, though, using that DSM-5 defined term, lurasidone was more effective than placebo for mixed features in a randomized trial.

Dosing

In schizophrenia, doses are in the 40-120 mg/d range. In bipolar depression, doses higher than 60 mg/d were proven not to be more effective than doses in the 20-60 mg/d range.

Side effects

The main side effects are extrapyramidal (EPS), especially akathisia but also parkinsonism. Unlike earlier modern dopamine blockers, this agent does not cause or worsen glucose or lipid profiles. It does not have appreciable weight gain, at least in initial clinical trials.

Fast Facts: Lurasidone

Typical dose: 20-60 mg/d (range 20-120 mg/d)

Biological mechanism: dopamine receptor blockade

Typical side effects: akathisia, parkinsonism

Medically important side effects: suicidality

Clinically proven efficacy: FDA indications for acute bipolar depression, schizophrenia

Akathisia is dose-related, thus the above dosing guidelines should be kept in mind. Sometimes, akathisia produces suicidal thoughts, which can be how it presents, as

opposed to obvious motor restlessness.

The PL Bottom Line

- Lurasidone is effective in schizophrenia and bipolar depression, but not proven in mania.
- It also is likely effective in mixed states.

NB: The PL editor has one disclosure in relation to pharmaceutical companies, which is that he has provided research consultation and lectures to Sunovion, the maker of lurasidone.

Case of the Month

Bipolar diagnosis or trauma?

A 21-year-old woman presented with a new diagnosis of bipolar disorder in the setting of a recent sexual trauma 2 months earlier. She had gone to the emergency room after the trauma, and had experienced anxiety and panic attacks in the week following it. She went back to the emergency room due to the latter symptoms, along with some suicidal ideation, which led to one-week psychiatric hospitalization.

In the psychiatric hospital, clinicians noted that the patient had a family history of bipolar illness in her maternal aunt and maternal grandmother. On history-taking from the patient as well as both of her parents, it was reported that the patient had not experienced past depressive episodes nor had she experienced past manic or hypomanic episodes. This denial was confirmed with multiple family members.

Until the recent event, she had never been treated with any psychotropic medications, nor had she ever received counseling. She had no prior psychiatric hospitalizations and no self-cutting or prior suicidality.

She and her family denied any prior physical or sexual abuse. Her medical history was normal; she took no medications and had no allergies.

She had many friends in college, and was sociable. She was sexually active, but interview with her and her family suggested that her sexual activity was within the normal range of her peers. She had prior sexual relationships which were not fleeting or inherently unstable, but lasted sometimes 6 months or longer.

In the psychiatric hospital, she was treated with lithium and risperidone. Upon discharge, she

stopped risperidone. A few weeks later, her anxiety symptoms had improved notably. She had avoidant behavior about the recent sexual trauma and was teary about it, but denied other depressive neurovegetative symptoms. She denied flashbacks or nightmares related to the trauma, but she reported being anxious when sleeping alone. She was still taking lithium 300 mg/d, reduced from higher doses due to cognitive side effects, but had not started psychotherapy. The family wanted to know if she had bipolar illness and what medication treatments were recommended.

On consultation, the diagnosis of bipolar illness was not confirmed, given the above history. It was recommended that lithium be stopped since she was not suicidal nor did she have any mood episodes currently or in the past. The bipolar genetics were noted, and the family was informed that if mood episodes should begin in the future, then the bipolar diagnosis may be valid at that time, and lithium treatment could be restarted.

Instead, the PL view was to recommend individual psychotherapy to help cope with the acute stress reaction of recent sexual trauma. The patient and family were informed that acute stress reactions to trauma occur in almost everyone, while post-traumatic stress disorder (PTSD) is defined as happening 6 months to a year after the traumatic episode. Further PTSD only occurs in about 10-20% of persons who experience trauma. Thus, the importance of psychotherapy is to help cope with the natural acute stress reaction, as well as hopefully to decrease the likelihood of future PTSD. Further, if there are aspects of the history that are unclear, or mild manic symptoms that might be difficult to observe, ongoing psychotherapy may be a place to make such subtle diagnostic observations.

Curbside Consults

Questions/comments/cases from you

Question: What do you think about Depakote and depression in bipolar illness? I've heard it causes it?

PL: This is a common misconception. In fact, there are multiple randomized placebo-controlled trials (RCTs) that show that divalproex is effective in acute bipolar depression. These multiple studies were meta-analyzed some years ago. Added up, they provide much more convincing data of efficacy than anything that can be mustered for monoamine agonists "antidepressants" in bipolar depression, as reviewed in February 2016 PL issue, even though those agents are so commonly used for that condition. The divalproex RCTs are much more consistent and effective also than the multiple lamotrigine RCTs in acute bipolar depression, which show that agent to be ineffective, contrary to popular opinion. In short, ignore the false clinical lore and look at the science: Divalproex doesn't cause bipolar depression; it treats it.

Question: I appreciated your Special Article in July PL issue on the clinical interview. I am now allowed one hour for the "diagnostic interview" and have learned to gather the data in a very effective way, but the problem remains that the patient may (and sometimes does) feel like an "object of study". Any suggestions?

PL: This is a good question. There's an old saying: People learn only if they think they aren't being taught. In the course of the diagnostic interview, information should be gleaned as much as possible through open-ended questions and then categorized as needed. Follow-up specific questions should only fill the holes. If you conduct a clinical interview with nothing but a barrage of questions, in the interests of time, the

patient indeed will feel like an object of study, rather than a patient. The old psychotherapeutic axiom applies: Patients listen only after they feel heard. Besides using psychotherapeutic techniques, not one question after another, PL agrees with the strong recommendation of Dr. Tammas Kelly that much information should be gathered beforehand through self-report forms, so that the interview can be used more efficiently.

Comment: (From Dr. Tammas Kelly) In your Classic Article of the month in the PL August 2016 issue on schizoaffective illness, you mention that the Roscommon study was a family study, where they actually interviewed family members, which produces much better family genetic data than family history, where the patient provides a report about family members. I'd like to point out that the questionnaire I use for my patients is helpful, among other things, for obtaining detailed family history not only from the patient but from family members.

PL: We agree with Dr. Kelly's comment. It makes sense to use a self-report questionnaire especially for straightforward factual matters, such as medication history details as well as family history details. We concur with Dr. Kelly that self-report questionnaires filled out before the clinical interview would be helpful on those topics, as well as others.

Question: I'm not sure I understand your discussion of mixed states in February PL issue. If mixed states are present, does the patient have bipolar disorder? Do you consider all states of psychomotor agitation to be mixed states?

PL: Mixed states are not related to bipolar illness. Remember that manic-depressive illness (MDI) meant manic or depressive episodes, not manic and depressive episodes (bipolar illness). Thus MDI meant unipolar depression plus

bipolar illness, not just the latter. Mixed states were the most common mood state in MDI, which means they are common in both unipolar depression and bipolar illness, occurring in about one-half of DSM-defined unipolar subjects. The term "mixed" is being used here in a non-DSM manner. The conundrum that arises is that if the term "mixed" is so much associated with DSM-defined bipolar illness that many clinicians can't start thinking outside that box. The term "mixed" precedes the whole unipolar/bipolar distinction, and in fact may refute it.

So when you think of mixed, put the term "bipolar" out of your head, and apply it to all mood conditions, whether unipolar or bipolar.

The concept of "agitated depression" doesn't differ from mixed states in the definition of Koukopoulos, who defined mixed states as depression with psychomotor excitation. Since agitation basically means psychomotor excitation, then depression with agitation is simply a kind of mixed state. This was the view of Kraepelin as well. The DSM-based refusal to care about psychomotor agitation - viewing it as diagnostically unimportant - is not a notion that has been proven on scientific grounds. Rather it is an unproven assumption.

PL Reflection

Many persons nowadays seem to think that any conclusion must be very scientific if the arguments in favor of it are all derived from twitching of frogs legs – especially if the frogs are decapitated – and that, on the other hand, any doctrine chiefly vouched from by the feelings of human beings – with heads on their shoulders – must be benighted and superstitious.

William James,
writing in the late 19th century

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THE PSYCHIATRY LETTER

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info@psychiatryletter.org

Antidepressants and suicide

The question of whether antidepressants cause or prevent suicide, or both, has been a subject of controversy for a decade or more. In this issue, PL examines the matter in detail in the Special Article and in the Article of the Month. PL concludes that these agents can cause suicide in young adults and children, as proven in a FDA analysis, but the frequency is low, and probably about equivalent to the small number of suicides prevented by improvement of depressive episodes with the agents.

The drug of the month is zolpidem, a GABA agonist, used for insomnia. PL examines evidence that, contrary to its marketing, it is addictive, like benzodiazepines, though perhaps less so at lower doses. The case of the month examines a case of manic episodes with long period of remission, raising the question of whether the diagnosis should change.

The Psychopathology article and By the Numbers column cover the topic of lack of insight, a key issue that is important in making accurate clinical diagnoses.

A question about lithium and dementia is addressed in Curbside Consults.

As with all issues this year, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

We appreciate your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: Do antidepressants cause or prevent suicide?

Both

The art of medicine is the art of balancing probabilities, said William Osler. To assess probabilities, we must use statistics. Thus, the art of medicine relies on the science of medicine, namely statistics. But, as PL readers well know, there are lies, damn lies, and then there are statistics (so said 19th century British Prime Minister Benjamin Disraeli). A humbling example of the misuse of statistics involves the controversy about whether antidepressants cause suicide. Immediately, two opposite views hardened: opponents of psychiatry saw antidepressants as dangerous killers, and the psychiatric profession circled the wagons, unwilling to admit any validity to the claim of a link to suicidality. An example of the former extreme was the emphasis on specific cases where antidepressant use appeared to be followed by agitation, worsened depression, and suicide. Such cases cannot be dismissed, but they are the weakest kind of evidence. An example of the other extreme was the report, put up with fanfare, by a task force of the American College of Neuropsychopharmacology (ACNP). By pooling different studies with each serotonin reuptake inhibitor (SRI) separately, and showing that each of those agents did not reach statistical significance in showing a link with suicide attempts, the ACNP task force claimed that there was no evidence at all for such a link. It is difficult to believe that the distinguished researchers on the task force were unaware of the concept of statistical power, and ignorant of the axiom that failure to disprove the null hypothesis is not proof of it. Nor is it likely that they were unaware of the weakness of a "vote-counting" approach to reviewing the literature.

"The absolute difference between placebo and SRIs was 0.1%..."

When the same data were analyzed more appropriately, by meta-analysis, as described in the April 2015 PL issue, the FDA was able to demonstrate not only statistical significance, but a concerning relative effect size of about two-fold increased risk of suicidality (suicide attempts or increased suicidal ideation) with SRIs over placebo (Relative Risk = 1.95, 95% Confidence Intervals 1.28, 2.98). (See the Web PL issue for an explanation of these terms).

This concerning relative risk needs to be understood in the context of the absolute risk, however, which is where the concept of a number needed to harm (NNH) becomes useful. The absolute difference between placebo and SRIs was 0.1%. This is a real risk, but obviously a small one absolutely: which is seen when converted to NNH ($1 / 0.01 = 100$). Thus, of every one hundred patients treated with antidepressants, one patient would make a suicide attempt attributable to them. One could then compare this risk, with presumed benefit, as done below.

This is the proper way to analyze such data, not by relying on anecdote to claim massive harm, nor by misusing hypothesis-testing (p-value based) statistics to claim no harm at all. Descriptive statistics tell the true story: there is harm, but it is small. Then the art of medicine takes over: Osler's art of balancing probabilities. The benefits of antidepressants

would then need to be weighed against this small, but real, risk.

The TADS study

Another approach to the problem would be to conduct a larger randomized clinical trial (RCT) to try to answer the question, with a specific plan to look at suicidality as a secondary outcome (unlike all the studies in the Food and Drug Administration, FDA, database). This led to the NIMH-sponsored Treatment of Adolescent Depression Study (TADS). Even there, though, where no pharmaceutical influence existed based on funding, the investigators appear to underreport the suicidal risks of fluoxetine by overreliance on hypothesis testing methods.

In that study 479 adolescents were double-blind randomized in a factorial design to fluoxetine vs cognitive behavioral therapy (CBT) vs both vs neither. Response rates were 61% vs 43% vs 71% vs 35%, respectively, with differences being statistically significant. Clinically significant suicidality was present in 29% of children at baseline (more than most previous studies, which is good because it provides a larger number of outcomes for assessment), and worsening suicidal ideation or a suicide attempt was defined as the secondary outcome of “suicide related adverse events.” (No completed suicides occurred in 12 weeks of treatment). 7 suicide attempts were made, 6 on fluoxetine. In the abstract, the investigators reported improvement in

suicidality in all four groups, without commenting on the differential worsening in the fluoxetine group. The text reported 5.5% (24) suicide-related adverse events, but it did not report the results with RR (relative risks) and CIs (confidence intervals).

When PL analyzed those data that way, one sees the following risk of worsened suicidality: with fluoxetine, RR 1.77 [0.76, 4.15]; with CBT RR 0.85 [0.37, 1.94]. The paper speculates about possible protective benefits with CBT for suicidality, even though the CIs are too wide to infer much probability of such benefit. In contrast, the apparent increase in suicidal risk with fluoxetine, which appears more probable

based on the CIs than in the CBT effect, is not discussed in as much detail.

The low suicide attempt rate (1.6%, n=7) is reported, but the overwhelming prevalence with fluoxetine use is not. Using effect estimate methods, the risk of suicide attempts with fluoxetine is RR 6.19 [0.75, 51.0]. Due to the low frequency, this risk is not statistically significant. But hypothesis testing methods (p-values) are inappropriate here; use of effect estimation shows a large six-fold risk, which is probably present, and which could be as high as 51-fold. In short, fluoxetine had about a six-fold increased risk of suicide attempts, a huge effect size.

Hypothesis-testing methods, using p-values, are biased toward the null hypothesis, meaning they tend to say that nothing is

“...fluoxetine had about a six-fold increased risk of suicide attempts, a huge effect size. ...”

happening unless there is overwhelming evidence otherwise. Effect estimation methods, less biased and more neutral, tell another story. For side effects in general, especially for infrequent ones like suicidality, effect estimation stories are closer to reality.

An Oslerian approach to antidepressants and suicide

Recalling Osler's dictum once again that the art of medicine is the art of balancing probabilities, we can conclude that the antidepressant/suicide controversy is not a question of yes or no, but rather of whether there is a risk, quantifying that risk, and then weighing that risk against benefits.

This effort has not been made systematically, but one researcher made a start in a letter to the editor commenting on the TADS study. Carroll noted that the NNH for suicide-related adverse events in the TADS study was 34 (6.9% with fluoxetine versus 4.0% without it). The NNH for suicide attempts was 43 (2.8% with fluoxetine versus 0.45% without it). In contrast, the benefit seen with improvement of depression was more notable; the NNT for fluoxetine was 3.7. So about 4 patients need to be treated to improve depression in one of them, while a suicide attempt due to fluoxetine will only occur after 43 patients are treated. This would seem to favor the drug, but we are really comparing apples and oranges: improving depression is fine, but how many

"...it comes out as a wash, at worst"

deaths due to suicide from the drug are we willing to accept?

One has to now bring in other probabilities besides the actual data from the study (an approach related to Bayesian statistics): Epidemiological studies indicate that about 8% of suicide attempts end in death. Thus, with a NNH of suicide attempts of 43, the NNH for completed suicide would be 535 (43 divided by 0.08). This would seem to be a very small risk; but it is a serious outcome. Can we balance it by an estimate of prevention of suicide?

The most conservative estimate of lifetime suicide in unipolar major depressive disorder is 2.2%. If we presume that a part of this lifetime rate will occur in adolescence (perhaps 30%), then an adolescent suicide rate of 0.66% might be viable. This produces a NNT for prevention of suicide with fluoxetine, based on the TADS data, of 560 (3.7 divided by 0.0066).

We could also do the same kind of analysis using the FDA database cited previously, which found a NNH for suicide attempts of 100 (higher than the TADS study) (Hamad et al., 2006). If 8% of those patients complete suicide, then the NNH for completed suicide is 800 (100 divided by 0.08).

So we save one life out of every 560 that we treat, and we take one life out of every 535, or possibly every 800 patients. Applying Osler's

dictum about the art of medicine meaning balancing probabilities, it comes out as a wash, at worst. It's also possible that the actual suicide rates used above are too conservative, and that antidepressants might have somewhat more preventive benefit than suggested above, but even with more benefit, their relative benefit would still be in the NNT range of over 100, which is generally considered minimal.

Overall, then antidepressants have minimal benefits, and minimal risks, it would appear, in relation to suicide.

Lessons learned

At some level, the controversy about antidepressants and suicide had to do with mistaken abuse of hypothesis testing statistics. The proponents of the association argued that anecdotes were real, and not refuted by the RCTs. They were correct. Their opponents claimed that the amount of risk shown in RCTs was small. They were correct. Both sides erred when they claimed their view was absolutely correct: Based on anecdote, one side wanted to view antidepressants as dangerous in general; based on statistical non-significance, the other side wanted to argue there was no effect at all. Both groups had no adequate comprehension of science, medical statistics, or evidence-based medicine. When effect estimation methods are applied, we see that there is no scientific basis for any controversy. There is a real risk of suicide with antidepressants, but that risk is small, and equal to or less than the

probable benefit of prevention of suicide with such agents.

Overall, antidepressants neither cause more death nor do they save lives. If we choose to use them or not, our decisions would then need to be on other grounds (e.g., quality of life, side effects, medical risks). But the suicide question does not push us one way or the other.

The PL Bottom Line

- Antidepressants cause and prevent about one suicide in every 500 adolescents or young adults.
- They thus both cause and prevent suicide, but their net effect is neutral.

BONUS MATERIAL

See the web version of the newsletter for bonus material: A section there summarizes the concepts of effect sizes and of confidence intervals and Number Needed to Treat/Harm in more detail.

PL Reflection

Men are born ignorant, not stupid; they are made stupid by education.

Bertrand Russell

Classic study of the month: *Suicide and antidepressants revisited*

Suicide risk during antidepressant treatment. G Simon et al. *Am J Psychiatry, Volume 163, Issue 1, January 2006, pp. 41-47*

“Data refute link between suicide, antidepressants”

A common comment on the above topic is that the FDA analysis of suicide is refuted by other huge studies which find that suicide rates went up after antidepressant use declined in response to the FDA warning. This study is one typical example of such research. PL will review it both to examine the data in these studies but also to explain to readers why such data do *not* refute the FDA analysis.

Method

Immediately after the FDA warning was issued in 2004, the psychiatric profession went into an uproar. The leaders of the profession consistently opposed the FDA warning, but they couldn't counter the meta-analysis which was conducted on dozens of randomized trials in children and adolescents.

Researchers began to look at the question in other datasets, and studies began to be published which stated the reverse of the FDA conclusion: antidepressants were *not* associated with suicide.

One of the first such studies, which received a great deal of attention, is this one.

This study examined computerized health plan records to identify 65,103 patients with 82,285 episodes of antidepressant treatment over about a decade in the late 1990s. The outcome was suicide attempt leading to hospitalization.

Readers will note that the sample size is huge: over 65,000 patients. That will seem impressive. But it comes at a cost.

This was not a research “study.” These 65,000 patients didn't sign a consent form to enter a study in which they were told they would be given antidepressants to see if they committed suicide or not. These patients weren't research patients.

They were clinical patients, treated by their doctors, on clinical grounds. In other words, they were seen as having depressive symptoms, and their doctors gave them antidepressants. Some of them made suicide attempts afterwards, some didn't.

“...antidepressants are not associated with suicide...”

The key point is that neither the treatment nor the outcome was preplanned. It was just observed. It was just standard clinical care over a decade, and then 10 years later, a researcher asked the question: I wonder how many of these patients tried to kill themselves?

Since a study hadn't been planned to answer that question, the researcher had to rely on standard medical charts for the “data” needed to identify the exposure and the outcomes and all the potential factors involved. PL readers will know that standard clinical charts aren't written to capture dozens or hundreds of potentially relevant research variables. Rather, clinical charts tend to be sparse, or at least very qualitative. In this case, to look at 65,000 charts by hand would

have been an impossible task. The researchers relied on data that were put into a computerized medical record. PL readers who use computerized medical records will know that some data are entered and requested, and many other pieces of data aren't requested or entered.

In short, the researchers had the advantage of a huge sample, but the disadvantage of very limited data recorded in the medical charts.

All they could really know was that some patients got antidepressants and some didn't; they don't know why some patients got antidepressants while others didn't. They don't know the differences between those groups: perhaps one group was more severely depressed, or less severely depressed; perhaps some patients were bipolar and some unipolar; perhaps some had more substance abuse and some less; perhaps some were delusional and others not; perhaps some had made past suicide attempts and others not. None of this information was recorded or included in the data analysis. But it should be obvious that it's all relevant. Such factors could influence the outcome of the study analysis quite importantly.

These factors are what are called "confounding" factors: the many and varied clinical variables that can influence an outcome.

This kind of study is called an "observational" study: it isn't preplanned and it simply observes what happens, without knowing about or controlling the many different potential confounding factors that can influence the results.

Results

The study reports that suicide attempts weren't higher after beginning antidepressant treatment,

but in fact were highest just before antidepressant treatment was started. This is interpreted straightforwardly as meaning that people don't get suicidal because they take antidepressants; they take antidepressants because they are suicidal. The study reverses the direction of causation from the FDA analysis.

Impact

Psychiatric News, the official newspaper of the American Psychiatric Association, was ecstatic, running a headline: "Data refute link between suicide, antidepressants." Many psychiatric leaders approved of the interpretation just provided.

But a standard application of scientific principles of clinical research would show that this

"....'confounding' factors [are] the many and varied clinical variables that can influence an outcome..."

interoperation cannot be made so simply. The results cannot be accepted at face value because of the description just given about the myriad number of other confounding factors that weren't measured nor included in the study analysis. This is the problem with observational studies: they can't be accepted at face value because of confounding bias.

Defining EBM

In fact that's the whole point of evidence-based medicine (EBM), namely, that we should privilege more valid data over less valid data. The whole point of randomization is to get rid of confounding bias. In the FDA analysis, all the factors just discussed are controlled, because all patients were randomly assigned to drug versus placebo, and thus the various confounding factors would be distributed equally in both groups, canceling each other out. In other words, in randomized data you can take the results at face value; in observational data, you can't. The former

studies are more valid than the latter, for this reason. This is a basic principle of EBM, or simply science applied to clinical research.

By saying that this observational study "refutes" the FDA analysis of randomized data, we would be saying the reverse - that less valid data can be used to ignore more valid data. This is not logical or scientific.

Observational studies

Since the 2006 study presented here, there have been a number of other observational studies, making the same claim. Some report that suicide rates rose after the FDA warning. But the economy also changed; and someone was elected president; and a certain team won the World Series. All these events occur, but one can't claim a causal link in observational studies, due to confounding factors. Randomized data provide the best evidence of causation. All these observational studies are irrelevant in claiming that the FDA analysis of randomized data was wrong. It doesn't matter how many observational

studies are published, nor how large they are; they always will be less valid than the FDA analysis of randomized data. Only new randomized data, like the TADS study examined above, could begin to contradict the FDA analysis, and, contrary to popular belief, no such conflicting randomized data have been published.

The PL Bottom Line

- These and similar large observational studies are less valid than the randomized studies in the FDA analysis of antidepressants and suicide.
- Thus these and similar large observational studies don't refute the FDA analysis.
- The FDA analysis is still our most valid evidence on this topic, with the following conclusion: Antidepressants are proven to increase suicidal ideation and suicide attempts in children, adolescents and young adults.
- As noted in the Special Article, the magnitude of that risk is small, but it's not zero.

PL Reflection

"I am not careful to justify myself.... But lest I should mislead any when I have my own head and obey my whims, let me remind the reader that I am only an experimenter. Do not set the least value on what I do, or the least discredit on what I do not, as if I pretended to settle anything as true or false. I unsettle all things. No facts are to me sacred; none are profane; I simply experiment, an endless seeker, with no Past at my back....Beware when the great God lets loose a thinker on this planet. Then all things are at risk."

Ralph Waldo Emerson

Drug of the Month: Ambien (Zolpidem)

It's addictive, despite the marketing

Biological mechanism

Zolpidem is a GABA-a receptor agonist, the same gamma-1 subunit of GABA that is affected by benzodiazepines.

Clinical efficacy

Zolpidem is FDA indicated for insomnia. It has been shown to increase overall sleep time by about 30 minutes on average. It doesn't improve the stages of sleep, but like benzodiazepines, it doesn't worsen sleep stage patterns, such as reducing restorative deep stages 3 and 4.

Many medications used for sleep actually worsen sleep cycles. They tend to sedate people, helping them fall asleep in the beginning of the night. But since they worsen sleep cycle phases, they don't improve sleep stages in the end. The

most important part of sleep involves the deep sleep stages 3 and 4. With more sleep in these stages, it's found that immune system function improves, neurons are repaired, and, upon awakening, there is a sense of well-being, with enhanced cognition and energy.

It should be noted that these important deep sleep stages aren't improved with zolpidem, although it doesn't worsen them.

Addiction risk

The standard way of assessing addiction risk is to give such agents to humans with substance abuse histories, and to compare the subjective effects to known addictive agents, like diazepam, and to do

so in a double-blind placebo controlled fashion. With this design, 40 mg/d of zolpidem was experienced as giving a "high" similar to 20 mg/d of diazepam, and more than placebo. But at lower doses of 10 mg/d, zolpidem produced a high similar to placebo. This is why the manufacturer sought FDA indication at a maximum of 10 mg/d so that the drug could be marketed as "non-addictive." In fact, the drug is proven addictive, only less so at the lower doses. Nonetheless, the FDA agreed to allow non-addictive marketing language at the lower dosage range.

Dosing

For the reason just stated, the company sought and received FDA indication for the dose range is 5-10 mg/d. It has a half life of only 2-3 hours, which is why its benefits are only

for helping patients fall asleep, as opposed to stay asleep. Its onset of effect is rapid, in 15-30 minutes.

Side effects

The main side effects are sedation and loss of coordination. Nightmares can occur.

The PL Bottom Line

- Zolpidem has minimal benefit for sleep.
- It doesn't worsen or improve deep sleep stages.
- It's an addictive GABAergic agonist, though less so at lower doses.

Case of the Month

Can bipolar illness go away?

A 45-year-old man presented with two past manic episodes, one of which led to hospitalization, as documented in discharge summaries which provided evidence for manic symptoms in those episodes as follows: 3 weeks of markedly increased energy, less sleep, rapid speech, grandiose thoughts that he would be a famous person in the next year (while a graduate student), and agitation and aggression leading his friends to call the police due to fear that he would get into fights and get hurt.

For the following 12 years, the patient was untreated and didn't have another manic episode. He never experienced depressive episodes. In application for work, he sought consultations from his psychotherapist and from two different psychiatrists. They all gave the opinion that the patient didn't have bipolar disorder since he hadn't experienced any further mood episodes despite absence of treatment.

PL's view is that these conclusions aren't valid scientifically. Bipolar illness is a historical diagnosis. It's defined as having a manic episode - at any point in life. In fact, DSM doesn't capture the range of manic-depressive conditions as PL has described previously. This patient is not "bi"-polar since he only has had manic episodes, not depressive episodes. But he doesn't have "unipolar" depression either, since he never has been depressed. Instead he has unipolar mania, a pre-DSM-III diagnosis ignored since 1980.

The concept of manic-depressive illness involved *recurrent* mood episodes, of either kind, depressive or manic. Recurrence was the central feature.

Thus, if someone only had a single depressive episode or a single manic episode, they didn't have manic-depressive illness. In fact, dating back to Kraepelin, single depressive episodes were identified, but there was no such thing as a single manic episode. If a manic episode occurred, future recurrent episodes occurred. That Kraepelinian concept has been confirmed by repeated studies over a century. For instance, a classic study from the 1990s found that after a first manic episode, 90% of patients would have a second one within 5 years.

So why has this patient not had any other manic or other mood episodes for 12 years? This is uncommon, but it doesn't mean he never had those manic episodes. In other words, it doesn't mean that he doesn't have the diagnosis of unipolar mania. Another aspect to the case that PL considers important is whether or not the patient has any affective temperament. He had evidence for hyperthymia (generally high energy, low need for sleep, high activity

levels, sociability, extraversion). PL has observed that patients with hyperthymic temperament often go for 40, 50, 60 years before having their first full depressive or manic episode. The PL editor has consulted on a patient with life-long hyperthymia who experienced his first manic episode at age 84 (with negative medical work-up)!

In short, not only can 12 years pass without an episode, so can 80 years. So too one can have a heart attack, and not have another one, even if untreated, for decades. The course of an illness can be variable, but it doesn't change the diagnosis if the basic definition is met. If a manic episode ever occurs, then manic-depressive illness (or bipolar disorder, if you prefer) is the diagnosis, even if the future course is benign.

Psychopathology

Insight

One of the least appreciated aspects of psychopathology is the phenomenon of insight. This usage doesn't relate to the psychoanalytic phrase, "insight-oriented psychotherapy," which refers to becoming conscious about unconscious emotions. More broadly, in psychiatric diagnosis, insight has meant awareness of illness. The psychiatrist and philosopher Karl Jaspers first advanced this idea in his classic 1913 text General Psychopathology. He made the key point that many patients don't realize that they're ill.

In the intervening century, a great deal of research on insight has led to a consensus that insight isn't a simple construct, but rather has different components. Three have been identified in empirical studies of various rating scales:

1. insight into illness
2. insight into need for treatment
3. insight into social consequences

Sometimes a person can have insight into one component but not the other. For instance, a person may deny being ill, but will agree to receiving treatment, often because of awareness of the consequences of treatment versus not being treated (like hospitalization or incarceration). Sometimes the reverse can happen: a person can accept being ill in some way, but refuse specific treatments, such as medications as opposed to herbal treatments or psychotherapies.

It should be emphasized that extensive insight research has shown that lack of insight is *not* synonymous with psychosis. In other words, people can have impaired insight, but not have any delusions or hallucinations. This is the case in

non-psychotic mania. Also, people can have delusions or hallucinations, and possess some insight; this happens with treatment with antipsychotics at times. A patient may go from having severe paranoid false delusions to having the same beliefs but saying that she understands that other people might not agree with her.

Lack of insight is most severe in mania and schizophrenia, among psychiatric conditions. It also occurs with Alzheimer's dementia and with right parietal stroke syndromes, which produce classic anosognosia, with lack of awareness of left-sided paralysis.

"...lack of insight is not synonymous with psychosis."

It's interesting to note also that lack of insight is *not* associated with severity of symptoms. For instance, in bipolar illness, there is less insight with hypomania than with mania. Further, about one-half of persons with severe mania have intact insight. Insight is not impaired in depression, as opposed to mania or hypomania, which produces an important clinical consequence:

You cannot rely on the patient's self-report to rule out mania or hypomania, but it likely is accurate in most cases to rule out depression. Research shows that family members report manic symptoms about twice as frequently as patients, but they report depressive symptoms to the same extent as patients. This is one reason why bipolar illness is underdiagnosed, and unipolar depression overdiagnosed, in persons with depressive presentations.

PL strongly recommends that family and friends be included in all diagnostic interviews. A good detective seeks as many lines of evidence as possible. Because of lack of insight, the patient can be the worst source of evidence.

By the Numbers

Insight

Marked impairment of insight is present to the following degree in studies of patients with the following diagnoses:

- Schizophrenia: 2/3
- Hypomania: 2/3
- Mania: 1/2
- Alzheimer's dementia: >95%

When lack of insight is present, the key clinical consequence is that the patient shouldn't be the primary source of diagnostic information. If the patient denies symptoms, clinicians shouldn't accept that denial. They should instead rely more on family and friends and other sources, like medical records, as is standard practice for Alzheimer's dementia and schizophrenia. In bipolar illness though, since patients aren't delusional or demented but rather seem "normal," clinicians are tempted to accept their self-reports as valid. In fact, ironically, the self-report of a patient with past hypomania is about as valid as that of a patient with schizophrenia. (In both cases, 2/3 of patients will provide incorrect denials of past or current symptoms).

Curbside Consults

Questions/comments/cases from you

Question: Does lithium prevent dementia, as suggested by Dr. Jim Phelps in a recent issue of Psychiatric Times?

PL: The PL website discusses this idea and provides a link to a systematic review of all the lithium studies in humans with both standard and trace doses. The human studies on lithium and dementia show a strong association of reduced risk of dementia. Many animal studies also provide evidence of lithium's robust benefit in keeping neurons alive (neuroprotection). A few randomized studies now exist too, generally supporting benefit with lithium. A New York Times article based on the above systematic review raises the question, "Should we all take a little lithium?" At our current state of knowledge, PL leans to thinking it's a good idea, with huge upside and very little risk at trace levels. At present, very low dose lithium (about 25 mg/d of lithium carbonate or 120 mg/d of OTC lithium orotate) can be considered in at-risk persons, such as those with genetics for dementia or middle-aged or older persons with mood illnesses.

PL Reflection

If a man is to achieve all that is asked of him, he must take himself for more than he is, and as long as he does not carry it to an absurd length, we willingly put up with it.

Johann Wolfgang von Goethe

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THE PSYCHIATRY LETTER

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Please send your
questions and
comments to
info@psychiatryletter.org

The oxcarbazepine myth

In this issue we discuss the use of a novel anticonvulsant, oxcarbazepine (Trileptal), which is increasingly popular as a purported mood stabilizer. This popularity is based on the assumption that it must be similar to carbamazepine in its efficacy, since it's similar to carbamazepine in its chemical structure. We discuss the general principle that structural similarity of drugs doesn't translate to clinical similarity of efficacy.

The drug of the month is trazodone, which is the only medication used for sleep which improves sleep cycles.

The case of the month examines a messy case where many drugs are used for unclear purposes for an unclear diagnosis. Such clinical scenarios are not uncommon, and PL discusses the concept of a "working diagnosis" that is testable, and thus can be confirmed or refuted, as a potential solution.

The topics of bupropion for bipolar depression, and the use of the TEMPS scale for affective temperaments, are addressed in Curbside Consults.

As with all issues this year, continuing medical education (CME) and continuing education unit (CEU) credits are available for the special article through the PL website.

We appreciate your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

CME Special Article: The oxcarbazepine myth

Overusing drugs like oxcarbazepine (Trileptal) and gabapentin and what to do about it

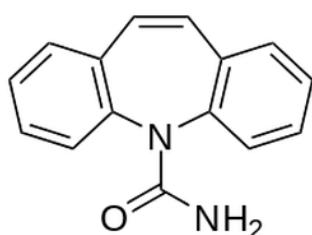
About two decades ago, a new class of anticonvulsants emerged, with clearly less side effects than prior agents. Today they are increasingly used. In addition to a Drug of the Month review of oxcarbazepine in PL May 2015 issue, this issue focuses again on that agent as a special article. This agent is used increasingly, and there is reason to examine in more detail whether this usage is justified.

The chemical analogy

The standard viewpoint these days, taught routinely, is that oxcarbazepine is just as effective as its chemical cousin carbamazepine, but it has much fewer side effects, and is thus preferable. Thus, one routinely sees that patients are given oxcarbazepine, and usually not given carbamazepine. Further they never have been treated with more effective mood-stabilizing agents like lithium, valproate or even lamotrigine.

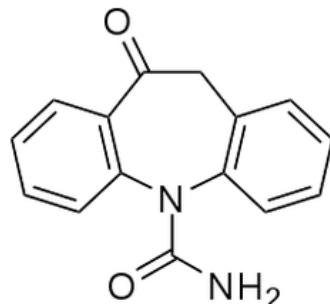
Let's begin with the chemical structure comparison. Most clinicians haven't seen those structures, and instead assume they're similar. It's worthwhile visualizing the claim, shown in the figures below.

First, there's **carbamazepine**:



You'll note the classic tricyclic structure. It shares that structure with tricyclic antidepressants and with phenothiazines. We'll come back to this point.

Now let's turn to **oxcarbazepine**:

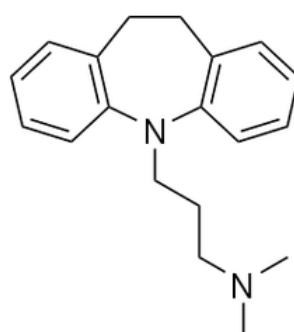


You'll notice the difference: a double bond oxygen side chain. That's it.

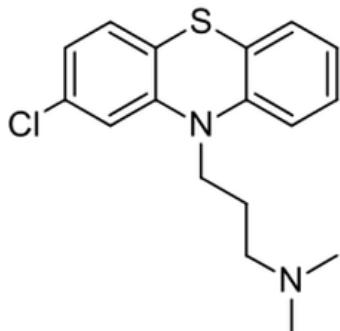
How much does an oxygen double-bond matter?

Before we answer that question, let's go back to the question of that tricyclic structure. How much does the tricyclic structure matter?

Let's look at two different tricyclic medications. First, **imipramine**, a tricyclic antidepressant:



Now let's look at **chlorpromazine** (Thorazine) the first classic phenothiazine antipsychotic:



What do you see that is different between a classic antidepressant and a classic antipsychotic: A sulfur atom and a chloride atom.

Those two atoms are sufficient for one agent to treat mania and for the other one to cause mania - in other words, completely opposite effects. Further, one agent improves depression, and the other does not. One agent treats schizophrenia, and the other does not.

A sulfur atom and a chloride atom - that's it. And the clinical effects are very different, sometimes even opposite.

Now let's turn to comparing these two: imipramine to carbamazepine. Look back at the bottom of the prior page. What are the differences?

Instead of an amine side chain (CNH₃) there is a carboxy-amine side chain (CONH₂). What's the difference?

An oxygen double bond - again.

And an oxygen double bond produces one drug which causes mania (imipramine), and one drug which treats mania (carbamazepine): Completely opposite clinical results.

What's the difference between oxcarbazepine and carbamazepine?

An oxygen double-bond!

Would you say that we should give imipramine to treat mania, since it only differs from carbamazepine by an oxygen double bond?

If not, then why do people say that we should use oxcarbazepine for bipolar illness, when it differs from carbamazepine in a similar way?

In short, there's no scientific chemical logic to the above claim.

Now let's turn from biological speculation to clinical data, which is more important scientific evidence.

Clinical data

Oxcarbazepine was used and studied in the 1980s in Europe, and there are two small double-blind studies comparing it to haloperidol in acute mania. In those studies, both agents improved. But there was no placebo control. Since mania improves spontaneously, and rather quickly, it isn't clear that such data would support efficacy in acute mania. In contrast, carbamazepine has been shown to be effective in multiple placebo-controlled studies of acute mania, and has an FDA indication for acute mania.

There is one maintenance randomized trial of oxcarbazepine in prevention of mood episodes in

bipolar illness. Compared to placebo, it was ineffective.

There are no randomized trials of oxcarbazepine in bipolar depression.

There are randomized data supporting benefit of carbamazepine for prophylaxis, but it too has not been studied much in acute bipolar depression.

Licarbazepine

There's an important twist to this story. Oxcarbazepine has an active metabolite, licarbazepine. This metabolite is the reason why oxcarbazepine would be effective. The parent compound, oxcarbazepine, is a prodrug; it has no efficacy itself. It only works through licarbazepine.

Since oxcarbazepine had been on the market for decades, and its patent life was ending, its manufacturer decided to try to patent its active metabolite licarbazepine. To that end, it conducted multiple placebo-controlled trials of licarbazepine in acute mania, thinking it would be the fastest way to bring that agent to the market.

Licarbazepine is not on the US market. If it had been shown to be effective, its manufacturer would have taken those data to the FDA for an indication for acute mania. That did not happen.

There is an important feature of the FDA indication process to appreciate here. If a drug receives an FDA indication, it must have at least two positive trials showing that it is effective. It may have any number of negative trials as well, but at least two of those trials must be positive for the FDA to grant an indication, which allows a

company to market and sell that product for that purpose.

A pharmaceutical company is obligated to provide all its data on all its studies, positive and negative, to the FDA, if it seeks and obtains an indication. It isn't under any obligation to publish any of those data, which are patent protected and considered proprietary. Typically what happens is that companies publish their positive data as prominently as possible, and market them extensively. Negative data either are not published, or are published as quietly and discreetly as possible, and certainly aren't marketed.

What happens if a drug is studied for an indication but it doesn't work at all? All its studies are negative. Well, in that case a company would

have no reason to seek an FDA indication, because it would be denied, given proof of inefficacy of its drug. In that case, the company simply would drop the whole process, and would not take those data to the FDA.

What then happens to those data, to the proof of inefficacy? The FDA has no access to such data, because they were never brought to the FDA for evaluation. The company is under no obligation to publish those data, and in fact they are private, proprietary data which are protected under US law. Who would know about those data? Company employees, obviously. Otherwise, the only outsiders who might know would be scientific consultants from the academic world. In those settings, though, the consultants have to sign confidentiality agreements such that they cannot publish or even talk about the private property (data) to which they become privy.

Which brings us back to licarbazepine. It was studied in acute mania in multiple placebo-controlled trials. That much is publicly known. It wasn't taken to the FDA to seek an indication. This would not occur if the drug had shown efficacy. The PL editor has spoken to academic consultants, who have seen the licarbazepine data. Within the constraints of not breaking US law, those consultants couldn't confirm or deny the inefficacy of licarbazepine, but they implied that the process provides the answer: If it was effective, it would have been taken to the FDA for an indication.

This process highlights a problem for the clinician:

If a drug works, you'll hear about it, loud and strong. You'll be marketed extensively.

But if a drug doesn't work, even if it's proven to not work, you may never be told.

PL is telling you: Licarbazepine very likely is proven ineffective in acute mania. And by extension, oxcarbazepine is proven ineffective.

Summary

What does this all mean for oxcarbazepine? It should be clear that the clinical research data for its efficacy is very weak, and if anything, mostly

proves inefficacy. These clinical research data are the most directly relevant data as to deciding whether to use this agent or not. These clinical data contrast with clear data of efficacy with carbamazepine in acute mania and probably prophylaxis.

The only remaining rationale for using oxcarbazepine is the pure chemical analogy hypothesis. But we've seen how weak that claim is. On those grounds, we should use chlorpromazine to treat depression, and imipramine to treat mania and schizophrenia.

Biological speculation is unscientific and dangerous. In this case, it's proven false.

“...if a drug doesn’t work, even if it’s proven to not work, you may never be told...”

The PL Bottom Line

- The biological speculation of oxcarbazepine efficacy based on carbamazepine efficacy is false and illogical. On that logic, imipramine and carbamazepine would be interchangeable, as would imipramine and chlorpromazine. All those agents have opposite clinical effects.
- Oxcarbazepine has little clinical research data evidence of efficacy.
- Its active metabolite, licarbazepine, was studied in acute mania and likely proven ineffective.
- Oxcarbazepine, in contrast to carbamazepine, likely is ineffective in bipolar illness.

PL Reflection

There is only one thing that I dread: not to be worthy of my sufferings.

Dostoevsky

Study of the month: Oxcarbazepine maintenance efficacy

A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. E Vieta et al. Int J Neuropsychopharmacology, 2008, 11:445-452

The only randomized trial for long-term prevention

There is only one randomized maintenance trial of oxcarbazepine in bipolar illness, conducted in Spain.

Method

55 patients with bipolar illness on lithium were randomized to oxcarbazepine versus placebo added. They were in remission but had experienced two or more mood episodes in the prior year.

...This is the only randomized placebo-controlled maintenance study of oxcarbazepine in bipolar illness...

Results

Time to a first mood episode was similar in both groups, being 19.2 weeks with oxcarbazepine versus 18.6 weeks with placebo. Patients were followed for one year. Relapse rates into a full mood episode were lower with oxcarbazepine than placebo (38% versus 59%), but the difference wasn't statistically significant.

Discussion

The main result here is the time to an event, which is the basis of survival analysis. How long did it take until the patient relapsed? The answer was that it was the same for oxcarbazepine as for placebo.

What about the apparent lower rate of mood episode relapse? This could be relevant, and a larger study might or might confirm it. But we don't have any replication studies to assess the matter.

This is the only randomized placebo-controlled maintenance study of oxcarbazepine in bipolar illness. Long-term treatment with this agent is not based on acceptable amounts of scientific evidence, since these very limited data aren't meaningful enough to support such long-term use in a routine or common manner.

The PL Bottom Line

- Oxcarbazepine was ineffective in prevention of mood episodes in bipolar illness, equivalent to placebo in time to relapse.
- Therefore, oxcarbazepine is disproven as a "mood stabilizer," if by that term we mean drugs proven to prevent mood episodes.

PL Reflection

Thankfully Sigmund Freud was spared knowing the concentration camps from the inside. His subjects lay on a couch designed in the plush style of Victorian culture, not in the filth of Auschwitz. There, the "individual differences" did not blur, but, on the contrary, people became more different; people unmasked themselves, both the swine and the saints.

Viktor Frankl

Clinical Tip

Treatment of akathisia: Use propranolol ER, not generic propranolol.

Standard propranolol only has a half of life of about 4 hours. Even if dosed twice or thrice daily akathisia will break through. There is a generic extended release version that can be given once at night. It comes in 60, 80, and 120 mg pill sizes. Start at 60 mg at night, and move up as needed. Check pulse before you start and increase dose if needed to a pulse that remains at 60 or above.

PL Reflection

“Most esteemed Lady, I have to disappoint you. I am not going to say ‘yes’ or ‘no’, nor shall I deal out question marks...It is quite evident that you...try in a visionary way to complete my fragments, build them into a structure....I feel you too might have slipped away from me to the system-builders, to Jung, or rather to Adler. But through the ego-libido you have observed how I work, step by step, without the inner need for completion, continually under the pressure of the problems immediately on hand and taking infinite pains not to be diverted from the path....in spite of advancing age I am not in a hurry.”

Sigmund Freud, private letter to Lou Andreas Salome, 1917

Drug of the Month: Trazodone

The perfect insomnia drug?

Biological mechanism

Trazodone is a serotonin reuptake inhibitor (SRI) with partial serotonin receptor 1 (5HT_{1A} receptor) agonism.

Clinical efficacy

Trazodone is FDA indicated for major depressive disorder, not insomnia. It was developed originally in the late 1980s as one of the first SRI antidepressants. It was found to have little to no sexual dysfunction, but it was too sedating at antidepressant doses.

This weakness became its strength, as it began to be used ubiquitously as an add-on treatment for insomnia, which was a side effect of other SRIs. Over the years, it has evolved into a standard treatment for insomnia, even though there are no randomized studies which prove its efficacy for primary insomnia, and it has no FDA indication for insomnia. Since it doesn't affect GABA receptors, unlike other sedatives, it isn't addictive.

Effects on sleep

There is a belief that trazodone improves sleep cycles, uniquely so among sedatives, the rest of which (including benzodiazepines and zolpidem and newer agents) either worsen sleep stage efficiency or are neutral at best. Specifically, the other agents add about half an hour of sleep but at the cost of less restorative deep stage sleep (stages 3 and 4). Trazodone instead appears to

improve sleep efficiency and increases those deep sleep stages.

One blinded study found that trazodone increases total sleep time by about 50 minutes, which is about double most other sedatives. Further deep stages 3 and 4 sleep are increased from about 19% at baseline and with placebo to about 31% with trazodone. Another study found 37 minutes increased total sleep with trazodone, and an increase in deep sleep stages from 56 minutes to 87 minutes. In sum, consistently replicated randomized data indicate that trazodone improves sleep efficiency, unlike all other sedatives.

Dosing

At 50-100 mg/d, trazodone is sedating and used for sleep. Antidepressant effects occur in the 200-400 mg/d range. In bipolar illness, such doses could be destabilizing and/or cause mania.

Side effects

The main side effects are sedation and possible priapism.

The PL Bottom Line

- Trazodone improves sleep cycles, in contrast to all other sedatives.
- It isn't addictive.
- Higher doses may produce antidepressant effects, for better or worse (e.g., bipolar illness).

Case of the Month

A messy case

A 48-year-old woman presented in referral after failing to respond to many different antidepressants and amphetamines and benzodiazepines. She had been diagnosed with major depressive disorder (MDD), adult attention deficit disorder (ADD), and generalized anxiety disorder (GAD). She had been treated for about 20 years with one serotonin reuptake inhibitor (SRI) or another. She had some improvement at times, but then she would have anxiety and depressive symptoms again. She was functional, able to work, even somewhat successful in her profession, but with great struggle. She felt that she could achieve even more if she didn't have so much anxiety and depression.

In prior evaluations, doctors had noticed some mood lability, but no definable hypomanic or manic episodes. She had refused to consider lithium due to its weight gain and stigma.

She had marked inattention, which led to the diagnosis of adult ADD and long-term treatment with a range of amphetamines, which helped her function at work. Anxiety was also treated with long-term clonazepam, which had mild benefit.

She also had been diagnosed with narcolepsy because she had periods where she would go for one week with much less sleep than usual, but then would fall asleep suddenly during the daytime. She denied manic symptoms during those one-week periods. She had severe insomnia most of the time, and had taken many sedating medications, with little benefit.

“...the patient has ‘manic’ symptoms, defined in the pre-DSM manner as ‘psychomotor excitation’...”

In her family history, she reported a lot of anxiety and depression but denied bipolar illness or schizophrenia.

She had occasional suicidal ideation (SI) but never had made an attempt. On evaluation, she was treated with oxcarbazepine 600 mg/d, fluoxetine 5 mg/d, Adderall (amphetamine/dextroamphetamine mixture) 20 mg/d, clonazepam 2 mg/d, and mirtazapine 10 mg at night.

On evaluation, the patient was very anxious, agitated, nervous, labile, worried, and had a number of depressive neurovegetative symptoms (low energy, interest, sad mood, poor concentration, and occasional SI). These symptoms had been present for months in a worsened state, and were present at least to a mild degree most of the time in the past year.

The entire history was based on the patient's self-report.

The PL consultant made the following observations: The patient's self-report is not sufficient for a dependable denial of past hypomanic or manic episodes, due to the problem of lack of insight, as described in the last PL issue. Thus, there was doubt whether the patient indeed did not have bipolar illness. It could be that what was called narcolepsy reflected cyclic manic/hypomanic episodes, which the patient couldn't describe in DSM-level detail. The recurrent decreased need for sleep that was described only occurs in manic/hypomanic episodes, not in narcolepsy, which is not a condition with weekly cyclic episodes, separated by periods of absence of narcolepsy symptoms.

The PL consultant raised the idea that the patient has “manic” symptoms, defined in the pre-DSM manner as “psychomotor excitation.” Clearly, this

patient is highly psychomotor excited, with marked agitation and lability, at the same time as she has clinical depression. This is the classic presentation for “mixed depression” as defined by Koukopoulos. As discussed on the PL website, mixed depression is treated by stopping all antidepressants and amphetamines, and using dopamine blockers and/or second messenger modifiers (mood stabilizers).

In other words, the PL consultant argued that the diagnoses of MDD, GAD, and ADD had been tried for 20 years, and had failed. It was time to have a different working diagnosis, and then to test it. The most likely working diagnosis, on the rationale given above, was “manic-depressive illness,” meaning recurrent mixed depressive episodes. Using DSM terminology, the diagnosis would still be MDD. Using non-DSM terminology, it would be manic-depressive illness.

In this case, the implication of that approach to mixed depression would be

to taper the patient off fluoxetine, Adderall and mirtazapine. Clonazepam is neutral in its effect, probably not helping or hurting at this time.

Oxcarbazepine would be stopped and replaced with an effective second messenger modifier, on the grounds that oxcarbazepine likely is ineffective as described in this issue of PL. Such scientific evidence of inefficacy is supported by the patient’s limited benefit with the agent.

As the patient is taken off the three antidepressants/amphetamines, the PL consultant recommended adding a dopamine blocker like aripiprazole or ziprasidone or asenapine or lurasidone (all do not have metabolic syndrome or cardiac risks or weight gain). If the patient improved, then the question of lithium or

“...the diagnoses of MDD, GAD, and ADD had been tried for 20 years, and had failed....”

valproate could be considered for long-term prevention of mixed states.

Another option would be to add low-dose lithium or valproate at present, holding off on the dopamine blockers. In the opinion of the PL consultant low dose valproate (about 500-750 mg/d) might be the most effective single treatment, with lower dose limiting weight gain. “Therapeutic” blood levels are irrelevant because we are not treating mania.

All these recommendations are made not because the patient has “bipolar” illness, as a DSM term, but because the patient has mixed depressive states. As noted on the PL website, mixed states are equally common in “unipolar” and “bipolar” illness, both of which can be seen as variations on the same disease: manic-depressive illness. This perspective is the original Kraepelinian view.

There was some resistance on the part of the treating clinicians to the PL consultation. It was argued that a very rapid diagnosis of bipolar illness had been made, and that the PL consultant wanted to treat everyone with mood stabilizers.

The PL consultant responded that bipolar illness was not being diagnosed, but rather manic-depressive illness, which is a larger and broader construct, as discussed above and in the PL website.

Further, the PL consultant suggested that there are more drugs in psychopharmacology than only antidepressants and amphetamines. This patient had been treated for two decades with only those two main classes of drugs (plus benzodiazepines). Why not try the two main drug classes - dopamine blockers and second messenger modifiers- that had not been used, at least on

pragmatic grounds? While doing so, it makes sense not to just add one drug after another, but to stop some of the drug classes that had not helped much, especially since those agents can worsen some of her symptoms (amphetamines worsen anxiety, SRIs cause mania/agitation).

This case is not presented with follow-up, but it is described here so that PL readers can think themselves about such complex mixtures of symptoms. It also is presented as a common scenario where patients are not exposed to standard second messenger modifiers, but only receive disproven ones, like oxcarbazepine. The case also highlights importance of stopping symptomatic treatments, like amphetamines, in patients with marked anxiety and depressive symptoms, which cause inattention.

Clinical Corner

What's a "working diagnosis"?

The above case raises the question of the relevance of the concept of a "working diagnosis." This old medical tradition appreciates two basic features of clinical practice: the uncertainty of diagnosis, but also its importance.

Your treatment is only as good as your diagnosis. Making a diagnosis is central to Hippocratic medical practice (defined not as "first do no harm", which Hippocrates never said; but rather defined as treating diseases not symptoms). If you don't work hard to make a diagnosis, and then obtain the scientific evidence regarding its treatment, then you are practicing unscientific medicine. If you only treat symptoms, you are practicing unscientific medicine. This is a matter of medical history: for 2500 years physicians treated symptoms with treatments (mostly bloodletting). The basic insight of modern scientific medicine, inaugurated by thinkers like William Osler about a century ago, is that we

should organize symptoms into diagnoses reflecting disease, and then treat the disease, not the symptoms directly.

So the first step is to realize the importance of diagnosis. It isn't optional. We *have* to make a diagnosis so that we can know if, and how, to treat.

The second step is to acknowledge uncertainty. There's always uncertainty in clinical diagnosis, even in parts of medicine with blood tests. There are false positives and false negatives even with HIV tests, much less with clinical diagnoses. So what do we do?

Since uncertainty is ubiquitous, since it is the norm in the practice of clinical medicine, it isn't an excuse for refusing to diagnose. It isn't good enough to say: I'm not sure what the diagnosis is, so I won't diagnose. I'll just treat the symptoms. This gets back to the Hippocratic insight that treating symptoms leads to more harm than good. (See the PL website for a discussion of this idea).

The concept of a "working diagnosis" provides a solution. The clinician says to herself: I'm not sure what the diagnosis is, but I'll make my best judgment. I'll diagnose what is most likely.

The next step also is important. The working diagnosis must be tested. It must be ruled in or ruled out. It isn't enough to make it, and then refuse to change one's mind for 20 years. Test it. In psychiatry we don't have blood tests, but one test (albeit sometimes inconclusive) is medication treatment. Give the proven treatment for your working diagnosis. If the patient improves notably and persistently, you've confirmed the diagnosis. If not, you've raised doubts about it, and, at some point, you should move to the next diagnosis on your list.

Curbside Consults

Questions/comments/cases from you

Question: What do you think of bupropion (Wellbutrin) for bipolar depression?

PL: Like all antidepressants, bupropion is ineffective in bipolar depression, proven to be equivalent to placebo. Thus PL thinks it should not be used. It is popular because it has been shown to have a low manic switch rate. This is probably because it is given at low dosages. But even if it doesn't cause mania, it is ineffective, and thus there is no point in using it.

It should be noted that bupropion is an amphetamine in its structure. Hence it isn't surprising that it causes weight loss and enhances sexual libido and causes anxiety. All amphetamines can cause mania and destabilize bipolar illness, as shown in some studies. Bupropion may be less potent than other amphetamines, and thus less likely to have those harmful effects in bipolar illness, especially at low doses. But if it is dosed high enough, it will cause mania and it will destabilize bipolar illness.

Question: Is there a good scale to assess affective temperaments?

PL: We recommend the TEMPS scale (Temperament Evaluation scale of Memphis Pisa San Diego). It is very well-validated and studied to assess hyperthymia, cyclothymia, and dysthymia. 39 item and 50 item self-report versions are available via the internet.

PL Reflection

Science is generally taken as meaning either (a) the exact sciences, such as chemistry, physics, etc., or (b) a method of thought which obtains verifiable results by reasoning logically from observed fact.

If you ask any scientist, or indeed almost any educated person, 'What is science?' you are likely to get an answer approximating to (b). In everyday life, however, both in speaking and in writing, when people say 'science' they mean (a).

Science means something that happens in a laboratory: the very word calls up a picture of graphs, test-tubes, balances, Bunsen burners, microscopes....

Scientific education for the masses will do little good, and probably a lot of harm, if it simply boils down to more physics, more chemistry, more biology, etc., to the detriment of literature and history....

Scientific education ought to mean the implanting of a rational, sceptical, experimental habit of mind. It ought to mean acquiring a *method* — a method that can be used on any problem that one meets — and not simply piling up a lot of facts.

George Orwell

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THE PSYCHIATRY LETTER

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The new year reviving old desires

This issue represents the end of the second year of the existence of this newsletter. We would like to thank you who continue to subscribe. The newsletter relies on you to keep going and to spread its influence.

In the past year we have been able to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to psychiatrists and nurses and psychologists. We hope you continue to benefit from that service.

Last December, in honor of the first year anniversary of the newsletter, we provided a special issue with a Top Ten list of events, studies, and topics in psychiatry in the past year. We continue that tradition with this issue. We also provide another Top Five list of great historical insights in psychiatry.

In reviewing published articles from the past year, it was difficult to identify one study as better than other ones which are excellent or important. Thus we stay with our usual format of a current article of the month instead of seeking to pick a top article for the year. The article chosen this month was released online just recently and provides empirical data on the developmental presentation of depression in children.

If you find PL helpful to you and your patients, please let others know so that more clinicians and patients may benefit.

Happy new year to you and yours,

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article I: Top Ten List of 2016

Our review of key topics in psychiatry this year

What's important?

As with the December 2015 issue, PL continues the tradition of thinking about the last year as the new year approaches, and discussing important topics or debates that have been active in the past year.

As usual PL provides its perspective frankly, though not necessarily here with all the evidence for its conclusions. On the PL website and in PL issues cited, relevant links are provided to articles which provide that further elaboration.

Number 10: The Snapchat generation

How should we, or could we, use telemedicine to connect to patients? How does the use of the internet and social media affect our patients? These are key questions that are arising in the last few years and promise to be major questions for the future.

As of now, there are some legal concerns with telemedicine as applied to psychiatry. State boards regulate clinical practice based on where the patient is examined, not based on where the clinician is located. Thus if you do a video interview of a patient in another state, you must have clinical license privileges in the patient's state, not your own. Given this important legal issue, it is questionable whether it is safe to interview and advise or treat patients in other states based on video or telephone interactions.

Legal and governmental bodies are slow to adapt so this process may prove to take a long time, but eventually telepsychiatry will become something more common. Until the legal aspects are worked out, though, it is important to realize that such

"Internet addiction is not limited any longer to sexual or pornographic content...."

clinical activity is not protected under current legal standards in relation to out of state interactions.

Regarding the use of the internet by patients, especially adolescents and young adults, it is likely that we are in the midst of a new kind of addiction. Internet addiction is not limited any longer to sexual or pornographic content. Many young persons are addicted to Snapchat or Instagram or other forms of (usually visual) communication. The related matter of cyberbullying has become important as well.

This problem isn't limited to young persons, as the older generations tend to be more connected to Facebook and Twitter, sometimes excessively so. The mental health professions will need to determine how to respond to these developing behaviors. The addiction model is likely to be the most relevant way of understanding the impact of these social media activities.

Number 9: Should we use mental health apps?

A related technological matter is the development of apps for mental health content on smartphones. These apps are in their infancy, and it is hard to know which will prove useful and which will not. But there is little doubt that they too will become important in the future as a means of interacting with patients as well as recording their symptoms and management. Currently, some sleep apps exist which provide sleep study-like measurements of the stages of

sleep. They may be useful for assessing the effects of insomnia.

Other apps are being developed to treat ADD purportedly, and others to measure or manage depression or bipolar illness.

In the world of hi-tech, behavior precedes proof. The scientific process of the academic world is slow, glacially so, compared to the practical process of the hi-tech world. Thus, many more apps will be available than are proven to be beneficial on scientific grounds. We will see how this process evolves. One important aspect is that Apple has developed an open free app platform called "ResearchKit" so that academic researchers can prove the benefit of different apps for medical conditions. If studies using those kinds of apps prove benefit, then clinicians in the near future may be in a position to be able to use those apps with their patients.

Most of that work is in non-psychiatric conditions, but interest is growing in psychiatric conditions like ADD and depression.

Number 8: The opiate epidemic

It is now clear that something has gone wrong with opiate prescription in the US. About a decade or two ago, the mantra was that physicians were being too Calvinistic, too conservative, in prescribing opiates for pain. The pharmaceutical industry benefited from, and helped spur, the campaign to prescribe opiates more liberally for pain syndromes. It is now clear that such increased opiate prescription has led to increased opiate abuse, and to intended and accidental deaths from overdose. This increase in mortality in younger populations has influenced the overall US population such that overall life expectancy in the US has plateaued for the first time in decades.

"It is now clear that something has gone wrong with opiate prescription...."

Some would say that we are in the midst of a public health emergency. Whether something will be done or not at the governmental level, and what, remains to be seen.

In the meantime, clinicians need to be aware of the extent of this problem and PL would encourage restricted and cautious prescription of opiate agents.

Number 7: Binge eating disorder - A DSM-5 fad

Many have criticized the DSM process for being too medical or biological, or being influenced by the pharmaceutical industry. While these specific criticisms aren't accurate exactly, in the PL view, there is reason for worry about such critiques in the case of this condition. Some have termed it "disease mongering"; that's when the profession creates a term that didn't exist before, and then the pharmaceutical industry markets it into the deep unconscious of prescribers.

This appears to be happening with binge eating disorder, which was included in DSM-5 for the first time in 2013, to the convenient profits of the makers of the amphetamine Vyvanse (lisdexamfetamine), who obtained FDA indication for the new DSM-invented label of BED in January 2015.

It isn't surprising that any amphetamine would reduce binging or any kind of overeating; this has been proven for over half a century. There isn't anything specific to Vyvanse for supposed BED.

One might ask how "BED" actually differs from overeating, but this kind of scientific question wasn't addressed in the DSM-5 process. As discussed in PL May 2016 issue, the DSM process is about "pragmatism" not science.

DSM invents a label. The pharmaceutical industry figures out how to make \$5 billion a year from it.

PL urges readers not to fall for this disease mongering.

Number 6: What should we do for adolescent depression?

It is estimated that about 10% of adolescents reported a clinical depressive episode in the prior year, with most not receiving treatment. But what treatment should they receive? Typically they are treated with antidepressants, but as reviewed in PL October 2016 issue, those agents appear to increase suicide risk to a small but notable degree. Further, early onset depression

in adolescence is the beginning of bipolar illness in about one-half of children, based on some studies. But the mental health profession is unwilling to diagnose bipolar illness in children and adolescents for cultural reasons, and even more unwilling to prescribe effective treatments like lithium or valproate.

The notable prevalence of adolescent depression is a problem that the mental health professions need to address more effectively. PL recommends a willingness to diagnose and treat bipolar illness in depressed children either when manic/hypomanic states have been present and/or when a family history of bipolar illness is present.

Number 5: The first antipsychotic that is not a dopamine blocker.

Rarely does a new medication for a kind of psychopathology involve a totally new mechanism of action. Pimavanserin (Nuplazid) is such an agent. It is now FDA indicated for psychosis in Parkinson's disease. It is a purely serotonergic blocker (being marketed as an "inverse agonist",

which seems to be the same thing as an antagonist). Prior research drugs that were pure serotonin blockers never made it to the US market because they didn't prove effective in schizophrenia. This agent was studied in Parkinson's disease, so it is unclear whether it will prove effective for psychotic symptoms in schizophrenia or mood illnesses, but if it turns out to be effective more broadly, it would be a key agent which would not have extrapyramidal side effects. We can wait to see how it will play out if further research is done in primary psychiatric conditions, and as clinicians get experience with it in Parkinson's disease.

"PL recommends a willingness to diagnose and treat bipolar illness in depressed children..."

Number 4: Treat to remission?

For about two decades, the teaching has been that clinicians should use medications to get rid of all symptoms, 100% of them, in conditions like depression and anxiety, if possible. Now we know that our antidepressants don't succeed at such complete remission in the vast majority of patients, even short-term. Some experts recommend doubling up, and giving more and more medications. PL recommends respecting the limitations of drugs, and thinking more carefully about which diagnoses we should treat with medications, and how far we should go. With multiple medications, further symptom benefit is minimal in almost 90% of persons with MDD, for instance, as shown in STAR*D, and yet side effects add up. The ratio of harm to benefit begins to veer strongly in the negative direction.

The Hippocratic tradition was about treating diseases, and not symptoms, otherwise much harm ensues. The obsession with removing all symptoms goes against that Hippocratic approach.

PL recommends more caution and more respect for the brain and body that is impacted by medications, all of which have some harms and side effects. Further, PL reminds readers, as described below, that such “resistant” symptoms sometimes reflect wrong or inadequate diagnosis, which is why ramping up of the same class of medications will not improve matters.

Number 3: Is pharmacogenetic testing helpful?

Some companies are now marketing pharmacogenetics testing to claim improved health outcomes. Most of these claims have to do with the serotonin transporter gene, the best studied genetic marker of treatment response for so-called major depressive disorder (MDD). Even if the claims are taken at face value, they often don't acknowledge that they reflect only short-term benefits, meaning acute response for about 2 months. They don't translate to long-term efficacy or treatment, although those companies usually want to presume so. Further, such claims don't take into account the reality of misdiagnosis. As discussed on the PL website, about one-third or so of cases of “treatment-resistant” depression (TRD) involves simple misdiagnosis of bipolar depression, where antidepressants basically are ineffective (as discussed in PL January 2016 issue). TRD also can be understood as reflecting not inefficacy of the drugs, but inefficacy of the diagnosis of MDD. As discussed on the PL website, many different depressive conditions, often unresponsive to antidepressants (like mixed states), have been combined in the broad DSM-III based MDD concept. TRD can be seen primarily as a problem of diagnosis, not just the drugs. The pharmacogenetic world ignores all these matters.

“TRD can be seen primarily as a problem of diagnosis, not just the drugs...”

Number 2: Amphetamine stimulants are the most rapidly increasing prescribed class of psychotropic medications

Recent clinical practice based data from the US indicates that amphetamine prescription is skyrocketing, unlike all other psychotropic drug classes, which are plateaued. It may not be a coincidence that most of the major antidepressants and neuroleptics and mood stabilizers are now generic medications, with no further major profits to be made by their manufacturers. In contrast, dextroamphetamine and methylphenidate are tweaked continually (lisdexamfetamine, Vyvanse; dexmethylphenidate, Focalin) so that pharmaceutical companies can continue to make immense profits. The related marketing ensures that the agents are prescribed.

PL July 2015 issue addressed the harms, including neurotoxicity, of these agents, as well as the questionable validity of the ADD diagnosis in adults, and sometimes in children. PL recommends that these agents be used much less frequently than is the case currently.

Number 1: What will be the impact of legal marijuana?

This is the question that the coming years will answer. Marijuana was legalized this year in a number of states. Will this legalization have a negative impact on substance abuse rates, or on psychiatric conditions that could be impacted by marijuana's effects (such as depression and paranoia)?

There has been an impression, especially among the younger generation, that legalization implies safety. Of course, older generations remember that cigarettes always were legal. And alcohol is

certainly still a major public health problem, especially in young persons.

Mental health clinicians shouldn't assume the safety of marijuana either, and should be cautious when they are asked, as will be the case in many situations, to support marijuana use for anxiety or depressive benefits. Nicotine cigarettes also are anxiolytic, but that is not a reason to prescribe or condone cigarette smoking for that purpose.

Whatever social benefits may arise from legalization of marijuana, the medical effects of wider use of this agent are a different matter, and will require some attention.

The PL Bottom Line for 2016

- Internet addiction is a new burgeoning problem.
- Mental health apps aren't ready for prime time but will be important clinically soon.
- The opiate epidemic should influence clinicians to be more cautious with prescribing them.
- Binge-eating disorder is a classic case of disease-mongering. Clinicians should reject the marketing of Vyvanse.
- Adolescent depression is a major problem that isn't effectively managed by just prescribing antidepressants.
- A new antipsychotic that is not a dopamine blocker is now available, and could be promising if effective outside Parkinson's disease.
- Don't treat to remission when symptoms are "resistant." Think more carefully about diagnosis.
- Pharmacogenetic testing for depression ignores the problem of misdiagnosis and the heterogeneous and potentially invalid nature of the MDD construct.
- Amphetamines are the most rapidly increasing class of prescribed psychotropic agents, for better or for worse.
- The impact of legal marijuana on clinical practice is unpredictable.

PL Reflection

...the very concept of objective truth is fading out of the world....I know it is the fashion to say that most of recorded history is lies anyway. I am willing to believe that history is for the most part inaccurate and biased, but what is peculiar to our age is the abandonment of the idea that history could be truthfully written....It is just this common basis of agreement, with its implication that human beings are all one species of animal, that totalitarianism destroys....There is, for instance, no such thing as 'Science.' There is only 'German Science,' 'Jewish Science,' etc. The implied objective of this line of thought is a nightmare world in which the Leader, or some ruling clique, controls not only the future but *the past*.

George Orwell

Special Article II: Historical Top Five List

Old lessons for a new year

Winston Churchill used to say that every time a new book was published, he bought an old one. What is old has stood the test of time, at least in terms of books. If you wait a few years before you read what's been published, you often weed out the temporary and insignificant.

There is a benefit to a longer perspective, so, as with last year, we provide another Top Five list of great insights from the history of psychiatry.

Just as a reminder, the 2015 list was as follows:

1. 1927: The first and only Nobel prize for a psychiatric treatment given to a psychiatrist was awarded to the chairman of the psychiatric department of the University of Vienna, Julius von Wagner-Jauregg, for malaria therapy of psychosis. Moral: The treatment worked for the highly prevalent psychotic disease of neurosyphilis, proving that careful clinical diagnosis in psychiatry can lead to biological cures.
2. 1954: A classic British textbook explains the problem of lack of insight. Moral: You can't simply believe the patient about presence or absence of symptoms.
3. 1845: Esquirol, the great French physician describes how bleeding makes sense, but doesn't work. Moral: Your treatments may make sense to you, but that doesn't mean they work.
4. 1878: Daniel Tuke, a British physician, describes hypomania, mild manic symptoms, as important precursors of more severe states. Moral: Hypomania is an old and well-recognized idea, not a modern fad.

5. 1930: The historian Paul Roazen interviewed Freud's ex-patients in the 1960s, one of whom (Dr. Imrita Putnam) recalled a 1930 psychoanalysis where Freud commented that psychoanalysis was "a fine thing for normal people." Moral: Psychotherapies are wonderful, maybe more so for the normal than the sick, because "everyone has problems," as Dr. Putnam said.

After this reminder of those five key lessons from the past, let's turn to this year's historical list.

Number 5: 1804 - Philippe Pinel develops "moral therapy" based on biological reductionism

Moral therapy is well-known, usually associated with removing physical restraints. One thinks of the paintings of Pinel, in the French revolutionary era, dramatically casting off the chains of the mentally ill in the famous Salpetriere asylum outside Paris.

It wasn't actually that dramatic. Pinel didn't just treat people nicely, and suddenly they didn't need chains anymore. Pinel's methods were more complex. What he meant by "moral" therapy doesn't have the same implications as the word as it is used now. It didn't mean "ethical" as much as "rational" treatment. Pinel was a young physician who joined the young generation of Frenchmen who supported the French Revolutionary ideals of science and reason, as opposed to religion and monarchy. Before the Revolution, insanity was seen as a moral failure and/or as a reflection of sin, interpreted religiously. God was punishing the insane. Pinel rejected all such religious talk and emphasized that insanity reflected disease of the body and brain (just as Hippocrates had claimed in the pre-Christian era), and thus it needed to be

treated humanely, since it didn't reflect sin of any kind.

In other words, Pinel was a biological reductionist; that's why he was a humanist. He didn't have effective treatments, and he knew so. But he also knew that the diseases of insanity could be divided basically into two groups: those which recovered naturally (episodic) and those which did not (chronic). In the case of the first conditions, humane care could be given until nature cured the disease. In the second case, humane care would be needed in a more prolonged fashion, since cure would never occur.

Pinel's classic textbook on insanity was revolutionary because it took this biological approach to psychiatry, with its humane and "moral" implications. In that era of the Enlightenment, science and humanism went hand in hand, contrary to many of our current postmodernist assumptions otherwise.

The moral: Biological psychiatry can be, and was, very humanistic.

Number 4: 1949 - John Cade discovers lithium.

John Cade was an Australian psychiatrist who developed the idea of lithium as being effective for psychiatric conditions while interned in a prisoner of war camp in the Second World War. His initial thought was that the active ingredient was the compound combined with lithium, namely uric acid. But lithium urate had the same effects as lithium carbonate, and Cade drew the conclusion that the active ingredient was lithium. First, he gave those agents to guinea pigs (literally), and then to himself (true), and then to about a dozen patients. He published his case series in Australia, a paper that likely would be rejected in most scientific journals today (case series are very unpopular and considered

"anecdotal"). Within a few years, the first randomized trials in psychiatry would be conducted with lithium, and would prove Cade right.

Nonetheless, there was great resistance, especially in the British leaders of psychiatry (like Aubrey Lewis and Michael Shepherd) to the idea that lithium worked for manic-depressive illness. It wasn't until 1970, a generation after the initial discovery, that lithium became available on the US market.

The moral: Perhaps the most effective medication in psychiatry was discovered in a few cases by an active clinician, not a prominent academic, and resisted by the psychiatric establishment for decades.

Number 3: 1975-80 - Thomas Wehr, Frederick Goodwin, and Athanasios Koukopoulos discover that antidepressants can worsen bipolar illness

Some PL readers may know that the PL editor has worked with the psychiatrists mentioned above on this topic, but that personal relationship notwithstanding, it is worthwhile noting that it was in this time that antidepressants were noted to have some negative effects in bipolar illness. They caused mania, and, more controversially, they worsened rapid-cycling, causing more and more depressive and manic episodes over time. Wehr and Goodwin first published their observations in 1975, based on careful study of a few patients at the National Institute of Mental Health, and they followed it up with a randomized trial supporting their observations. Similar findings were published by Koukopoulos and colleagues based his active clinical practice in Rome.

PL readers know the topic remains controversial and clinical practice has not changed much since

the 1970s, with antidepressants remaining widely used in bipolar illness, as discussed in February 2016 issue.

The moral: Clinicians accept benefits of medications much more quickly than they admit potential harms.

Number 2: 1946 - Viktor Frankl publishes "Man's Search for Meaning"

There are profound and superficial ways of assessing the importance of Frankl's masterpiece. The superficial one is that it is still widely read 60 years after it was written. The profound one is that it is one of the few books in psychiatry that speaks directly to all people about basic human dilemmas. It's worthwhile noting that its original title in German translated to: "Nevertheless, Say 'Yes' to Life: A Psychologist Experiences the Concentration Camp." Its first English translation in 1959 was titled: "From Death-Camp to Existentialism." Frankl was a psychiatrist from Vienna who had trained in psychoanalysis in the 1930s under Freud's first prominent pupil, Alfred Adler. Frankl was not an intimate of Freud himself, though living in the same city, but he had learned psychoanalytic ideas from the source. When he was interned in the Nazi concentration camps, he observed that much that he had learned in his psychoanalytic training was of little use. He observed that most of his fellow inmates didn't dream about sex or aggression, but rather about food. They didn't yearn to satisfy their sexual or aggressive instincts, but rather merely to survive. He observed further that those who survived were those who suffered. Those who perished were those who could find no meaning in their suffering. Apathy - the loss of all emotion - was the worst outcome, much worse than the despair of unremitting anguish. At least in despair, one experiences an emotion; one is still alive. When all emotion is gone, one dies, first

mentally, then physically. This is one of the insights that Frankl described so well, and which led him to move away from psychoanalysis and towards a new approach, existential psychotherapy, a way of thinking that had been started by Karl Jaspers.

In a way the concentration camps were the ultimate - immoral - test of the psychoanalytic hypothesis as opposed to other approaches to understanding human existence. Freud's thinking, for all its insights, failed to be sufficient. Another approach, existential psychiatry, seemed more adequate.

Number 1: 1913 - Karl Jaspers publishes General Psychopathology

Around the turn of the century, Emil Kraepelin, the great German psychiatrist, became chairman of the department of psychiatry at Heidelberg, one of the most prominent universities in Germany. A few years after he moved onto Munich, a young resident entered the program. Karl Jaspers learned Kraepelin's objective-descriptive approach to psychiatry well. Jaspers also studied and learned about a new thinker in the field, Freud, who taught of the importance of the subjective meaning of psychological experiences. These two approaches conflicted, and Jaspers sought to find a way to make sense of the best approaches to psychiatry. He came upon a way of thinking that can be seen as scientific thought applied to psychiatry; he called it "methodological consciousness", by which he meant that different methods in psychiatry have different strengths and weaknesses. No single method is the best or explains everything. Thus, Kraepelin's approach made sense for severe psychotic or affective diseases, while Freud's approach worked in traumatic neuroses. One approach wasn't inherently better or worse; it depended on what they were being used to study

or treat. In addition to this central conceptual insight, Jaspers himself developed a third method: he called it “phenomenology”, and it has come to be called the existential-phenomenological approach in psychiatry. Jaspers went on to work as a philosopher most of his life, and founded the school of existentialism in philosophy (along with his colleague, initially a friend and later an enemy, Martin Heidegger). The existential approach (if we may shorten the title thus) is a method that is valid in psychiatry to address all patients as human beings. It views everyone in terms of the basic human dilemmas we all share, and the limits we all experience that cause sadness or despair. Many life problems come to psychiatrists where neither psychotic nor affective diseases are present, nor are there traumatic neuroses. In such settings, Jaspers offered a new approach centered on the method of empathy, a concept first advocated by Jaspers and now taken for granted and often understood superficially. These ideas were best laid out in his classic text General Psychopathology, which he published in the final year of his residency training.

For those readers who wish to read more about Jaspers' ideas, a more readable and less daunting

source is “Way to Wisdom,” which is a summary of his philosophy given as radio lectures in the 1950s. Though it isn't directly about psychiatry, it lays out Jaspers' basic thinking in general, and the links to psychiatry can be seen in many places.

The PL Bottom Line

- The humanistic approach in modern times in mental health was linked to biological psychiatry.
- The greatest drug discovery in psychiatry, lithium, was based on a few cases observed by an astute clinician, not a complex large university-based research study.
- Clinicians are more likely to accept research that shows benefits with medications as opposed to harms.
- The concentration camp experience failed to validate psychoanalytic ideas, but supported existential approaches.
- Empathy was promoted by Karl Jaspers as the core method of the existential approach to psychotherapy.

PL Reflection

The death rate in the week between Christmas, 1944, and New Year's, 1945, increased in camp beyond all previous experience....It was simply that the majority of the prisoners had lived in the naive hope that they would be home again by Christmas.... Nietzsche's words, ‘He who has a *why* to live for can bear almost any *how*,’ could be the guiding motto for all psychotherapeutic...efforts regarding prisoners. Whenever there was an opportunity for it, one had to give them a *why* - an aim - for their lives, in order to strengthen them to bear the terrible *how* of their existence. Woe to him who saw no more sense to his life, no aim, no purpose, and therefore no point to carrying on. He was soon lost....What we really needed was a fundamental change in our attitude toward life...*that it did not really matter what we expected from life, but rather what life expected from us*. We needed to stop asking about the meaning of life, and instead to think of ourselves as those who were being questioned by life - daily and hourly....

Viktor Frankl

Current Study of the Month: *Predicting depression in kids*

Antecedents of New-Onset Major Depressive Disorder in Children and Adolescents at High Familial Risk. F. Rice et al, JAMA Psychiatry. Published online December 7, 2016.

A new study confirms that in children anxiety precedes depression

In prior PL issues we raised the idea that anxiety is the fever of psychiatry. It is more often an effect than a cause. It happens for a hundred reasons. In this newly published paper, we read about another aspect of anxiety: It is the nonspecific expression of psychopathology in children, before more specific conditions like mood diseases or schizophrenia become apparent.

In this study, 304 children (aged 9-17 years) of depressed parents were followed prospectively for four years. 20 children met MDD criteria in follow-up. Anxiety and irritability at baseline predicted later development of clinical depression, but disruptive behavior and low mood did not.

Anxiety is like fever in infections. If a patient has HIV, with a high fever, and complains terribly about the fever, and the fever is so obviously a problem, it doesn't follow that the main attention in diagnosis or treatment should be given for the fever. This doesn't mean that the fever is to be ignored, but only that its symptomatic treatment with Tylenol is only partially important. Treating the underlying cause of the fever - the infection - is even more important.

So it is with anxiety in psychiatry, especially in children. The child or adolescent presents with terrible anxiety; the parents complain bitterly about it. The serotonin reuptake inhibitors are available to treat the anxiety symptomatically. The prescription follows. But this decision doesn't get at the cause. This study shows that anxiety is a common early presentation of

"Anxiety and irritability at baseline predicted later depression..."

recurrent depressive illness in children and adolescents. It's not that the anxiety "causes" the depression, but rather that the mood illness presents initially as anxiety, and later as depression. It's the same disease from day one, when the child is born; the genes are the same and they are expressed in the brain developmentally such that anxiety follows first, and then depression. In the end, though, it is a disease of mood, with anxiety as an early presentation. These clinical presentations aren't the disease itself - which is the biological abnormality in the brain - but rather they are the effects of the disease.

As noted earlier, also, apparent "MDD" in children is not just MDD since early-onset depression was the hallmark of bipolar illness, and the whole concept of MDD was based on the idea that it began later in life, around age 30. As discussed on the PL website, about one-half of children with depressive episodes only (supposed MDD) later have manic or hypomanic episodes (and thus have bipolar illness). Hence, the simple prescription of SRIs for anxiety in such children is not risk-free, given the risk of causing mania or worsening the course of the mood illness. This effect may underly the increase in suicidality caused by SRIs.

Irritability can be seen as a manic symptom, and it too predicted depression. These observations all are in line with the traditional concept of manic-depressive illness, as described on the PL website.

Curbside Consults

Questions and cases from you

Question: I have learned from PL that diagnostic validators, like course and family history, are essential to diagnose manic-depressive illness. A question arose for me on this topic in relation to a new patient I saw recently. He is a man in his mid-30s, dismissed from his military job a few years ago. He presented to our hospital with severe paranoid delusions, along with psychomotor retardation and social withdrawal.

Past psychiatric history identified a severe depressive episode with serious suicide attempt by firearm at age 27. His father described three clear manic episodes (lasting over a week each) in the following years, alternating with more frequent depressive episodes. Military service likely exposed him to some head trauma. Family history identified a similar condition in a paternal uncle, with age of onset of 30 years.

My question: How do we explain this relatively late-onset of manic-depressive illness in the patient (late 20s) as well as his uncle (age 30)? Is it due to genetic anticipation? Or is it secondary to head trauma or a schizoaffective condition?

PL: Thank you for this thoughtful clinical evaluation. As you know, the mean age of onset of bipolar illness is about 20, while for unipolar depression it is about 30. But this is an average, with a normal curve to each side of this peak. Certainly 5-10 years would be a reasonable range

on either side of the average, which means that bipolar illness begins in the range of 10-30 years of age, with 20 being the average. (Similarly, unipolar depression can be seen as occurring mainly around age 20-40, with 30 as the mean).

Thus, the onset of late 20s in this case, though less common than an earlier age, is consistent with the usual course of bipolar illness. Further, it should be noted that the first depressive episode was quite severe. It is possible that the patient had milder to moderate clinical depressive episodes earlier in life which he and his family may not have noted, but which would establish an earlier age of onset. Finally, about one-half of such patients have an affective temperament. In the PL view, the age of onset is when the affective temperament starts, not when the first mood episode occurs. In other words, some patients have their first depressive episode in the 40s, 50s, 60s, or even later, but they had cyclothymic or hyperthymic all their lives, from childhood onwards. In such cases, the official age of onset of the mood disease is late, but the actual onset of the affective condition is in childhood with the affective temperament.

Given these considerations, the case is within the range of typical for manic-depressive illness. That said, there is some evidence for genetic anticipation in some families with bipolar illness, with earlier age of onset with succeeding generations. This family doesn't follow that pattern though.

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THE PSYCHIATRY LETTER

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From below/from above

Welcome to the third full year of *The Psychiatry Letter*. Some new subscribers are joining us, and we welcome them.

Through our collaboration with PeerPoint Inc, we continue to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to psychiatrists and nurses and psychologists. We hope you continue to benefit from that service.

We also have begun to work with the New England Educational Institute for marketing and for production and mailing of the printed copies of the newsletter. We hope our print subscribers will see benefits of that collaboration leading to regular monthly delivery of the newsletter.

The first issue of this new year begins with a discussion of the clinical concept of mood stabilizing "from below", a term often associated with the anticonvulsant lamotrigine, as opposed to other "mood stabilizers." PL discusses how these are marketing phrases without serious scientific support. PL examines how clinicians can avoid being misled in important treatment decisions by such marketing phrases.

If you find PL helpful to you and your patients, please let others know so that more clinicians and patients may benefit.

Happy new year to you and yours,

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Mood stabilizing “from below”?

A marketing phrase that misleads

Two vignettes

Consider the following case vignettes:

1. A man in his mid 40s has a two decade history of manic and depressive episodes. He is treated for his bipolar illness with lamotrigine 200 mg/d, and lithium 600 mg/d (level 0.6). He experiences breakthrough depression, and his new psychiatrist recommends olanzapine/fluoxetine combination (OFC). The PL consultant recommends increasing lithium instead of adding OFC. The treating psychiatrist responds that lithium is more for “top-down” control while lamotrigine is for “bottom-up” control. He is skeptical that increasing lithium will help with further depression prophylaxis.
2. A man in his mid 30s has rapid-cycling bipolar illness type I. He has 6 mood episodes yearly, alternating between brief hypomanic states and longer depressive episodes, lasting one month or so each. His life is very disrupted.

He is treated with lamotrigine 200 mg/d plus lithium 900 mg/d (level 0.6, higher doses could not be tolerated) for 8 months, without benefit. Lithium was switched to divalproex (1000 mg/d, level 65 added to lamotrigine without benefit. Pregabalin was added without benefit. His psychiatrist is avoiding antidepressants and dopamine blockers. The PL consultant recommends switching lamotrigine to lithium, combined with divalproex, and adding a dopamine blocker. The psychiatrist refuses, insisting that the patient needs more mood stabilization “from below” as opposed to more “anti-manic” medication.

“... lamotrigine had a problem: it was proven ineffective for acute mood states of all varieties - depressive or manic....”

These two cases demonstrate how false pharmaceutical marketing continues to influence clinical decision-making years after a drug, now generic, is marketed no longer.

“From below”: The history of lamotrigine

The PL editor was present at the creation, one of the investigators in the first maintenance studies of lamotrigine, and a member of Glaxo’s national advisory board for lamotrigine over a decade ago.

At the time, lamotrigine had a problem: it was proven ineffective for acute mood states of all varieties - depressive or manic. It further was proven ineffective in acute depression in both unipolar or bipolar illness. All these negative randomized studies had been conducted by Glaxo but they didn’t plan to publish them anytime soon. They didn’t even tell the academic members of the national advisory board. A few years later, in the setting of a lawsuit against Paxil,

a judge ordered Glaxo to put all its material online for the public to see. That’s when these negative studies came to light, though most still remain unpublished, except for a summary of them published by the PL editor based on the court-ordered website data.

These negative studies provide the context for the marketing decisions made by Glaxo regarding their two positive prophylaxis studies with lamotrigine. In those two maintenance studies of bipolar I illness, lamotrigine was more effective than lithium and placebo, and it received an FDA indication. The marketing question was: How do you convince clinicians to prescribe a drug for

prevention when it isn't effective for the acute episode?

The solution was a marketing slogan: "Stabilizing from below." As many clinicians know, this slogan was based on the observation in the lamotrigine maintenance trials that this agent was more effective than lithium and placebo in prevention of depressive episodes but less effective than lithium and placebo in the prevention of manic episodes. The origin of the marketing slogan came from an academic consultant: lamotrigine stabilizes "from below" and lithium stabilizes "from above."

The slogan could translate to convincing clinicians to give lamotrigine in their patients with mostly depressive episodes, which, not by coincidence, is the case in the vast majority of persons with bipolar illness. By sleight of hand, the Glaxo marketing team had a way to convince clinicians that lamotrigine should be preferred to lithium in the vast majority of persons with bipolar illness. And this

effect was achieved despite the fact that lamotrigine was completely ineffective (repeatedly shown to be the same as placebo in randomized trials) for treating acute bipolar depression (a fact kept hidden from clinicians by not publishing those negative studies).

The biased "enriched" design

The claim that lamotrigine is more effective than lithium for depressive episode prophylaxis can be challenged based on the validity of the research method used in those maintenance studies: the "enriched" design. As described also on the PL website, this method involves pre-selecting treatment responders to the medication being studied (i.e., lamotrigine) for the maintenance study. Those who had failed to respond to

lamotrigine before the maintenance study began would be excluded from the maintenance study. Yet lithium was not similarly pre-selected so as to include only lithium responders in the maintenance study.

In the two prophylaxis trials, patients were initially treated with lamotrigine for an acute mood episode, in one trial depression and in the other trial mania. This treatment occurred openly and was not part of the randomized maintenance trial itself. All this initial treatment was just for preparation to enter the actual research study: the randomized maintenance trial. If they improved and tolerated lamotrigine, they were then entered into the research study, i.e., the randomized maintenance trial, where they were randomly assigned to stay on lamotrigine or to switch to lithium or to switch to placebo.

Notice that these were all patients who at least tolerated lamotrigine and improved, and then they stayed on it. If they didn't stay on it, they were switched to lithium

(or placebo) but they had not been recently treated with lithium and preselected to improve on lithium and to tolerate it. In other words, it should be clear to readers that this is not a fair comparison. About half the patients tolerated and responded to lamotrigine in the prior 2-3 months, and this "enriched" group of responders was then compared to people given lithium *de novo*, as opposed to also being preselected to having just improved with lithium over the prior 2-3 months.

An unfair comparison produces biased results. Thus, one cannot fairly say that lamotrigine was more effective than lithium in depression prophylaxis, when the sample is biased to include only prior lamotrigine responders but it is not biased to include only prior lithium responders.

It is notable that, even with this heavy bias in favor of lamotrigine, lithium still was more effective than lamotrigine in mania prophylaxis. Clinicians can believe that result because it means that even with a strong handicap, lithium still beats lamotrigine for mania prophylaxis. But the opposite is not the case. Since lithium was being studied with a strong handicap, one cannot accept the findings at face value that lithium was less effective than lamotrigine for depression prophylaxis.

These same considerations about the inherent bias of the “enriched” maintenance design would apply to placebo, in the sense that the study is so biased in favor of the drug being studied, one cannot be sure that the drug truly is better than placebo. This concern would throw into doubt the inherent efficacy of all drugs studied with the enriched maintenance design, including antidepressants in MDD and antipsychotics in bipolar illness. The details of this larger conclusion will be addressed in future PL issues. For now, PL is only claiming that the lithium versus lamotrigine comparison cannot be accepted at face value given the above concerns.

Further, one should not ignore the rest of the scientific literature besides these Glaxo studies:

First, in unipolar depression, dating back to the 1950s, there are many randomized trials that show that lithium is very effective in prevention of depressive episodes, greater than placebo. There also are many randomized trials supporting acute efficacy of lithium in the current major depressive episode, both in unipolar depression and bipolar depression. These positive results in many studies contrast with the consistent negative results of lamotrigine for the acute depressive episode, in

both unipolar and bipolar depression. In other words, outside of the two Glaxo studies, the rest of the scientific literature is much more supportive of greater depression treatment and prevention benefit with lithium, rather than lamotrigine.

Second, the best recent study to compare to the Glaxo trials is the large UK-based BALANCE study which compared lithium versus divalproex in maintenance treatment of bipolar illness. That study was not enriched, and not biased to either agent, unlike the Glaxo trials. In BALANCE, lithium was *more* effective in prevention of depressive episodes than in prevention of manic episodes. Given that the BALANCE trial is more valid (less biased) than the Glaxo trials, it argues for the reverse: lithium is not an agent that mainly stabilizes “from above”, if you wish to use the marketing slogan; lithium also “stabilizes from below.”

Instead, PL prefers to drop all the marketing slogans and instead use scientific terms.

Lithium robustly prevents depressive and manic episodes, whereas lamotrigine is better at the former than the latter. There are no head-to-head valid data that lamotrigine is better than lithium, or vice versa, in depression prophylaxis in bipolar illness.

The PL Bottom Line

- “Mood stabilizing from below” is a false marketing slogan.
- Lithium is highly effective in depression prophylaxis in bipolar and unipolar illness.
- Lamotrigine is not proven to be more effective than lithium in depression prophylaxis in bipolar illness, using unbiased research designs.

Special Commentary: Distinguishing grief from depression

Ronald Pies MD

As many mental health professionals may recall, there was a heated controversy over DSM-5, as the mood disorders work group debated whether or not to retain the so-called “bereavement exclusion” (BE) in the diagnosis of Major Depressive Disorder (MDD). My colleagues, Dr. Sidney Zisook, Dr. Katherine Shear, and others of our group, favored elimination of the BE for a variety of reasons, and I have provided several links on the web version of PL for further reading. Suffice it to say that the DSM-5 ultimately did eliminate the BE - which means, basically, that someone meeting the full symptom, duration, and severity criteria for a MDD within 2 months of the death of a loved one is no longer excluded from receiving the diagnosis of Major Depressive Disorder. That's really all the change means, and, based on informal feedback, I don't believe that elimination of the BE has caused major problems for most clinicians.

However, clinicians are left with the conundrum of distinguishing what is sometimes called “normal” or “ordinary” grief from major depression—though I would argue that nobody's grief is really “ordinary.” One of the arguments put forward by those who wanted to retain the BE was that it's almost impossible to tell normal grief soon after the death of a loved one (bereavement) from a mild episode of MDD. Our group disagreed. We believe that there are quite substantial differences between grief and major depression, even though there are overlapping features—and even though the two states can co-exist. That is, one can be grieving the death of a loved one and have—or not have—major depression. Conversely, one can

have major depression and be grieving - or not grieving - the death of a loved one.

It is best to conceptualize grief and major depression as separate, though overlapping realms. We can analogize them to two countries with a sector of land common to both. But whereas grief is a normal, and usually adaptive, response to a significant loss, major depression is neither normal nor adaptive—at least in its most severe forms (e.g., MDD with melancholic features). Vohringer and colleagues argue convincingly that the DSM construct of MDD is very heterogeneous, and that "...our diagnostic definitions of MDD are too diverse." In my view (RP), this marked heterogeneity is one factor contributing to the difficulty of distinguishing grief from clinically significant depression.

Moreover, there are substantial differences in the way grieving people without MDD think and act, vs. people with MDD. I have summarized these differences

in the table on the following page. Before delving into those differences, consider the following composite vignette—what would you diagnose in this case?

Mr. Smith is a 72-year-old retired businessman whose wife died after a brief illness, 3 weeks ago. He tells his family doctor, “I feel down in the dumps and weepy every day, Doc—really lousy! I don't get any pleasure out of anything anymore, even stuff I used to love, like watching football on TV. It's the same way every day. I don't enjoy life at all anymore. I wake up at 4 in the morning almost every day, and I have zero energy. I can't keep my mind on anything. I barely eat, and I've

“...there are substantial differences in the way grieving people without MDD think and act...”

lost 10 pounds since Mary passed away. I can't stand being around other people! Sometimes I feel like I didn't do enough for Mary all those years—maybe I deserved to lose her." On exam, Mr. Smith shows significant psychomotor slowing.

After reviewing the table, one can return to the vignette and make the following comments: Though it's still very early after his wife's death—and the prudent clinician may want to withhold a formal diagnosis for another week—I would be very concerned about Mr. Smith. He easily meets DSM-5 symptom and duration criteria for MDD. He has several neurovegetative features of MDD, and rather pronounced anhedonia, guilt, and lowered self-esteem. He is clearly not consoled by friends or family. A previous bout of MDD in his history, and a strong family history of depression, might tip the scales further, but I would argue that Mr. Smith's picture is consistent with MDD—not what we could call "ordinary" or "normal" grief.

PL Comment: We appreciate Dr. Pies' excellent essay. The perspective PL would add is that PL would emphasize the course of illness to differentiate normal grief from abnormal depression. This would be the case with any depressive episode in which the question is whether it is "normal" or "situational", or as used to be said "reactive" or "exogenous", as opposed to being abnormal or part of an illness (or "endogenous"). The problem is that the presence of a life stressor doesn't mean that a depressive episode is merely normal. Grief is the most common example because death and taxes come to all (at least the former), as Benjamin Franklin said. All people experience the death of a loved one. But only about 10% of the population experiences clinical depression. So why do 90%

of people *not* have clinical depression, while 10% do, with the same kind of stressor?

The best explanation is that the 10% has a biological susceptibility, absent in the 90%, to depression with the same stressor. That's the disease: the biological susceptibility, not the presence or absence of the stressor. How can one know if the biological susceptibility is present? Not by the symptoms, which can be similar whether the depression is normal or abnormal. Not by the stressor, which usually is the same. Rather, one must turn back to those classic four diagnostic validators: symptoms, genetics, course of illness, and treatment. In this case, symptoms are nonspecific and treatment is not diagnostic, which leaves genetics and course. Unipolar

depression is genetic (though "MDD" is not, since MDD is a broad invented category of many other kinds of depressive experience other than the biological unipolar

depressive illness that used to be seen as part of manic-depressive illness; see the PL website for further clarification). Importantly, unipolar depressive illness is also recurrent and episodic by definition; it doesn't happen just once, but many times. This was Kraepelin's classic diagnostic key: How do you know if it's normal depression or depression as part of an illness? Normal depression happens once, maybe twice. Depressive illness happens over and over again. Thus, while Dr. Pies' table is very informative, PL would place course at the top of the list, and emphasize it over and over again. (NB: PL prefers the term "clinical depression" to "MDD" for reasons explained in March 2015 PL issue, regarding the scientific weakness of DSM terms. Since the essay was written by Dr. Pies, the term "MDD" was retained).

"PL would emphasize the course of illness to differentiate normal grief from abnormal depression..."

Table 1. Distinguishing “Normal” Grief from Major Depression

	Grief	Major Depressive Disorder (MDD)
Definition/concept	The range of thoughts, feelings, and behaviors in response to death of a loved one, close friend or family member; or to other major loss. After bereavement [death of a loved one], grief often accompanied by culturally-based rituals of mourning.	Psychiatric illness in which distress and suffering are marked and normal function is significantly impaired; the most severe forms of MDD are “melancholic” and psychotic major depression.
Characteristic mood, affect, feeling tone	In acute form, profound sense of loss, intense sadness, longing, yearning for the deceased; tearfulness; feeling of “aching void” early in grief process. Anguish, anger, anxiety, loneliness are sometimes present, especially in initial period after loss.	Usually, profound and pervasive sense of despair, hopelessness, helplessness, gloom, nihilism, “time standing still.” Markedly diminished pleasure in nearly all activities.
Variability of mood, feelings	Changes from hour to hour and day to day; sadness, longing, tearfulness often come in “waves” or pangs in response to reminder (external or internal) of deceased; usually interspersed with periods of positive emotions, happy recollections & memories of deceased. Bereaved is usually “consolable” by friends, family.	Very little change from day to day; positive feelings diminished or absent (inability to experience positive emotions is hallmark of major depression); markedly depressed mood most days of the week for > 2 weeks. Rarely consolable by friends, family.
Sleep, appetite	Bereaved may have trouble falling asleep because thoughts of deceased are triggered, e.g., if bed previously shared with deceased, or by rumination about troubling aspects of the death. Awakenings may occur but sleep physiology usually normal. Appetite and usual scheduling of meals may be disrupted by heightened emotionality related to reminders of the deceased. Weight loss usually minimal.	Early morning awakening (e.g., 4 a.m.) is classic finding. (Rarely: excessive sleep/hypersomnia). Reduced REM latency (time to REM sleep from sleep onset), and increased amount of REM sleep commonly found. Loss of appetite often leads to significant weight loss. (Rarely: weight gain in “atypical” depression). Anorexia often severe, with substantial weight loss (>10 lbs).

Table 1. Distinguishing “Normal” Grief from Major Depression (continuation)

	Grief	Major Depressive Disorder (MDD)
Energy, psychomotor change	Intense emotions may disrupt sleep and interrupt the bereaved person's usual rhythm of daily life. In some cultures, dramatic expressions of grief resemble psychomotor agitation but are more ritualized.	Often marked slowing of mental processes & decreased energy; markedly decreased or increased motor activity (e.g., speech volume and output greatly diminished; marked agitation, hand-wringing, twisting hair, etc.).
Reality testing	The recently bereaved may transiently appear “lost” or confused; may briefly hear voice or see image of deceased; but is in touch with other aspects of reality (not delusional).	Severe MDD with psychosis may show delusions of bodily decay, “rotting away”, being “punished by God”; may experience derogatory auditory hallucinations.
Self-image	Self-esteem largely preserved though often with feelings of identity and/or role confusion; Guilt or remorse is common but usually fleeting and focused on the deceased (e.g., “If only I had said or done X...”)	Self-loathing, feelings of worthlessness, being an “unforgivable” person or “terrible sinner;” profound, corrosive guilt without evident reason.
Thoughts of death, dying	Sometimes, feelings of not wanting to live without the deceased; or fantasies of “re-uniting” with deceased; usually without suicidal plans or intent.	Suicidal ideation and plans are common; person may feel, “I don’t deserve to live.”
Social/vocational function	Early in bereavement, socializing may feel difficult, but bereaved usually desires, enjoys company of friends & family, at times. Feelings of disconnection from others may occur, but deeper emotional bonds usually preserved. Vocational function usually maintained, but person often distracted at work, preoccupied by loss.	Social withdrawal often profound; person feels deeply estranged from others; may isolate self in room; refuse any visitors. Vocational function usually significantly impaired, often with missed work days.
Course/Outcome	Typically, acute grief evolves over time, though progression is erratic; no “set” duration for acute grief. <i>Integrated grief</i> is often life-long, but grief is transformed such that bereaved person is able to re-engage with life, with “bittersweet” acceptance of loss.	Variable duration, often lasting many months and sometimes years, if not adequately treated. In general population (naturalistic data), median duration of major depressive episode is about 3 months. Suicide is outcome in around 4% of those with major depression.
Treatment	Support, guidance, education, may be helpful, but grief is not a mental disorder and needs no professional “treatment.”	Usually requires professional treatment, either with psychotherapy, medication, or both. Melancholic subtype less responsive to psychotherapy.

Classic Study of the Month: *Lamotrigine prevents manic episodes*

A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder.

G. Goodwin et al, J Clinical Psychiatry. 2004, 65(3):432-441

A pooled analysis shows more efficacy than placebo

In this PL issue, we have focused on lamotrigine, and rebutting the marketing dogma that there is something special about it mood stabilizing “from below.” Rather, the PL analysis is that lamotrigine is less effective at preventing mania than depression, but it is not more effective in preventing depression than lithium, for the reasons given above. However, the false conclusion is drawn sometimes that since lamotrigine only stabilizes “from below”, then it doesn’t have any appreciable preventive effect on manic episodes. Some clinicians would conclude then that lamotrigine should not be used by itself in monotherapy of bipolar illness because it only prevents one pole of the illness (depressive episodes), not the other (manic episodes).

In this analysis of the two major lamotrigine prophylaxis trials, the data were pooled to add up to n subjects. Granted this analysis was conducted by Glaxo, the maker of that agent, but the analysis can be reviewed on its own merits. When pooled, lamotrigine was more effective than placebo, with statistical significance. When studies have to be pooled to get large numbers so as to achieve statistical significance, this usually means that the effect size is small. So the claim is not that lamotrigine robustly prevents manic episodes, but that it is better than nothing (placebo).

A warning about bipolar illness type II: Many clinicians infer that lamotrigine can and should be

used in type II bipolar illness, given its depression better than mania prophylaxis profile. But lamotrigine is not FDA-indicated in type II bipolar illness. And the issue is not so much the severity of the manic symptoms (although that can be relevant) but the frequency of episodes. Thus if a patient has numerous hypomanic episodes, such as in rapid-cycling illness, lamotrigine will not be very effective, despite the presence of many depressive episodes. Again, clinicians should understand they are treating the cycling, not each episode pole in isolation of the other. In fact, two randomized trials have shown that lamotrigine monotherapy is ineffective versus placebo in rapid-cycling bipolar illness (just as all mood stabilizers are ineffective in rapid-cycling bipolar illness in monotherapy).

The clinical inference would be that if a patient has mild or infrequent manic episodes (or hypomanic episodes), then lamotrigine monotherapy could be effective for that person.

The PL Bottom Line

- Lamotrigine prevents manic episodes in monotherapy more than placebo.
- Lamotrigine can be given in monotherapy, as long as manic episodes are infrequent and/or not severe.

Drug of the Month: Paroxetine (*Paxil*)

The worst withdrawal

Biological mechanism

Paroxetine is a serotonin reuptake inhibitor (SRI) with some additional anticholinergic effects. It has a short half-life, which probably implicates its main problem, very severe serotonin withdrawal syndrome. A slow-release form (*Paxil CR*) exists, but it doesn't provide much likely benefit in terms of lower serotonin withdrawal.

Clinical efficacy

Paroxetine is FDA indicated for major depressive disorder, generalized anxiety disorder, obsessive-compulsive disorder and panic disorder. It was introduced in the mid 1990s in the US after fluoxetine (*Prozac*) and sertraline (*Zoloft*). It struggled to find a niche in the clinical market, eventually emphasizing its anxiolytic effects.

It is the best studied SRI in bipolar depression, with multiple studies demonstrating a low mania switch rate, as well as complete lack of efficacy.

Dosing

Typically efficacy is found at 20-40 mg/d, with a range of 10-60 mg/d. Lower doses are more purely anxiolytic, with pure serotonin reuptake blockade. Higher doses (probably beginning at 30 mg/d and higher) produce norepinephrine reuptake blockade, similar to venlafaxine.

Side effects

Like all SRIs, this agent has notable sexual dysfunction. It can be somewhat more sedating than other SRIs, probably due to its anticholinergic effects, and, unlike most other SRIs, it can have some weight gain.

Serotonin withdrawal syndrome

This withdrawal syndrome has become an increasingly troubling long-term effect of SRIs. In the PL experience, if any SRI is given for longer than one year, then there is likely to be some serotonin withdrawal syndrome upon its discontinuation, even with slow tapering.

Half-life seems relevant for some agents, like venlafaxine, which have severe withdrawal effects. It is unclear why paroxetine (21 hour half-life) and duloxetine (12 hour half-life), also have severe withdrawal syndromes. The agent with the longest half-life agents, fluoxetine (4-6 days), has the least withdrawal syndrome.

The PL Bottom Line

- Paroxetine is a standard SRI for efficacy, with strong anxiolytic effects and some benefit for some types of depressive states.
- It has low mania switch risk but is ineffective in bipolar depression.
- It has the worst serotonin withdrawal syndrome of all SRIs.

Case of the Month:

Adolescent bipolar illness

The following history is provided by a colleague treating a patient recently admitted to hospital:

Case Presentation

A 15-year-old male is admitted after banging his head on the wall and floor such that he put a hole in the wall. He comes from a high functioning professional family. His mother reports that the boy was "bipolar at birth;" i.e., screaming because he wasn't getting enough breast milk but refusing the bottle. He had prolonged 1-2 hr rages in early childhood, sometimes 2 to 3 times per day. Until a few years ago, he attacked his mother during those rages. Then he switched to self-injury.

He was diagnosed with bipolar illness at age 7 and treated with medications. His mother reports that "until then he never had a normal night's sleep."

He has classic seasonal affective disorder, getting depressed in the autumn & early winter, and starting to improve in the spring, becoming euthymic in the summer. Recently, this fall, he was okay during the day but became severely depressed and suicidal as the sun starts going down. Has been doing light therapy in the morning for a few years, which is "somewhat helpful."

Past medication treatment has been extensive. He did well on aripiprazole 7.5 mg/d and bupropion SR 300 mg per day. He has been hypomanic in the past on bupropion XL and also on Prozac. He did well on lithium for a year; but it was stopped 4-5 years ago by a child

psychiatrist who didn't want to use it. A brief trial of divalproex was stopped due to excessive sedation. He sleeps well on melatonin 3mg. If he doesn't take it he will be up for 5 hours or more.

He was a "total pussycat" at school, well liked by teachers and kids, and with good grades. In the hospital unit, he also behaved quite well.

On admission, lithium was restarted, and we discussed possibly taking him off bupropion in the summer to see if it is necessary. Light therapy was moved to early afternoon since it has been reported that it may be better for bipolar depression, and amber glasses were added in the evening to help with evening depression.

He reports improvement in his evening depression but it isn't clear whether he was really better or simply wanted to be discharged. Transfer to residential care was discussed.

He was eventually discharged to outpatient care on lithium 900 mg/d (level 0.9), aripiprazole increased to 10 mg/d, and bupropion SR 300 mg/d, along with light therapy as above.

The consultation questions are:

What are your thoughts about bupropion SR?

He became hypomanic on XL, and on fluoxetine, and parents are wondering if he should be on an antidepressant at all. What about a lamotrigine trial when his mood stabilizes in the summer?

Is the light therapy appropriate?

PL Commentary

Antidepressants have been proven ineffective in bipolar depression. There is absolutely no reason to use them. Further, they cause rapid-cycling in about one-third of subjects, thereby worsening the illness. In that sense, they are mood destabilizers, counteracting the benefits of mood stabilizers. In this case, bupropion should be stopped without doubt. It doesn't matter what formulation it is, the chemical molecule is the same. Since he got into a hypomanic episode on bupropion (and fluoxetine) in the past, he has bipolar illness by definition (assuming the hypomanic episode was correctly diagnosed). DSM-5 has removed the antidepressant exclusion for bipolar illness, as it should have, since many studies show that manic and hypomanic episodes happen commonly in persons with bipolar illness (10-20% or more) and very uncommonly in non-bipolar depression (<1%). Thus, the diagnosis likely is bipolar illness based on that central aspect of the history.

If this diagnosis is correct, the main PL recommendation would be to taper off bupropion over about 2 weeks, to continue lithium plus aripiprazole, and then to see how the course of the illness evolves. It may be that a second mood stabilizer might be needed, whether lamotrigine or valproate, or a different dopamine blocker may be needed in place of aripiprazole, like lurasidone or asenapine. But whatever combinations of second messenger modifiers plus dopamine blockers are used, they will not be effective in the

presence of the mood destabilizing effects of bupropion. Nothing will work unless bupropion is stopped.

Light therapy in the fall can be an important added intervention for the seasonality of bipolar illness. It is just as important to provide reduced light exposure in the spring and summer, as discussed in January 2015 PL issue.

Lamotrigine can be given at any time, but it is useless unless bupropion is stopped. Once the mood destabilizing effects of bupropion are removed, he may respond better to his current regimen, and not need other added agents. It's possible also that lithium and/or aripiprazole doses can be reduced in the absence of bupropion.

In short, when you have some medications that help an illness (lithium and aripiprazole) and some medications that harm an illness (bupropion), the former work better in the absence of the latter.

PL Reflection

Science and opinion are different.
Science is the father of
knowledge, while opinion breeds
ignorance.

Hippocrates

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THE PSYCHIATRY LETTER

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Mixed States

In this issue, PL addresses the general issue of mixed mood states, as mentioned in a number of prior issues. This topic is complex but, in the PL viewpoint, it is central to a new and powerful way of thinking about the diagnosis and treatment of so many patients with mood and anxiety symptoms. This issue presents these ideas more systematically than has been the case either in prior issues or on the PL website. Due to the complexity of the topic, it is discussed in two PL issues, part I on diagnosis now and part II on treatment next month.

In this issue, we also have a new guest columnist, Ed Mendelowitz PhD, who discusses the basic perspective of existential psychotherapy.

The Article of the Month relates to the concept of mixed states, discussing a new systematic review on the concept of psychomotor excitation, or activation, as being the core feature of mania. The Drug of the Month is ziprasidone, a unique dopamine blocker which also is a serotonin and norepinephrine reuptake inhibitor. By the Numbers provides summary numbers for clinicians to know and think about in relation to diagnosis of mixed states.

Through our collaboration with PeerPoint Inc, we continue to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to psychiatrists and nurses and psychologists.

If you find PL helpful to you and your patients, please let others know so that more clinicians and patients may benefit.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Mixed States - Part I: Diagnosis

A key concept for understanding “depression”

Definitions

A key issue in understanding the phenomenon of depression is knowing how it contrasts with mania. One approach is the DSM approach: compare this number of criteria versus that number of criteria for this or that amount of time. This is how most clinicians are taught. What they don't realize is that the DSM definitions are based on very broad concepts of depression and very narrow concepts of mania. We'll return to this idea.

For now, let's go the classic psychopathology literature and ask the question, decades and centuries before DMS-III in 1980: How did the great thinkers of medicine and psychiatry define depression versus mania?

The answer is simple: Depression meant a slowing down of one's thinking, feeling, and moving. Mania meant a speeding up of one's thinking, feeling, and moving. Translated to current terms, depression was equivalent to psychomotor slowing and mania was equivalent to psychomotor excitation.

Mood is secondary

Readers will note that in this classic psychopathology, mood is not central to the definitions of depression or mania. Psychomotor slowing can come with sad mood, or it can come with normal mood. One sees this kind of depression in the classical seasonal depression of the fall/winter: patients describe loss of motivation and anhedonia but not sadness of mood. Similarly psychomotor excitation can come with euphoric mood, or it can come with

irritable mood, or with sad mood, or with anxious mood, or with none of the above.

The term “mood disorders” is false in both words. The term “disorder” is a DSM phrase that is applied to all conditions so as to produce a purposeful vagueness (in an effort to be “atheoretical”), as discussed in the May 2016 PL issue. The use of “mood” implies that a mood change is central to these conditions, whereas in fact psychomotor activity appears to be central and primary; the mood experiences is epiphenomenal and secondary. Perhaps the older term “affective” would be preferable, as it implies a larger and more complex construct as opposed to the subjective mood experience.

For our purposes, this distinction is important in understanding mixed states. In the article of the month, PL reviews a newly released systematic review that provides the empirical evidence in support of this classic psychopathology. Specifically, it shows how psychomotor excitation or activation is central to the phenomenon of mania.

If mania is thus understood, as opposed to solely accepting the DSM criteria, then some major changes follow in our understanding of affective states like depression.

The primacy of mania hypothesis

Athanasiou Koukopoulos was a Greek psychiatrist, who practiced most of his life in Rome. He passed away a few years ago, after about 50 years of active clinical practice in a prestigious private practice in Rome. He published some of his observations and ideas over

the years, and, in his last decade, he summarized his central thinking in the theory of the “primacy of mania.” On this theory, depression is the effect of mania. Mania is the cause, the primary driver, of depression. This idea turns traditional psychiatric thinking upside down in at least two ways. It has been taught for a century that mania is a “flight from depression,” that manic states are superficial reactions to not being able to acknowledge and experience the painful state of depression. As with most psychoanalytic thinking, there has never been any empirical scientific proof of this hypothesis. In current DSM-based thinking, depression (MDD) and mania (bipolar disorder) are viewed as two distinct and separate conditions. They overlap in symptoms of depression, but they are different “disorders” and are assumed by most clinicians to be different illnesses. As discussed in many PL issues and the PL website, this DSM belief

contrasts with the older Kraepelinian theory of manic-depressive illness (MDI), which

held that all depressive episodes and manic episodes were part of the same illness, MDI. In other words, unipolar depressive illness was the same disease as bipolar illness. Koukopoulos adds a twist to this Kraepelinian idea. He holds that depressive episodes do not happen unless they are preceded by or caused by manic episodes or symptoms. *Mania is the fire, depression is the ash.*

Defining mixed states

Another large category of persons with depressive episodes have manic episodes during the depressive episodes, i.e., mixed states. This group of patients was of most interest to Koukopoulos. These mixed states can be defined in different ways, outside of DSM constraints. The simplest approach is the “bipolarity specifier” described by Benazzi; on this definition a mixed state would be

defined by a clinical depressive episode in which three or more DSM-defined manic symptoms occurred for any amount of time (not limited to the 4 days or longer DSM criterion of duration for hypomania or one week or longer for mania). On this definition, Angst and colleagues found that 47% of a large sample of 5635 outpatients with depressive episodes met the mixed state definition. One could also use Koukopoulos’ own definition of “mixed depression”, which is even broader than the bipolarity specifier because it goes beyond DSM criteria. In Koukopoulos’ definition, as described in more detail below, mixed depression involves the presence of a clinical depressive episode along with psychomotor excitation, which can be limited to psychomotor agitation and/or marked rage. Using Koukopoulos’ definition of mixed depression, in his own Rome clinic, 51% of 435 consecutive patients with clinical depressive episodes had mixed depressive states.

“Mania is the fire, depression is the ash...”

If we combine the approach of Angst and Benazzi on one hand, and Koukopoulos on the other, we can conservatively estimate that about 50% of all depressive episodes are mixed with manic symptoms, and thus are mixed states, not pure depression. The theory of the primacy of mania would apply if we accept the notion that these mixed states are driven by their manic components; in other words, one cannot separate the depressive from the manic symptoms; they come from the same pathophysiological source. Without the manic symptoms, the depressive symptoms would not occur.

So here are another 50% of depressive episodes, the largest chunk, which would not happen without mania. Combined with the 15% of classic manic-depressive cycles in bipolar illness, we account for the majority, 65%, of depressive

episodes so far, meeting the definition of the primacy of mania.

Affective temperaments

What about the remaining 35%? Are they purely depressive cases, so-called “unipolar” depression? Now we turn to the concept of affective temperaments, described in detail in the June 2016 PL issue. The idea was that mild mood symptoms could occur in persons with mood illnesses, in between the severe episodes, and these mild symptoms were present all the time, as part of one’s temperament. These conditions were defined as dysthymia, hyperthymia, cyclothymia (mild depressive, manic, and manic-depressive symptoms, respectively). In various studies, it’s been found that manic temperaments - hyperthymia or cyclothymia - are present in about 1/3 of persons with recurrent unipolar depressive episodes. If so, these calculations would explain one-third or so of the 35% of remaining persons with depressive episodes (i.e., about 12%). We now have explained 77% of all persons traditionally diagnosed with severe clinical depressive episodes (50% + 15% + 12%). This would be almost 4 out of 5 of such persons.

Affective temperaments appear to predispose to a later risk of depressive episodes. Often these depressive episodes are mixed with manic symptoms, in the case of cyclothymia and hyperthymia, because the baseline manic symptoms of those temperaments remain, and are mixed with new onset depressive episodes. Sometimes, people with cyclothymia and hyperthymia have pure depressive episodes, not mixed states. Often these depressive episodes are of the melancholic type.

[DSM-5 MDD with mixed features is] like excluding pain in the head from a diagnosis of headache..."

Thus, affective temperaments are relevant in two ways: 1) If present, patients often have mixed states when they become depressed; 2) many people with pure or melancholic depressive episodes have manic temperaments before or after their depressive states. In the latter case, Koukopoulos would argue that long-standing hyperthymic or cyclothymic temperaments predispose such persons to depressive episodes. Again, manic symptoms cause depressive symptoms.

Neurotic depression

This leaves 23% of people with clinical depression. As noted on the PL website, “MDD” is not the same thing as unipolar depression. Unipolar depression was seen always as a subtype of manic-depressive illness: it was severe, episodic, recurrent, highly genetic, and biological. In contrast, neurotic depression was mild, chronic, and not highly genetic. The PL view is that the remainder of depressed persons would be of the neurotic variety, with brief severe exacerbations leading to clinical attention. This group of depressed patients does *not* have mixed states. They are notably anxious, but they are not markedly agitated, and not rageful or impulsive.

DSM-5: MDD with mixed features

In DSM-5, there is acknowledgment of much of this work demonstrating that mixed states occur in depressive episodes that are diagnosed as MDD, without full DSM-based manic episodes allowing the diagnosis of bipolar illness. Thus, mixed episodes as a subtype of bipolar disorder was removed from DSM-5, and replaced with mixed features which could be applied to both bipolar disorder and MDD. MDD with mixed

features was limited, however, on conceptual grounds, to “non-overlapping” symptoms. Thus, if a patient has depression, they cannot be diagnosed as having mixed features according to DSM-5 if they also have psychomotor agitation, irritable mood, or distractibility. Those manic symptoms are excluded from the mixed features definition in MDD. The only manic symptoms that can be used are classic euphoric ones, such as euphoric mood, grandiosity, flight of ideas, along with evidence of increased energy, such as increased goal-directed activities. The problem with this DSM-5 approach is that it excludes the most common manic symptoms that occur in mixed states, namely: psychomotor agitation, marked anger/irritability, and distractibility. This would be like excluding pain in the head from a diagnosis of migraine. Thus, the DSM-5 mixed concept has been criticized by the primary researchers in mixed states as being, as is typical with DSM, based on conceptual concerns (a narrow definition to avoid “overdiagnosis) as opposed to following the empirical, scientific evidence (allowing those symptoms that are most common in mixed states to be included in the diagnosis).

Clinical Scenarios

So what are the clinical scenarios of these different kinds of mixed states? Here are typical examples of how patients would present:

Bipolarity specifier (Angst and Benazzi): These patients have brief manic periods, lasting hours to days, as part of a longer depressive episode. Thus, a person might be severely depressed for 2 months, with low sleep and appetite and interest and energy, and then suddenly for a weekend he has high energy and is sexually impulsive and talking fast, and then he has another 2 months of low sleep and appetite and interest and energy.

Mixed depression (Koukopoulos): These patients are markedly agitated, highly angry and rageful, and very labile in mood, alternating from angry to sad to tearful. These symptoms are constant for months on end, along with classic depressive symptoms (low energy, appetite, interest, sleep, concentration).

Mixed hypomania (DSM-5): MDD with mixed features excludes the classic irritability and agitation of Koukopoulos’ mixed depression. It also excludes the brief manic states of Angst and Benazzi’s bipolarity specifier. In effect, it represents a hypomanic state with some depressive symptoms, rather than a depressive state with some manic symptoms (as in the other two mixed states above). These patients are energetic and grandiose and highly active most of the time, but have dysphoric mood and some depressive symptoms like poor appetite and guilt.

Summary

In summary, mixed states are an important concept to understand when thinking about “depression.” The DSM approach to life tries to force all patients into one of two categories: depression or mania. (Hypomania is just mild mania, and captured in the same category, just as mild depression -to be consistent we should speak of “hypodepression” - is part of the category of depression). Instead, a large clinical and scientific literature supports the view that most mood states are mixed states, not purely depression or mania, but both. Often the depressive features predominate but notable manic symptoms of psychomotor excitation are present. In the DSM-based ideology, mania is restricted to a very small definition, excluding the classic psychopathology of psychomotor excitation (often referred to colloquially as “agitation” or “stimulation”, but then not seen as “manic”). The classic pre-DSM tradition in psychiatry, dating to Kraepelin, can be

supported with newer research by thinkers like Koukopoulos. This literature resuscitates the concept of psychomotor excitation as being diagnostically very important, and as identifying mixed states. Further Koukopoulos' hypothesis that mania causes depression can be supported by the high frequency of manic states occurring either just before or during depressive states, as reviewed above (with the proviso, in the PL view, that neurotic depression is a different condition in which manic states are not present).

Treatment

In next month's PL issue, we will review the treatment of mixed states, highlighting the problems when these mixed states are misdiagnosed only as "depression" and treated with so-called antidepressants. It will be shown that the latter agents worsen these mixed states and that dopamine blockers and second messenger modifiers (mood stabilizers) improve mixed states. This issue emphasizes the point that these mixed states occur primarily in patients diagnosed with "MDD", not in bipolar illness. This key point is central to understanding the diagnosis and treatment of mixed states.

The PL Bottom Line

- Mixed states are the most common type of mood states
- They occur in about one-half of depressive episodes, even in patients diagnosed with "MDD," i.e., not bipolar illness.
- Mixed states may reflect the primacy of mania, meaning that manic symptoms or episodes caused depressive symptoms or episodes.
- Neurotic depression may be an exception to the concept of the primacy of mania.
- Manic temperaments are common in persons with depressive episodes, often leading to mixed states.
- MDD with mixed features in DSM-5 is narrow on conceptual grounds, while broader mixed state definitions have stronger research evidence for them.
- Mixed states are key to the proper diagnosis and treatment of "depression."
- Treatment implications will be discussed in detail in the next PL issue.

PL Reflection

We work in the dark.
We do what we can.
We give what we have.
Our doubt is our passion.
And our passion is our task.
The rest is the madness of art.

Henry James

The Middle Years, 1893

Current Study of the Month: *Agitation/activation is mania*

Activation in bipolar disorders: A systematic review. J. Scott et al, *JAMA Psychiatry.* Published online December 21, 2016.

A confirmation of classic psychopathology

This systematic review examined 56 studies of the psychopathology of bipolar illness, using different methods, such as factor analysis (29 studies), or actigraphy (20 studies), among other methods.

Factor analysis is a statistical method used commonly to analyze symptoms. Basically, this approach quantifies if and how much certain symptoms group with other symptoms. For instance, in clinical depression, the symptom of insomnia will tend to group with the symptom of low energy. If a patient has one symptom, she will tend to have the other. Those symptoms will load onto a single factor, which might differ from other symptoms (such as suicidality) that might not occur commonly or regularly along with insomnia and low energy. The number of factors found can be added up to explain all the symptoms in a study (the “variance”, which reflects how many symptoms are observed and how much they correlate with each other).

Overall, these studies identified 2 to 7 factors in the psychopathology of mania, which explained 52% of the variance (meaning they explained about half of the observed symptoms; the other half can be seen as being extremely variable and now loading onto any factors of notable size). The top two factors in these studies were examined, and consistently, the most common or primary factor was psychomotor activation. This was a separate factor from mood (elation or depression/dysphoria), which was the second most common factor. Some studies included mixed

“...psychomotor activation is the most common and primary psychopathology in pure mania...”

manic states, and reported that depressed/dysphoric mood was the primary factor, with activation being a secondary factor. In both cases (pure mania and mixed mania), activation was a separate factor from the mood state (euphoria or dysphoria).

In the actigraphy studies, which involve wearing a device that measures and records one's physical movements, it was found that mean daytime activity was higher in manic states than in depressive or euthymic states, as one might expect. It was interesting that an even more consistent finding was that there was more variability to activity levels in manic states, compared to depressed or euthymic states. In other words, activity was more unpredictable and less rhythmic in manic states, compared to depression or euthymia. One conclusion one could make is that “goal-directed” psychomotor activity is increased in mania, but perhaps more commonly, it is agitated and unpredictable in nature.

The PL Bottom Line

- Psychomotor activation is the primary abnormality of pure mania.
- Psychomotor activation is a separate factor from mood state in mania.
- Increased “goal-directed” activity is present in mania, but unpredictable agitation is even more common.

Drug of the Month: Ziprasidone

A combined dopamine blocker (antipsychotic) / monoamine agonist (antidepressant)

Biological mechanism

Ziprasidone is a dopamine-2 and serotonin-2 receptor blocker, with potent norepinephrine and serotonin reuptake inhibitor effects. The latter monoamine reuptake effects are equivalent in potency to imipramine, a classic tricyclic antidepressant.

Clinical efficacy

Ziprasidone is FDA indicated for schizophrenia and mania. It has been shown to be effective in mixed depression, but it was found to be ineffective in two randomized trials of acute bipolar depression. Many

clinicians have the experience that it is not effective enough for severe psychosis or mania, but can be effective for moderate cases. It seems to have benefit for depressive states based on the mixed data above, but the negative bipolar depression studies should be noted. Its large dosing range, along with varying biochemical effects based on dose, as described below, have made it complicated to use. It has an intramuscular injectable formulation for acute agitation.

Dosing

Like most dopamine blockers, its dopamine blockade is dose-related in a curvilinear fashion, reaching classic antipsychotic thresholds of 80-90% dopamine blockade at 80-160 mg/d. In

contrast, its potent norepinephrine and serotonin reuptake inhibition is present at all doses. Thus, at low doses, it has more antidepressant-like, and less anti-manic or antipsychotic, properties.

Side effects

The most common side effect is akathisia, which is dose related. Other parkinsonian side effects also can occur. Ziprasidone does not have any cardiovascular or diabetes harms, nor does it cause weight gain. In the CATIE study, it was the agent with the best profile on lipid and diabetes parameters and in weight. It does increase QT length, which can increase the risk of cardiac arrhythmias. Due to its monoamine reuptake effects, it has been reported to cause manic episodes in some persons, and it may have some risk of serotonin withdrawal syndrome.

The PL Bottom Line

- Ziprasidone has norepinephrine and serotonin reuptake blockade, like tricyclic antidepressants.
- It isn't effective for severe psychosis or mania, but can help moderate states.
- It works in mixed depressive states.
- It has no metabolic harm or weight gain, but it can cause cardiac arrhythmia.

Fast Facts: Ziprasidone

Typical dose: 80-160 mg/d

Biological mechanism: Dopamine/serotonin blockade plus norepinephrine/serotonin reuptake blockade

Typical side effects: akathisia

Medically important side effects: cardiac arrhythmia

Guest Column

Existential Psychotherapy: The uses of adversity

Edward Mendelowitz PhD

Clinical Psychologist, Quincy MA

A Consultation

Dr. Reilly: You have reason to believe that you are very ill?

Edward: I should have thought a doctor could see that for himself. Or at least that he would enquire about the symptoms. Two people advised me recently, almost in the same words, that I ought to see a doctor. They said—again, in almost the same words—that I was on the edge of a nervous breakdown. I didn't know it then myself—but if they saw it I should have thought that a doctor could see it.

Dr. Reilly: "Nervous breakdown" is a term I never use. It can mean almost anything.

T. S. Eliot, *The Cocktail Party*

According to existential perspectives in psychology and psychiatry regularly considered in the *Psychiatry Letter*, it may be suggested that the greatest proportion of human strife fundamentally relates to our existential predicament, whether in terms of the inherently overwhelming nature of this predicament or in terms of the constriction necessitated by too rigid an attempt at its suppression. This basic premise is implicit throughout the works of the late existential psychologist and author Rollo May, who observed that we defend much more vehemently against thoroughgoing existential awareness than, for example, instinctive drives. The psychoanalyst Allen Wheelis wrote in this regard of "problems of being," suggesting further that the typical doctor/patient arrangement does

not entirely apply to the psychotherapist's consulting room. Clinically speaking, it makes sense to view the individual, insisted Freud's erstwhile colleague and confidant Otto Rank, as a "suffering being" rather than as merely instinct-ridden or determined exclusively by her or his past, present distress, or otherwise clinically disordered mind. Our problems reside in our very arrival on the planet.

Although this perspective may be more or less implicit in the literature of existential psychiatry/psychology, it contrasts significantly with clinical perspectives that view psychological problems as deviations from some standard of presumed normalcy. It differs, too, from perspectives that seek to locate the source of conflict exclusively in historical events or distorted thoughts. These are very likely to be aspects of the problem, yet the fundamental problem may well be life itself. An examined life presses the individual into an encounter with existence (from the Latin *ex sistere*: "to stand forth," "to emerge") and demands a worthy response. Psychotherapy today not infrequently is presented with less clear-cut symptoms than was once the case. The finding that individuals frequently embark on psychotherapy out of feelings of purposelessness, boredom, diffuse anxiety, and vague feelings of dissatisfaction points to the existential bases of a great deal of psychological disturbance. Those who are honest with themselves (the most common lie, observed Nietzsche, is the lie that we lie to ourselves) will be aware of such feelings, and in this regard we must conclude that there is more similarity than difference between therapist and patient. Psychotherapy clients do not necessarily present with explicitly existential agendas but, rather, embark upon therapy with all manner of "everyday," as opposed to "ontological," concerns. From an existential vantage point, the therapist is attentive to the manner in which even these

normative foci may manifest presentations of deeper confrontations with life and the world. "Psychotherapy," writes May, "reveals both the immediate situation of the individual's sickness and the archetypal qualities and characteristics which constitute the human being as human." Effective psychotherapy is attuned not only to clients' stated complaints but also to underlying bedrock existential themes.

Existential psychotherapy is attentive to what everyday life attempts so vehemently to ignore. Through struggle and fortitude, we are capable of fashioning something uniquely meaningful out of our unique sufferings and shared fleeting, finite selves. Although the "theory" of existential psychotherapy may appear abstrusely philosophical (or, conversely, conceptually lean) as contrasted with more conventionally formulaic approaches, we may understand such an approach is more an attitude than a circumscribed system of

knowledge or thought. Existential psychotherapy is interested in all the extant theories, but these are nonetheless bracketed and left behind upon entering the consulting room. Theory, though important, is secondary to the phenomenological moment and to the real encounter between client and therapist. Otto Rank once remarked, provocatively, that all theory was essentially dead, referring as it did to something found in the past and thereby occluding what was unforeseen—the moment unfolding in the here and now. Technique can be a protection from consciousness just as easily as an extension of the same. Fanatical attention to theoretical conjecture, from this point of view, may well be a flight from that which is most essential: the immediacy of experience and the anxiety and possibility that inhere in the acceptance of

"Existential psychotherapy is attentive to what everyday life attempts so vehemently to ignore..."

responsibility for the turbulent creation of a more conscious self.

"But I do urge that we not let the drive for [objectivity] put blinders on us and cut off our range of vision so that we miss the very thing we set out to understand—namely, the living human being. We must go beyond the naiveté of the faith that if we can only get somehow and ultimately to the 'bare empirical facts' we shall at last have arrived safe and sound in the harbor." Rollo May, *Psychology and the Human Dilemma*

PL Commentary: Dr. Mendelowitz studied under Rollo May, whose ideas he describes here, back in the 1980s. May was a psychologist who is acknowledged as the leading American thinker in the field of existential/humanistic psychology and

psychiatry. May himself had studied under the existential theologian Paul Tillich, an emigre from Germany in the 1930s. Beginning in the 1950s, May introduced the German and French existential literature to American clinicians. He wrote a number of well-received books throughout the following decades, all of which, especially *Man's Search for Himself*, are recommended to PL readers. After May's death in 1994, his legacy has been carried on by Ed Mendelowitz, whose expertise in literature and film theory produce his unique take on existential psychology. Widely published in psychology journals, Ed Mendelowitz was the recipient of the American Psychological Association's 2016 Rollo May award, given for lifetime achievement in humanistic psychology. PL appreciates Dr. Mendelowitz' essay and hopes share more of his columns with PL readers in the future.

By the Numbers

Mixed States - Diagnosis

Frequency of mixed states defined as a full clinical depression with some manic symptoms ("mixed depression" or the "depressive mixed state"), as discussed in the Special Article. Percentages refer to frequency of all "major" depressive episodes (MDEs; percentages are rounded):

In DSM-defined "MDD": 50%

In DSM-defined bipolar disorder type I: 50%

In DSM-defined bipolar disorder type II: 60%

Most common manic symptoms in mixed depression:

Psychomotor agitation: >90%

Marked anger/rage/irritability: 80%

Flight of ideas/racing thoughts: 50%

Distractibility: 50%

Grandiosity: 20%

Euphoric mood: 10%

Frequency of DSM-5 defined "MDD with mixed features," as percentage of all MDEs: 10%

Frequency of "mixed depression," as defined in Special Article (using bipolarity specifier or Koukopoulos' criteria), as percentage of all MDEs: 50%

Frequency of mood episodes in unipolar depression and bipolar illness combined:

Pure depression: 20%

Pure mania: 20%

Mixed states (mixed depression and dysphoric mania): 60%

Curbside Consults

Questions and cases from you

Question: Is there sufficient evidence to recommend lithium, divalproex, carbamazepine, or a dopamine blocker as the first drug of choice in a particular bipolar patient? For example, divalproex/ziprasidone over lithium for a mixed, dysphoric bipolar depression or lithium for the MDI pattern (mania, M, followed by depression, D, followed by a normal interval, I) patient with euphoric mania?

PL: In general the PL view is that if we were to generalize to the average patient with bipolar illness with the most common types of symptoms, all other things being equal (i.e., proneness to side effects, medical illnesses), lithium is the most proven and most effective second messenger modifier overall.

All other things being equal, the PL view is that lithium is the "drug of choice" for bipolar illness.

The reasons for this general preference for lithium are as follows: Lithium is the most proven agent for prophylaxis, both for depression and mania. No agent is proven more effective than lithium for prevention of either pole, including lamotrigine for depression (see the prior PL issue, January 2017). Unlike other second messenger modifiers lithium has the added benefit of being the only agent proven to prevent completed suicide. Further, unlike other agents in this class, lithium is the only agent with notable evidence of dementia prevention and of biological neuroprotection benefits in animals and humans in replicated studies. Lithium also is the only agent proven to reduce overall mortality, extending the average lifespan in bipolar illness by a decade (due to reduced cardiovascular mortality as well as suicide prevention). Many of these lithium benefits occur at low doses, as discussed

on the PL website, and thus low-dose lithium (300 mg/d or less) can be considered for all patients with bipolar or unipolar mood illness, for these proven or likely mortality reduction and dementia prevention benefits.

However, there are some provisos to this general recommendation, and there are some specific situations where other agents might be preferred to lithium. In the acute mixed manic episode, divalproex and carbamazepine are proven more effective than lithium. In rapid-cycling bipolar illness, lithium alone is proven ineffective (as is divalproex alone and lamotrigine alone), but lithium should be combined with divalproex or carbamazepine. Regarding other patterns of course (mania followed by depression or depression followed by mania), that literature is mostly observational and PL would not draw strong conclusions. With active severe substance abuse comorbidity, divalproex has somewhat more evidence of benefit than lithium.

Perhaps the most important issue with lithium is its long term renal impairment. The risk is about 1% at 20 years of treatment, as reviewed on the PL website. This risk can be lowered by giving lithium once daily, which reduces constant renal exposure to lithium levels, and by keeping the overall level as low as possible. Many people, especially with non-type I bipolar illness, will respond to levels below 0.6. That said, in choosing to use lithium, another factor to take into account is when to start the clock, so to speak, on its renal effects. In a 50 year old, 1% at

20 years is not as much of a concern, as opposed to a 20 year old, who will only be 40 years old with potential renal impairment, and who will have more likelihood of renal impairment by his/her 60s, when they still will have many years of life ahead of them in most cases. Thus, the PL preference is to use lithium less, all other things being equal, in adolescents and twentysomethings, and to use it more in middle age. Obviously, there is also higher risk of toxicity with lithium in the elderly, especially at standard levels. Very low doses of lithium, specifically for suicide prevention in the young (300 mg/d or less), or for dementia prevention in the elderly (150 mg/d or less), would still be feasible and recommended where either suicide risk or dementia risk was notable. But, as the primary "mood stabilizer" for prevention of full mood episodes, if all other things were equal, PL would lean away from lithium in adolescents and young adults, and toward lamotrigine or carbamazepine (neither of which cause weight gain) or divalproex (in males, due to PCOS risks in young women). Similarly, in those above age 70, PL would lean way from standard dose lithium and towards lamotrigine preferably, and divalproex secondarily (if manic states are more prominent). Divalproex is secondary in the elderly because it has been shown to cause cortical atrophy in that age group. Carbamazepine should be avoided in this age group due to notable hepatitis risk as well as the many unavoidable drug interactions in most persons at this age who will need medications for other common medical conditions.

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THE PSYCHIATRY LETTER

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Questions, comments, cases?

Mixed States - Part II

In this issue, PL continues a discussion of mixed mood states, as begun in last month's issue. This issue focuses on treatment implications of the mixed state concept, and reviews studies and evidence that indicate that antidepressants are ineffective or even harmful in such mixed states, and that dopamine blockers or second messenger modifiers appear to be effective.

In this issue, we also have another new guest columnist, Brianne Fitzgerald NP, a psychiatric nurse practitioner who treats addictions a great deal. She explores ways of understanding addictions beyond the standard medical model of a "brain disease."

The Article of the Month relates to the concept of mixed states, discussing a classic study of the common frequency and importance of manic symptoms during depressive episodes. The Drug of the Month is carbamazepine, a highly underappreciated second messenger modifier that does not cause weight gain. The case of the month and curbside consult questions are provided.

We invite readers to attend either of the two summer CME courses described in the side bar, one in Eastham, Cape Cod, and the other in Martha's Vineyard. They are both taught by me, and will provide an extensive opportunity for PL readers to interact with me and with other clinicians about many of the ideas discussed in PL. I hope some PL readers can make it part of their summer vacation, as well as a good opportunity to receive extensive CME credits, and to interact with other like-minded colleagues.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Mixed States - Part II: Treatment

A key concept for understanding “depression”

Definitions

In the last issue of PL, we looked at an important non-DSM approach to understanding depression, the concept of “mixed states,” defined as depression mixed with manic symptoms. As a reminder, the DSM system defines mania as being allowed to be diagnosed only if it lasts 7 days or longer, and hypomania as occurring when manic symptoms occur for a shorter amount of time: 4 days or longer. But what if manic symptoms occur for 3 days and 23 hours? Or 2 days or 1 day or 12 hours or 3 hours?

The current mainstream DSM approach, preached now for 4 decades, tells clinicians to ignore all manic symptoms, as if they didn’t matter at all, or didn’t happen at all, if they last 3 days and 23 hours or less.

In the last PL issue, we reviewed some scientific studies that show that this claim is false, that manic symptoms of any duration, occurring in a clinical depressive episode, are similar to manic symptoms of longer duration, occurring in hypomanic or manic episodes. This similarity is based on the scientific standards of diagnostic validation: genetics, course, and treatment effects.

In other words, it doesn’t matter whether manic symptoms are brief or long; they have the same genetics, course, and treatment effects. This means they are not different diagnoses, but the same diagnoses. Put otherwise, DSM-based bipolar diagnoses cannot be shown to change into different diagnoses when manic symptoms are less than 4 days to 1 week in duration. Or stated again

differently, there is zero evidence to support the DSM cutoff of 4 days or longer for manic symptoms, as representing a bipolar diagnosis as opposed to non-bipolar diagnoses.

If we take manic symptoms seriously then at all times, and refuse to ignore them as DSM wishes us to do when they are less than 4 days in duration, then we would pay attention to diagnosing those depressive states with manic symptoms as “mixed states,” the term that Kraepelin and others used for these common mood states.

In this issue we now turn to the treatment implications of the mixed state concept: which treatments worsen and which treatments improve mixed states.

Antidepressant effects

“Antidepressants are known to cause mania, but many clinicians don’t realize that the main kind of manic state produced is a mixed state....”

Perhaps the most important relevance of the mixed state concept is that antidepressants worsen these states. Since most mixed states are diagnosed in current practice as “major depressive episodes,” and antidepressants are given for such purported major depression, it would be quite important if it were true that these clinical presentations instead are mixed states that worsen with antidepressants.

Antidepressants are known to cause mania, but many clinicians don’t realize that the main kind of manic state produced is a mixed state, in other words manic symptoms and depressive symptoms mixed together. These mixed states are the highest risk states for suicide, which is one reason why antidepressants can cause suicidality.

As noted in the classic article of the month in the current PL issue, antidepressant-induced mania is about four times more likely in persons with mixed states, as defined by having multiple manic symptoms for any duration, along with depression (Angst's "bipolarity specifier," see prior PL issue and the classic article of the month in this issue). In a study using Koukopoulos' definition of mixed states (depression with psychomotor excitation, usually marked anger; see prior PL issue), antidepressant induced mixed depression was associated with over twice as many suicide attempts, when compared with spontaneous mixed states (occurring without antidepressant use).

So the first and most important step of understanding mixed states is to conclude that antidepressants shouldn't be used, and if they are present, they should be stopped.

Dopamine blocker effects

If antidepressants add fire to mixed states, dopamine blockers are the water brigade. There are only two medications proven in randomized studies to improve mixed depressive states, specifically in so-called MDD (i.e., unipolar mixed states, as described in the prior PL issue): ziprasidone and lurasidone. Probably all dopamine blockers are beneficial, but these two are best proven.

In contrast to monoamine agonists ("antidepressants"), which have been proven ineffective in mixed depressive states, and in fact worsen them, dopamine blockers are effective and improve mixed depressive states. There may be some special utility to those dopamine blockers that have some monoamine agonist properties also (meaning they are either partial dopamine

"...lamotrigine is not effective for acute mixed depressive states...."

agonists, like aripiprazole and brexpiprazole, or they are serotonin/norepinephrine reuptake inhibitors, like ziprasidone).

Lurasidone has been shown to be effective in a large randomized trial of DSM-5 defined MDD with mixed features, which is a narrowly defined mixed state concept (see prior issue). Despite this efficacy greater than placebo, the FDA did not grant an indication to allow the maker of lurasidone to market this agent for unipolar mixed states.

Second messenger effects

In mixed manic episodes, it has been shown that divalproex and carbamazepine are more effective than lithium. Whether this enhanced efficacy

translates to mixed depressive episodes is unknown, but it may. Since the mixed depressive concept has been ignored for decades, no randomized research has been conducted on it with these agents. However, it may be reasonable to extrapolate from studies of mixed manic episodes, and from manic episodes in general. We know that valproate and carbamazepine are effective in treating acute mania, more than placebo, and they work reasonably rapidly. Lithium is proven effective also, but works somewhat more slowly. Lamotrigine is proven ineffective repeatedly for acute mania, as well as proven ineffective repeatedly for acute depressive episodes (whether bipolar or unipolar). Thus it may be rational to conclude that lamotrigine is not effective for acute mixed depressive states, since it is ineffective for all acute mood episodes. In contrast, valproate and lithium likely are effective, as is lithium. Given some uncertainty about the extent of benefit with these agents, though, it may be wise to use dopamine blockers

along with them, or even in place of them, for more severe acute mixed depressive states.

Nonetheless, these agents likely have a role in long-term prophylaxis of mixed states, even if they are not effective sufficiently for improving acute mixed symptoms. With the exception of lamotrigine, which is proven less effective in preventing manic than depressive episodes, there is no evidence that the other three second messenger modifiers (“mood stabilizers”) are more or less effective than each other in prevention of manic episodes. Thus it would seem reasonable to conclude that any of them could be used for prevention of mixed states.

The PL Bottom Line

- The treatment of mixed states begins with avoidance and discontinuation of monoamine agonists (antidepressants).
- Monoamine agonists are ineffective, and double the suicide attempt rate in mixed states.
- Dopamine blockers, specifically ziprasidone and lurasidone, are the most proven treatments for acute mixed depressive states.
- Second messenger modifiers also are effective, especially for prophylaxis, with the likely exception of lamotrigine, which probably is ineffective acutely in mixed depressive states.

PL Reflection

We have to remind ourselves that a flight to sanity is not health. Health is tolerant of ill health: in fact, health gains much from being in touch with ill health in all its aspects.....

In between the two extremes of the first or lucky group and the second or unlucky group (in respect of early environmental provision), there is a big proportion of persons who successfully hide a relative need for breakdown, but who do not eventually break down unless existing environmental features trigger it off....

So we ask ourselves the question: how wide a spectrum of these people who are making good in spite of what they carry around with them (genes, early let-downs and unfortunate experiences) do we include among those who are healthy? We have to take into consideration the fact that in this group are many uncomfortable people whose anxiety propels them to exceptional achievement. They are difficult to live with, but they push the world forward in some area of science, art, philosophy, religion or politics....

*Donald W. Winnicott MD
Home is where we start from*

Classic Study of the Month: BRIDGE study

Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. J. Angst et al, Arch Gen Psychiatry. 2011 Aug;68(8):791-8.

Half of “major depressive episodes” are mixed states

This study was a large international cross-sectional evaluation of DSM-IV-defined major depressive episodes in 5635 patients around the world. Only 14% were found to meet criteria for bipolar disorder (past manic or hypomanic episodes), thus 86% were diagnosable with DSM-defined major depressive disorder (MDD).

The main outcome examined was the presence of multiple manic symptoms irrespective of duration, called the “bipolarity specifier.” In other words, the DSM-based cut-off of 4 days for hypomania was ignored. The question was: Do depressed patients experience multiple manic symptoms at all? The researchers did not simply accept the DSM edict to ignore all manic symptoms if they last less than four days. They were doing what researchers should do: they tested that hypothesis to see if it was valid.

Their main result was that 47% of the sample was diagnosable with the “bipolarity specifier.” In effect, they disproved the DSM-based duration cut-off criterion for manic symptoms. If DSM was correct, then there should be very few patients who have manic symptoms that last less than 4 days. In fact, about half of all depressed patients have this experience.

Further, the presence of these manic symptoms during depressive episodes - which defines mixed states - was confirmed as being diagnostically important because it correlated with standard validators of diagnosis, like genetics and treatment effects. Patients who had the bipolarity

“In effect, they disproved the DSM-based duration cut-off criterion for manic symptoms.”

specifier were about four times more likely to have family genetic history of bipolar illness (odds ratio 3.8) and almost ten times more likely to experience mania with antidepressants (odds ratio 9.6). In both of these associations, the bipolarity specifier had a much larger effect than even the official DSM-defined bipolar diagnosis.

Another relevant point is that the primary author of this paper, Jules Angst, is the same researcher whose work in the 1960s and 1970s was used by the makers of DSM-III in 1980 to make the radical distinction between bipolar disorder and MDD. In other words, Angst’s work back then found that bipolar and unipolar definitions differed in diagnostic validators of symptoms, genetics, course and treatment effects.

Half a century later, the same researcher now finds the reverse: much of DSM-defined MDD is *not* different from DSM-defined bipolar disorder in symptoms, genetics, course, and treatment effects. Science is about falsifying hypotheses. This study falsifies the DSM distinction between bipolar disorder and MDD, but the profession doesn’t want to hear it.

The PL Bottom Line

- Half of all major depressive episodes, whether unipolar or bipolar, are mixed states because they include multiple manic symptoms.
- Such patients are at high risk of mania with antidepressants, and have strong bipolar genetic loading in family history.

Drug of the Month: Carbamazepine

A neglected second messenger modifier without weight gain

Biological mechanism

Carbamazepine exerts its psychotropic effects likely by blockade of cyclic AMP transmission. It shares this kind of second messenger type of effect with lithium and divalproex, but not with other anticonvulsants which are not effective psychiatrically. Its anticonvulsant effects occur through the standard mechanism of blockade of sodium channels, which has no psychotropic influence.

Clinical efficacy

Carbamazepine is FDA indicated for acute mania and epilepsies. It also has a number of randomized trials for maintenance treatment of bipolar illness showing similar efficacy to lithium.

Dosing

The standard dose is about 600 mg/d, with a blood level of around 8, range being 4-12. The level is not associated with efficacy strongly, and thus it is a general guide only. The half-life is about 12-17 hours in long-term treatment, thus twice daily dosing has been standard practice. Given that blood level stability is relevant to seizures but not to mood episodes, once daily dosing at night can be considered also.

Side effects

Nuisance side effects are diplopia, ataxia, paresthesias, and cognitive impairment. These

side effects are reduced markedly with the generic slow release formulation, carbamazepine ER. PL strongly recommends that only this slow-release formulation be used, otherwise unnecessary side effects will lead to discontinuation.

Medically important side effects are very rare, with (probably less than 1:10,000) risk of agranulocytosis and Stevens-Johnson syndrome, and more common non-serious rash.

Importantly this agent has no weight gain, and it is a better alternative to lamotrigine for that purpose in persons who have notable manic episodes or symptoms (for which lamotrigine is minimally effective if at all).

Other potential side effects include hyponatremia (with risk of seizures) and hepatitis (liver function tests should be monitored).

The PL Bottom Line

- Carbamazepine has no weight gain and is effective in mania.
- The generic ER formulation is highly tolerated, and much preferable to standard generic use.
- It works in mixed depressive states.
- It has no metabolic harm or weight gain, but it can cause cardiac arrhythmia.

Guest Column

Substance abuse and mental illness: Chicken or egg?

Brianne Fitzgerald RN, MSN, NP, MPH

Psychiatric Nurse Practitioner, Quincy MA

Depending on who you ask you may get a different response to the question of whether someone has mental illness or substance abuse/dependence. Questions that explore the matter include the following:

Are you using cannabis to relax, or to improve your depressed mood?

Are you using Xanax to address panic attacks or social anxiety?

Does your use of cocaine or dextroamphetamine increase your energy?

Does your chronic use of methamphetamine or cocaine deepen an underlying depression?

“...addiction is a learned behavior...”

The American Society of Addiction Medicine tells us that addiction is a primary, chronic disease of the brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substances and other behaviors.

DSM-5 no longer uses the terms substance abuse and substance dependence; rather it refers to substance use disorders, which are defined as mild, moderate, or severe to indicate the level of severity, in turn determined by the number of diagnostic criteria met by an individual. Substance use disorders occur when the recurrent use of alcohol and/or drugs causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet

major responsibilities at work, school, or home. According to DSM-5, a diagnosis of substance use disorder is based on evidence of impaired control, social impairment, risky use, and pharmacological criteria.

DSM-5 is purely descriptive though. It leaves open the questions of what causes addiction. The mainstream view, in places such as the NIH, is that addiction is a “brain disease.” There are other perspectives though, such as the 12-step tradition about addiction as being completely outside the medical model.

For me, neither of these extremes makes sense. As I’ve struggled with treating many persons with addiction, I’ve looked for other ways of understanding this problem. One approach that agrees with my experience has been proposed by Maia Szalavitz in Unbroken Brain (Saint Martin’s Press, 2016). She tells us that addiction is a learned behavior or disorder, an over-focus on self and a coping mechanism for emptiness. She posits a developmental model for addiction that

theorizes timing, family peers, culture, genes and chemicals coming together at a point in time that can contribute to both addiction and recovery. Consistent with the stages of human development she believes that most people eventually outgrow addiction.

How do these confusing definitions and etiologies impact practice?

Psychiatric disorders by definition are conditions that cause significant distress and suffering. Many of the addictive drugs are used to relieve this distress. I often tell the patients I serve that their drugs work better than the drugs that I offer. It is a Sisyphean task to unpack the nuances, presentations and goals of this population.

The good news is that many addicts mature out during early middle age and most without any formal treatment. Those who do not are more likely to have a co-morbid mental health issue; particular anxiety, mood and personality

disorders. (Compton, W.M, Thomas, Y.F. Stinson, F.S. and Grant, B.F. 2007 Archives of General Psychiatry, 64(5), 566-76). The work of a psychiatric provider then ultimately comes down to a cost benefit analysis done in concert with the patient. It is a time-consuming process that requires patience, some knowledge of street drugs and their interactions with prescribed medications (often learned from the patient themselves) and a very well-honed "BS meter."

The essential issue can be stated simply. What does the patient value: Immediate relief or uncertain future improvement in life? And, related: How do we get there, to the goal of creating a life worth living?

These questions raise the importance of complex sociocultural aspects of addiction that go beyond simply viewing these conditions as brain diseases.

In this essay, I haven't tried to present simple answers for these complex problems, but to remind readers that most simple answers won't work and that to begin to move in the right direction, we have to admit that the matter is complex, and stop looking for easy solutions.

PL Comment:

We appreciate this thoughtful essay from Ms. Fitzgerald. It is based on years of extensive clinical experience with persons with substance addiction. In the context of the current epidemic

"What does the patient value: Immediate relief or uncertain future improvement?..."

of opioid addiction and overdose-related deaths, this essay is timely and should lead clinicians to think about different ways they can engage with their patients/clients besides simply the medical model. These days, common responses to the opioid epidemic include Narcan, Suboxone, and methadone. None of these pharmacological symptom-based approaches get at the causes of these addictions. Where underlying psychiatric disease is present, it should be diagnosed and treated, and the opioid drug substitutes might direct attention away from where it should go.

Where no underlying psychiatric disease is present, then the other causes of addiction should be sought and addressed forthrightly. This is where the 12-step tradition is strongest, rooted in a recognition of the existential and even spiritual sources of addiction. Mental health clinicians need to be at the forefront of reminding the world that though the outcome might be medical, like opioid-related death, the causes can be quite personal, spiritual, and even social. When life becomes meaningless, we have to ask why, and it is a species of denial to ignore poverty and the emotional superficiality of daily life in our digital age. We may not be able to change those realities as individual clinicians, but at least we can be aware of and talk about them, which is the beginning of any lasting change.

PL Reflection

Irrationally held truths are more harmful than reasoned errors.

T. H. Huxley
Maxims and Reflections

Case of the Month:*Pre-adolescent depression versus bipolar illness*

A 12-year-old female has experienced depression for three years. During this time, she has had extensive periods of being very sad, low in her energy, and socially reclusive. She also has spurts lasting 3 to 4 days at a time of high excitability, along with impulsivity, like jumping on a sand castle at a party and ruining it. During these impulsive times, she talks rapidly, and she is very irritating to others. Afterwards, she becomes unhappy, because others have been bothered by her, and she has suicidal thoughts of not wanting to live.

She is also a dancer, and has lost weight extensively. She has been hospitalized repeatedly for anorexia, and has received a feeding tube at times. She has been diagnosed with obsessive-compulsive disorder, because she focuses on her weight and food and is constantly worrying about what others think about her.

She has no history of sexual trauma and has never cut herself. She has made no suicide attempts. She has no substance abuse or other medical history. No known drug allergies.

In her multiple hospitalizations, she has been treated with multiple serotonin reuptake inhibitors. Recently she was tried on venlafaxine, and later switched to duloxetine. She did not improve on any of these medications, and eventually aripiprazole was added.

Her family history is questionable, because she was adopted. Her biological mother reports that her biological father, who is now dead, had been diagnosed with bipolar illness and also had substance abuse.

Consultation was obtained with a child psychiatry expert in mood disorders. The expert believed that the diagnosis was a major depressive disorder, along with anorexia nervosa. When asked about a possible bipolar diagnosis, the child psychiatry expert opined that a bipolar diagnosis is unlikely for multiple reasons. First, she does not meet full criteria for a DSM-defined manic episode. Second, the possible bipolar diagnosis in her family is questionable, and frequently people get over diagnosed with bipolar illness. Third, even if her father has bipolar illness, the majority of children of bipolar parents do not develop bipolar illness; rather, major depressive disorder is the most common diagnosis in such children. Further use of antidepressants and more extensive psychotherapies were recommended by this expert.

PL consultation:

This kind of case is extremely common in children and adolescents. One might divide the world of child psychiatry into pro and anti-bipolar groups, with the latter being much larger. The anti-bipolar perspective is mainstream and follows DSM to the letter. This case is a good example of the approach. One problem with it is that it provides no hope of any better or improved outcomes beyond the repeated use of already failed medication classes such as antidepressants in this case. The anti-bipolar perspective does not subject itself to refutation based on treatment outcomes. Rather, this perspective is held based on a specific approach to diagnosis, without ever testing the diagnosis by its therapeutic results.

There are a number of fallacies in the anti-bipolar viewpoint expressed by the child psychiatry expert in this case.

First, the child psychiatry expert refuses to view manic symptoms as being relevant at all to

diagnosis or treatment if those symptoms are more brief than the DSM duration cutoffs. This approach ignores the fact that the DSM duration cutoffs have no scientific basis in research studies that prove that those cutoffs differentiate bipolar illness from non-bipolar illness. In fact, as discussed in this issue, good scientific studies show the reverse. In other words, manic symptoms lasting a few days or less are important diagnostically and therapeutically, predicting bipolar genetics and poor antidepressant outcomes.

Second, the child psychiatry expert was skeptical about the bipolar diagnosis in the patient's biological father. There is no way to confirm in this case since there is no access to the father. However, on the general issue of bipolar illness being overdiagnosed in adults, there is reason to be cautious. The usual studies cited do not in fact show overdiagnosis of bipolar illness in adults; in fact, they show underdiagnosis. They appear to be misinterpreted by those researchers who want to support the concept of overdiagnosis. This matter has been reviewed in articles in which opposing views have been debated. Further, there are other studies which indicate underdiagnosis, not overdiagnosis, of bipolar illness in adults.

Third, the claim that children of bipolar parents are unlikely to have bipolar illness is a misunderstanding of the nature of psychiatric genetics. Psychiatric illnesses, when genetic, are not Mendelian: they are not autosomal dominant or recessive. It's not a matter of 50% or more relatives having a disease. Rather they are non-Mendelian genetic, which means that many genes are needed for an illness to occur. This is a quantitative risk. The two most genetic psychiatric diseases are schizophrenia and bipolar illness; they are almost completely genetic. In the

case of bipolar illness, the baseline risk in the general population is about 1%. In family members of a proband with bipolar illness, the observed risk is about 10-20%. This is a much higher risk than the general population, about 10-20 fold higher, which is a huge effect size, equivalent to the risk of getting lung cancer by smoking cigarettes. But the absolute numbers could be emphasized rather than the relative risk: it could be claimed that 80-90% of children of a parent with bipolar illness will *not* develop bipolar illness (the most common diagnosis being "MDD"). The claim that bipolar illness is "unlikely", as if one doesn't need to worry about it much, is not rational for a non-Mendelian disease.

Here is an analogy: Lung cancer as a result of cigarette smoking is also non-Mendelian in its risk. There is a genetic component; some people smoke and develop lung cancer; others smoke and do not. The absolute risk rates are low; in fact: even after 50 years of very high smoking rates, only 20% of smokers would develop lung cancer; 80% do not. These figures are the same as the risk of bipolar illness in children in bipolar parents. Should we then say that cigarette smoking doesn't matter? Why should 80% of the population be restricted and discouraged from smoking for the sake of a minority 20%? (This is actually one of the arguments made by pro-cigarette civil rights groups). The reality is that relative risks matter, not just absolute risks. And 20% is a lot of people in the general population; if they are worsened by antidepressant treatment for misdiagnosed bipolar illness, it matters.

A final point that the child psychiatry expert didn't address: Even the concept that children of parents with bipolar illness "only" have MDD is an illogical concept, since, as PL readers know from the discussions of manic-depressive illness

(MDI), the whole concept of “MDD” is based on the notion that it is genetically different from bipolar illness, i.e., that it should not happen, or very infrequently, in families of persons with bipolar illness. Thus, the claim that most children of parents with bipolar illness have MDD, or unipolar depression, only argues against the concept that unipolar depression is a different disease than bipolar illness. It argues for the old MDI concept, namely that unipolar and bipolar subtypes are part of the same disease.

If one thinks about these factors, whether this child has bipolar illness of some variety or MDI, then it would not be reasonable to continue to go down the path of antidepressants, and refuse to use lithium or mood stabilizers. Further, if we are able to take bipolar or MDI concepts more seriously, we could take the step that most child psychiatry clinicians refuse to take in cases like this one, namely, to stop duloxetine and all antidepressants altogether, and to use lithium or mood stabilizers without any antidepressants.

The PL recommendation in this case was to switch duloxetine to fluoxetine 20 mg/d, and then to taper the latter over 3 months, while starting lithium for the mixed depressive state along with suicidality, as well as to add aripiprazole 2 mg/d for the acute mixed states.

PL Reflection

It takes 20 years to mature a child from pure animality to the beginning of reason. It has taken 30 centuries to learn a little about man's body, an eternity to learn of his soul, and an instant to kill him.

Voltaire (paraphrased)

Curbside Consults

Questions and cases from you

Question: Last week, *JAMA Psychiatry* has published an online-first discussion between two groups regarding complicated/prolonged grief disorder. We would like to hear your clinical insight about it, and how to get a sound attitude between pathologizing normal experience and caring for suffering patients

PL: In the January PL issue, we heard from an expert on this topic Dr. Ronald Pies, and PL commented briefly on his article. Overall, the PL view can be simplified to focus on the course of the illness, rather than on cross-sectional symptoms. Going back to Freud's *Mourning and Melancholia*, it is clear that the experience of grief is similar in its phenomenology to clinical depression. Thus, it likely isn't profitable to try to tease out nuances of difference in symptoms and subjective experiences of grief versus depression. The two states of mind are similar. In the past, clinicians tended to focus on duration of symptoms. If grief lasted longer than a 6 months or so, then it became “complicated grief,” which meant grief that began to border on depression, and if it persisted much longer, the diagnosis of clinical depression was made. In DSM-5, a definition for “bereavement” was excluded altogether, and a separate category for grief doesn't exist.

The PL view is that all these debates focus on the wrong points. It is frequent in psychiatry that symptoms will overlap, both between syndromes and with normality. A century ago, Emil Kraepelin saw this problem clearly, and devised a solution: Focus on the course of illness. When an illness is present, it doesn't go away. Either it's chronic, and its symptoms are present all the time (as in schizophrenia), or it's episodic, and the

symptoms go away temporarily when the episode ends, but they always return with a new episode.

So how can you tell if it's grief or depression? Grief goes away, and never comes back, because your loved one can die only once. Depression, as an illness, is recurrent; it goes away, but always comes back. So if it's depression, and not just grief, then the person will become depressed again on another occasion, not only when someone dies, but also when other things happen (or don't happen), such as losing or gaining a job, losing or gaining a spouse, and financial difficulties.

In sum, the answer is the same as how one distinguishes happiness from hypomania, according to the quip of the great mood researcher Hagop Akiskal. The difference, he said, is that hypomania is recurrent; happiness is not. Similarly, depression as an illness is recurrent; grief is not.

Thus, one knows when the course of illness plays out: Time tells the truth. Grief may last a long time, even up to a year in some cultures, but then it goes away, and in the ensuing years and decades, the person may be sad and miss the loved one, but clinical depression criteria are no longer met, and never return in the form of a full episode. If depression returns in the future, then it's depression, and the first episode was depression after all, and not just grief.

So how would you manage a patient with grief? PL recommends that you first assess whether the patient had prior clinical depressive episodes. If so, then PL would see the death of a loved one as just another life event that triggers depressive episodes, not as a uniquely different entity altogether ("grief"). If there are no prior depressive episodes, then the symptoms related to the death of a loved one could be seen as grief until proven otherwise. In other words, if they do not resolve after an extended period of time (6-12 months), or if they resolve but then return again in the future with other life stressors, then the diagnosis of a depressive illness would make sense.

PL Reflection

When I see a spade

I call it a spade.

I am glad to say

I have never seen a spade.

Oscar Wilde

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THE PSYCHIATRY LETTER

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Diagnostic interviewing

In this issue, PL presents the first of two parts of special articles on diagnostic interviewing. In this issue, the symptoms and course and other diagnostic aspects are examined. In the next issue, we turn to treatment history and discussion of diagnostic and therapeutic recommendations in an initial interview with patients.

This issue introduces a new column, *From the Bookshelf*, where PL excerpts sections of writings from thinkers in psychiatry and psychology, or other fields relevant to psychiatric practice. In this first column, we discuss the ideas of the Catholic thinker in spirituality and psychology, Thomas Merton, on the nature of the inner self.

The Article of the Month examines a meta-analysis of the utility of the PHQ-9 to screen for depression in primary care. It is found wanting. The Drug of the Month is asenapine, a new dopamine blocker which could be an alternative to older agents with more medical harms.

On the final page of this issue, we inform readers about three upcoming CME courses, two in the summer in Cape Cod and Martha's Vineyard, and one in the fall in Santa Fe, New Mexico. We hope readers attend and/or let colleagues know about these special opportunities for us to interact directly with each other, and with other like-minded colleagues.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Diagnostic interviewing - Part I

An approach to the initial hour

It has been said the main goal of the initial interview is to have a second. This is true, but at the same time, clinicians need to make diagnoses. How to get diagnostic interview data that are valid, while establishing a rapport with the patient, is an art that is difficult to learn. In the next two PL issues, we'll discuss some aspects of how to interview patients for the most common scenarios of mood and anxiety conditions.

The interview can be divided up into 7 sections, as shown in the table.

Table 1. Steps in the diagnostic interview

Section	Duration (minutes)
Identify the current depressive episode or anxiety state. Explore phenomenology.	5-10
Assess the course of depressive and/or anxiety illness	10-15
Assess past mania or hypomania	5-10
Assess baseline temperament/personality	5
Obtain past treatment history	5-15
Discuss the rationale for the diagnosis	5
Discuss treatment options	5-10

Before the interview: Ask for family and friends to be present

Usually, when you go to the waiting room to find your patient, someone else is there, a family member and friend. About half the time, that other person remains seated. Most clinicians do not invite that person to join the interview. We should. Not only that, we should inform patients before their first interview that they should seek to bring a family member or friend along with

them. This is for two reasons: first, family members and friends can corroborate the history or, in the case of some symptoms like mania, actually provide accurate history whereas patients, due to lack of insight, often invalidly deny the presence of manic episodes in their personal history. Second, when discussing treatment options, the presence of others in the office improves the likelihood that the treatment plan will be understood and implemented; frequently, patients are depressed and cannot clearly understand the complex treatment options being described – family members can hear and repeat what was said later to the patient. Further, if family members are not present, the patient will later have to explain what clinicians said to them; it is better for the family to hear what clinicians have to say directly from me, rather than secondhand.

If there are concerns about certain confidential topics (which usually do not directly impact on the diagnostic interview anyway), family can be asked to leave the room for a few minutes in the middle of the interview, and then invited to return toward the end when clinicians provide diagnostic impressions and treatment recommendations.

In sum, don't interview patients alone. Ask for family members or friends to be present at the first diagnostic interview.

Begin by asking about depression or anxiety

In the outpatient setting, the most common presenting complaint is depression or anxiety. As the psychotherapeutic saying goes, it is best to meet patients where they are; so start by the non-controversial and straightforward determination

of the presence of clinical depression or the nature of anxiety.

At one level, one simply identifies depression and anxiety to get beyond it. In other words, it often is relatively easy to know that a patient has a current clinical depression – it may only take five minutes to quickly review current neurovegetative symptoms – but that is not the end of the evaluation, only the beginning. This is because depression is not a diagnosis, but only a constellation of signs and symptoms. Diagnoses are bipolar depression, or secondary depression, or unipolar depression – with unipolar depression signifying that the bipolar and secondary diagnoses have been ruled out.

It is irrelevant, for instance, to spend much time assessing how depressed the patient is, whether she is hopeless or helpless, whether her symptoms are atypical or typical, and so on. All those features are important perhaps prognostically and therapeutically, but they are unimportant diagnostically. They do not differentially diagnose bipolar as opposed to secondary or unipolar depression.

After a certain point, detailed evaluation of current depressive symptoms is not diagnostically valuable.

The main exception to this rule is the identification of a mixed state, as discussed in the last two PL issues. If the current depression has marked agitation and rage and mood lability as part of it, then it is a mixed state and not pure depression. In the case of a mixed state, the current depression phenomenology is important diagnostically.

Similarly for anxiety: As discussed in PL issue X, anxiety is the fever of psychiatry, a troublesome symptom of other diseases, but not usually a disease in itself. It is often an effect, not a cause. Look for the other causes: depression, mania, psychosis. You can identify the severity and frequency of anxiety symptoms but your main goal is to move away from anxiety to seek other causes.

Most clinicians spend excessive time on current symptoms and insufficient time on the course of the illness.

Obviously an assessment of concurrent psychotic symptoms can be diagnostically and therapeutically

relevant, and an evaluation of suicidality is clinically necessary; but soon after identifying depression or anxiety, the clinician should shift the focus to the more onerous task of looking for past mania or hypomania.

Spend more time on assessing the course of depressive illness

Most clinicians spend excessive time on current symptoms and insufficient time on the course of the illness.

The reader will recall that the course of depression, unlike the details of current depressive symptoms, can differentiate between bipolar and unipolar conditions, as well as help identify secondary depression. Too often clinicians simply say: “The patient has major depression,” as if that is enough to make a diagnosis. They have no idea when the depressive episodes began, how many there have been, how long they have lasted, precipitating factors, interepisode symptoms, and so on.

Here is what is diagnostically important: age of onset, number of episodes, duration of major depressive episodes, and interepisode status. Ask

patients how far back they can remember depression or anxiety for the first time, refreshing their memory as to the definition of a clinical depressive episode (daily depressed mood or anhedonia with multiple neurovegetative symptoms, day in and ay out, most of the day nearly every day, for weeks on end or more).

Then ask how long their depressive episodes have lasted in the past. Here patients usually throw up their hands and claim ignorance. The clinician can say, "I could make it

up, but your guess is better than mine."

Patients need to know that this is important; force them to think about

it. Usually they can give an average duration; it need not be precise – if they are especially exasperated, give them options: more than a month, less than a month, about six months, over a year. These are the time-frames that are diagnostically relevant, since unipolar depression lasts 6 months to a year or longer while bipolar depression is shorter, usually 3-6 months or less. Also assess the durations ideally in untreated periods to understand the natural unmedicated history, but if a patient has been non-responsive to medications, then treated periods should reflect the natural history of the illness.

Then ask how many episodes the patient has had: "How many times in your life have you felt very depressed like that?" Usually, if currently depressed, patients overestimate their past depression: "Forever" is the common desperate answer. "Really?" the clinician can reply, "All your life, every day, day in and day out, without ever having one day of being different, forever?" Usually, they back off fat that point. "So how many times?" "I don't know, doc." Again one can offer multiple choice answers: "Just once? A few

The presence or absence of manic/hypomanic episodes are not life and death matters for the diagnosis.

times? More than five times? More than 10 or 20 times?" Sometimes it is obvious in the history that the patient has had many episodes, more than 10 or 20; in that case the exact number matters little. What does matter diagnostically is that if a patient has one or two or three episodes, this is common in unipolar depression and uncommon in bipolar disorder. Many episodes is more common in bipolar illness, especially if they are brief (less than 3 months in duration).

Finally, once you have identified the ballpark number of episodes, determine if there are periods of wellness between episodes. This is usually not

difficult; either patients will claim they are always depressed, which may reflect interepisode dysthymic or cyclothymic temperament, or they have periods of euthymia, which they or their family can clearly describe: "Were there ever times when you were not depressed and were your normal self, or normal like everyone else, in your mood energy, for weeks or months on end or longer?"

Assess past mania or hypomania but don't dwell on it

If you take the DSM approach to diagnosis of mood illness, then it is essential to know whether mania/hypomania is present or not. The whole bipolar/unipolar distinction depends on it.

But if you take the non-DSM approach to manic-depressive illness, as described on the PL website, which subsumes bipolar and unipolar variants as part of the same illness, then the presence or absence of full manic or hypomanic episodes is important therapeutically more so than diagnostically. In other words, if the patient has severe mania, then treatment will change

somewhat as opposed to mostly depression. But the absence of full manic episodes doesn't mean the patient is radically different than someone with some manic symptoms (e.g., mixed states of depression; in both cases dopamine blockers would be used and lithium and second messenger modifiers also considered, especially long-term).

In other words, in the PL approach, while it is important to assess mania/hypomania, the presence or absence of manic/hypomanic episodes are not life and death matters for the diagnosis.

In the typical interview, it might have taken five minutes to establish that the patient has a current clinical depressive episode. If a mixed state is present, one might spend another 5 minutes or so clarifying the details of the mixed state. If there is a pure depressive episode (non-mixed), then more time can be spent, like another 10 minutes, on the depressive course of illness (onset, duration, frequency of episodes).

Next, one should examine possible past mania or hypomania. Sometimes, this matter is denied clearly by the patient and family. As long as family is present, this denial can be accepted in most cases, and the interview can continue in another direction. If only the patient is present, then, based on the research literature, one cannot believe the patient, since about two-thirds of patients with type II bipolar illness will deny any past hypomanic episodes and about one-half of patients with type I bipolar illness will deny any past manic episodes. Yet, for the purpose of the interview, the topic can be dropped, with the plan to get consent from the patient to call a family member or close friend after the interview to further examine past manic/hypomanic episodes.

Write down what the patient says verbatim.

If the clinician has reason to believe that some past manic/hypomanic episodes were present, then a more detailed interview can be made of the topic in the following manner:

The clinician should take his or her time, and come at the question slowly and in a roundabout fashion, so as to avoid patients' natural defensiveness about the stigma of bipolar illness.

One can begin by an open-ended question, especially if you have established a period of normal or euthymic mood in the past in the assessment of the course of depressive illness: "Did you ever feel the opposite of depressed, where you were not sad and down and depressed, but you also weren't just your normal self?" With equivocal responses, one might get more specific: "Did you ever have times where you were more energetic than normal, compared to when you were not depressed, or more energetic than most people around you, so that you were doing lots of things or not sleeping much and not feeling tired?" Or perhaps: "Did you ever have periods where you were angry and irritable but not depressed, and full of energy, doing lots of things?"

If a somewhat positive response is elicited, or if the patient comes to the appointment with possible past mania as a clinical question, the clinician can ask an open-ended question of the patient, so as not to direct the patient toward manic criteria, but seeking to get his/her own words about it: "Tell me about how you felt, and how you behaved, or what people told you about how you were, during that time (when you felt hyper or more energetic than usual or where you or your doctor or others said you might be manic or hypomanic)?"

Importantly, write down what the patient says verbatim. It is very important to do this. Bipolar

illness is such a controversial topic, with patients getting different opinions from different doctors, that it is important to avoid miscommunication by letting patients speak for themselves. Consider if you write: "The patient had elevated mood, with decreased need for sleeping, flight of ideas, distractibility, and increased goal-directed activity for five days." The patient may disagree and go to another clinician, who is skeptical about the bipolar diagnosis, and that clinician might simply disbelieve your interpretation of what the patient had said. But no one could deny mania if you write: "The patient

stated that he would feel 'hyped up and like I could do anything, I was a tyrant, felt I was smarter than everyone else, like there was nothing I couldn't do, I didn't need to sleep for days on end yet I was full of energy, I was giddy at times, my thoughts were all over the place, I couldn't keep up with them, I would wake up in the middle of the night and clean the house five times over, then the next day I would paint the house inside and outside even though it was perfectly fine, and a week later I would do it again with a different paint color."

If mania or hypomania cannot be identified, the interview is still not over; then the absence of mania/hypomania needs to be confirmed by third parties. This is done most efficiently if family or friends are present at the interview.

Assess temperament/personality

Frequently, much of the above interview will have been negative in content. The patient will have denied manic or hypomanic episodes; she will have denied even depressive episodes. She may report constant anxiety, but nothing more in detail, with no obsessions or compulsions for instance. She may report "ADD" and inattention, and little else.

"Once episodes are ruled out, then temperament needs to be assessed."

For many clinicians, the interview then ends in the somewhat generic diagnosis of "generalized anxiety disorder", or adult ADD, or both.

It is here that the concept of affective temperament is a final step that is often missed in the diagnostic interview. There may not be full manic or depressive episodes, but one should assess whether there are mild and constant manic and depressive symptoms. In other words, once episodes are ruled out, then temperament needs to be assessed.

Since temperament is part of personality, this aspect of the interview also has to do with what usually is viewed as personality "disorders" in the DSM approach. There may be some overlap between temperament concepts and DSM personality disorders: a patient with cyclothymia will seem "borderline" to someone who sees constant mood swings only through a DSM lens. But for the purposes of this discussion, we will limit comments here to assessing affective temperaments primarily.

PL would like to emphasize the importance of asking patients about their normal personality, about who they are when they are not depressed or manic or markedly anxious. This is important on multiple grounds: not only to assess affective temperament, as is the emphasis here, but also to get to know patients, if only briefly, for who they are as persons. If the patient remarks on some personality trait to which the clinician can connect, it can help establish rapport. For instance, if the severely depressed patient remarks on loving to travel when well, the clinician might ask where the patient has visited, and perhaps connect a personal anecdote to a specific location.

“You went to Greece? I loved it too when I went to Santorini.”)

Returning to the focus of affective temperament, the best way to start is to be general: “Tell me what you are like, in your normal personality.” If people aren't sure where to start, you can ask them if they're sociable much or not, active much or not, how much energy they usually have, what kind of activities they like to do. Often patients will be specific and talk about working all the time, or having tons of friends, or being the life of the party. In those cases, the notion of hyperthymia will arise in the clinician's mind. Sometimes it is less clear but there are hints, and then a TEMPS scale will help clarify temperament (see web edition for link to the TEMPS). Sometimes people are just plain normal. They sleep 8 hours nightly, work 40 hours weekly, are moderately sociable and active in what feels like the middle of the normal curve for personality traits. In that case, the clinician senses euthymia, or normothymia, i.e., the absence of any affective temperament between mood episodes.

Besides affective temperament, the other personality traits clinicians can keep in mind as they assess the baseline personality of patients are the three major traits of the NEO scale: neuroticism, extraversion, and openness to experience. Ask about how anxious patients generally are (neuroticism), how sociable they are (extraversion), and how curious/ risk-taking they are (openness to experience). Have a normal curve in your mind for these traits, and mentally place your patient somewhere in the middle, or to one of two extremes. This can help give you a sense of the patient's basic personality.

“Tell me what you are like, in your normal personality.”

Ask family to comment on the patient's personality as well; often patients can downplay some aspects of themselves that might be seen as less desirable. Someone who is shy, for instance, might not admit to having few friends.

After assessing temperament, clinicians can make diagnoses more scientifically than might be the case otherwise with DSM standards: GAD becomes neuroticism as a personality trait; adult ADD becomes cyclothymia.

Sometimes this temperament assessment can inform other diagnoses. Recurrent clinical depressive episodes in the setting of baseline hyperthymic temperament is a very different problem (see PL issue X) than the same depressive episodes with baseline normal temperament. (The former might be treated with low-dose lithium long-term; the latter might not).

The next PL issue will examine the final half of the initial interview, focusing on assessing past treatment effects and having a diagnostic and therapeutic discussion.

The PL Bottom Line

- Include family in the initial interview.
- Focus more on course of illness rather than current symptoms
- Write down what the patient says verbatim on key diagnostic aspects, like manic symptoms
- Assess temperament and normal personality

From the Bookshelf

Insights from thinkers in psychiatry/ psychology: Thomas Merton

*Thomas Merton was a Trappist monk, peace activist, and thinker and writer in spirituality and psychology. In his last work, *The Inner Experience*, he writes about “contemplation”, or getting to know oneself in one’s inner being. Here is an excerpt followed by commentary:*

The inner self is not a part of our being, like a motor in a car. It is our entire substantial reality itself, on its highest and most personal and most existential level. It is the life by which everything else in us lives and moves. It is in and through and beyond everything that we are....It is not reached or coaxed forth by any process under the sun, including meditation. All that we can do with any spiritual discipline is produce within

ourselves something of the silence, the humility, the detachment, the purity of heart, and the indifference which are required if the inner self is to make some shy, unpredictable manifestation of his presence... (pp. 6-7, Harper edition, 2003, NY)

Merton then cites an ancient Chinese poem symbolizing finding your true self, as found in the center of this page. Merton goes on to explain the poem:

Why “old”? Because of the Buddhist belief that the true self has existed from all eternity in the

uncreated Absolute and is itself “uncreated.” Such a self is ever old and ever new because it is beyond old and new. It lives in eternity....

The inner self is not an ideal self, especially not an imaginary, perfect creature fabricated to measure up to our compulsive need for greatness, heroism, and infallibility....Our self in all our uniqueness, dignity, littleness, and ineffable greatness: the greatness we have received from God our Father....

The laconic little poem, then, expresses the full sense of liberation experienced by one who recognizes, with immense relief, that he is not his false self after all, and that he has all along been nothing else but his real and “homely” self, and nothing more, without glory, without self-aggrandizement, without self-righteousness, and without self-concern. (pp 10-11)

PL Comment: PL readers need not identify with the explicitly Christian or religious aspects of Merton’s thoughts to relate to the general insight about one’s true self, as opposed to what Winnicott called the false self. The true self is presented in an image: a humble old man, who is new to us, a liberation from all our seeking, a realization of someone simple yet great in his own way, overlooked in our culture’s wish for recognition and glory.

Current Study of the Month: *Is the PHQ-9 useful?*

Case finding and screening clinical utility of the Patient Health Questionnaire (PHQ-9 and PHQ-2) for depression in primary care: a diagnostic metaanalysis of 40 studies.

AJ Mitchell et al, British Journal of Psychiatry. 2016; 2:127-138

Not much

The most commonly used screening tool for depression, especially in the primary care setting, is the 9 item Patient Health Questionnaire (PHQ-9).

This paper is a meta-analysis of 40 studies of the PHQ-9 as a screening tool for depression in primary care. The overall sample was 14760 adults of whom 14.3% were diagnosed clinically with major depressive disorder (MDD).

A few definitions:

Sensitivity means whether a test is positive if a diagnosis is present.

Specificity means whether a test is negative if a diagnosis is absent.

So if the PHQ-9 was positive for depression, and MDD really was present (let's say defined by a clinician's diagnosis using standard criteria and with full historical information), then we would say there was good sensitivity. The reverse would hold for good specificity.

What's "good"? It depends on what is being studied. For HIV testing, for instance, we want sensitivity of 99% or higher; we don't want to miss the disease, which would be deadly if untreated.

In the case of many standard clinical diagnoses of less immediate danger, like MDD, it is generally accepted that 90% or higher would represent very good sensitivity or specificity, and that 80% or higher would be adequate and helpful in clinical practice. Once you get closer to 50%, then a test

"You might as well flip a coin."

is less helpful, as one could flip a coin to get similar results.

The meta-analysis assessed the PHQ-9 in a few different ways, but using the standard approach, which just adds up the numbers, it found a sensitivity of 81% and a specificity of 85%.

At first glance, these numbers look good. But this is only the first step: it shows that the scale measures depression. Whether it is useful as a screening tool is a different question. Or as the authors put it, whether it is good for "case-finding" is another question.

So let's turn it around: You don't know if the MDD diagnosis is present or not, and you use the PHQ-9 to screen for it. This is the opposite of sensitivity and specificity. It is referred to as predictive value:

Positive predictive value (PPV) means whether a diagnosis is present if a test is positive.

Negative predictive value (NPV) means whether a diagnosis is absent if a test is negative.

The researchers found that here the PHQ-9 failed. The PPV at best was 47%. In other words, if the PHQ-9 was positive, it was right half the time and wrong half the time. You might as well flip a coin.

The NPV was much better, being 97%. This means that if the PHQ-9 is negative, it is more informative, suggesting absence of depression.

Why is this the case?

This is what happens when a disease occurs in some people, but not in everybody. We say depression is common, but MDD definitions are met by about 5-10% of the general population. In this primary care sample, it was slightly higher, about 14%. That means that 86% of the primary care population did not have MDD.

So it isn't so surprising that the PHQ-9 had good NPV. If you had a scale that was terrible for depression, and never diagnosed it, and it always was negative, it would be correct 86% of the time in this sample. In other words, since most people don't have depression, almost any scale will have a good NPV. What is more important is to identify that 14% who had depressive illness, and there the MDQ failed, only identifying about half of them.

So what are clinicians to do?

Do what you always have done: conduct a careful diagnostic interview, as in the special article in this PL issue. There is no substitute for a diagnostic interview and adequate history-taking. Scales like the PHQ-9 are at best screening tools. In other words, they can be used initially to get some idea about a patient's symptoms, but whether they are positive or negative, they still

should be followed up with adequate history-taking.

They are better than nothing, but they are nowhere near replacing the diagnostic interview as the only accurate way to rule in or rule out psychiatric illnesses like depression.

One last comment, all this research on the PHQ-9 completely ignores the differential diagnosis of depressive illness. The assumption is that a positive PHQ-9 translates into "MDD"; but the latter diagnosis implies, at least, absence of manic or hypomanic episodes at any time in the past. The PHQ-9 does not assess manic states at all, and thus, by itself, even if it was an accurate diagnostic scale, it does not diagnose "MDD." For the latter diagnosis, a clinical history about past manic/hypomanic episodes, at the least, would be needed, with all the complications inherent in such an investigation, as discussed in the special article in this PL issue.

The PL Bottom Line

- The PHQ-9 by itself is not accurate to diagnose the presence of depressive illness.
- As an initial screening tool, it can be used to add to, but not replace, a full diagnostic interview.

PL Reflection

The characteristic of heroism is its persistency. All men have wandering impulses. But when you have chosen your part, abide by it. The excellence of heroic actions outruns sympathy and appeals to a tardy justice. Always do what you are afraid to do.

Ralph Waldo Emerson

Drug of the Month: Asenapine (*Saphris*)

Quetiapine-like without metabolic syndrome

Biological mechanism

Asenapine is a dopamine and serotonin receptor blocker, like most second-generation agents in its class. Its difference with other agents is that it is a mild 5HT_{1A} agonist. It has strong antihistamine and antiadrenergic effects, but it is not anticholinergic.

Clinical efficacy

In the US, asenapine is FDA indicated for acute mania and schizophrenia. It has some randomized data of efficacy for mixed states in its mania trials, where it was effective in patients with

dysphoric mania. Thus it may help in mixed states and bipolar depression, based on clinical experience, but has no FDA indication yet for those uses, and no randomized studies of depressive states.

Dosing

The standard dose for bipolar illness is 5-10 mg/d given all at night. Doses up to 20 mg/d can be used in schizophrenia. It has a 2.5 mg pill size, which is useful as a starting dose in the outpatient setting. It is taken sublingually and now given in a flavored form due to the bad taste of the unflavored agent. Its half-life is 24 hours so it should be dosed only once nightly.

Side effects

The main side effect is sedation, which is a reason to dose low and slow. In this effect, it is similar to

quetiapine, and a good alternative for those patients who benefit from quetiapine's sedating effects for sleep or anxiety.

Unlike quetiapine and olanzapine, this agent does not cause metabolic syndrome, or have direct harmful medical effects on cardiovascular or diabetes risks. It does not tend to cause weight gain as a common side effect.

Fast Facts: Asenapine

Typical dose: 5-20 mg/d

Biological mechanism: Dopamine/serotonin blockade

Typical side effects: sedation, akathisia

Medically important side effects: none

Clinically proven efficacy: FDA indication for acute mania and schizophrenia

The most common other side effect is akathisia, which occurs similarly to other agents in its class. Parkinsonism also occurs as is typical for its class.

The PL Bottom Line

- Asenapine has no metabolic syndrome harms, and no/little weight gain.
- It is sublingual and can taste bad.
- It is sedating and can help sleep.
- It is effective in mania and may help in mixed states.

PL Reflection

Life without enemies is impossible. We can only hear the truth from our enemies.

Plutarch

Upcoming Courses/Seminars

by PL Editor Nassir Ghaemi MD

July 2017 - Cape Cod, MA

Becoming a Master Clinician: Diagnosis, Drugs and Existential Psychotherapy,

New England Educational Institute,

July 24 - 28, 2017, Cape Cod, MA.

www.neei.org

August 2017 - Martha's Vineyard, MD

Clinical Psychopharmacology: Principles and Practice,

Harvard Medical School CME series

August 21-25, 2017, Martha's Vineyard, MA

www.capecodsummerseminars.com

October 2017 - Santa Fe, New Mexico

Becoming a Master Clinician: Diagnosis, Drugs and Existential Psychotherapy,

New England Educational Institute,

October 25 - 28, 2017, Santa Fe, NM.

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THE PSYCHIATRY LETTER

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Hippocratic psychopharmacology

In the prior PL issue, a discussion of the diagnostic interview, was presented, with a plan for two parts. However, the material in the July 2016 PL issue already covers that topic more fully, so this month PL will proceed to new but related material.

The importance of diagnostic interviewing has to do with the perspective that clinicians should treat diagnoses or diseases, not symptoms. The Special Article this month is about Hippocratic psychopharmacology, or the notion of treating diseases not symptoms.

The Article of the Month and the Case of the Month both relate to first-episode or treatment-naïve depression. The Drug of the Month is fluoxetine, Prozac, the classic modern antidepressant. A new Concepts and History of Psychiatry column provides ideas from the famed British psychiatrist Aubrey Lewis on the nature of knowledge in psychiatry. Curbside consult questions are provided.

We invite readers to attend either of the two summer CME courses described in the side bar, one in Eastham, Cape Cod, and the other in Martha's Vineyard, or the fall CME seminar in Santa Fe New Mexico. The last page provides details.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Hippocratic psychopharmacology

Treat diseases, not symptoms

As discussed in the last issue of PL, making a correct diagnosis is central to psychopharmacology. This approach is not followed in practice, where most clinicians simply treat symptoms. In this issue, PL analyzes this symptom-oriented psychopharmacology, with a critique derived from the Hippocratic tradition in medicine.

Principles of psychopharmacology: Implications of a Hippocratic approach

The father of modern medicine William Osler advised his students: "Read the journals and the old books." The journals keep us up-to-date on recent research; the old books give us perspective and provide universal principles. Among the old books, none are more central than the Hippocratic writings.

The principles of psychopharmacology follow from the principles of medicine, among which the Hippocratic approach is oft-misquoted and misunderstood. Hippocrates' view of medicine, in contrast to other schools, was that disease comes from nature: it is not unnatural. It's not something to fight against, but rather a natural process which nature itself can heal. The job of the physician is to help guide nature towards health, using measures such as diet and exercise, rather than to engage in combat with nature through medicines and toxins. The key Hippocratic idea is that nature heals, and doctor is only to handmaiden into nature. Nature cures, the doctor assists.

"Practice two things with disease: Either help or do not harm the patient."

Many, if not most, illnesses improve naturally, and our role is to not get in the way of nature, but to help nature along. Hence, the Hippocratics divided diseases into the self-limited, the treatable, and the incurable. In the first and third cases, treatments in general are unnecessary and often harmful; in the second case, they are needed. The art of medicine is to distinguish between these three cases.

It's important to realize that Hippocrates never said "First do no harm." This is a false statement, made up by a 19th century British physician and attributed to Hippocrates. In fact, Hippocrates is quoted as saying: "Practice two things with disease: Either help or do not harm the patient." (Epidemics, Book I, Chapter II) This correct quotation makes the point that there was no "First" to not harming. The first job of the physician was to help diseases, to treat diseases, not to take a generic conservative attitude of not harming. The idea of not harming grows out of treating those diseases we can treat, and not treating those diseases we cannot treat, as well as not treating those symptoms which don't reflect diseases.

Many clinicians practice non-Hippocratically. They think they should treat everyone who enters their offices. There is precedent for this view in the founder of American psychiatry, Benjamin Rush, who directly attacked the Hippocratic philosophy of treatment and who was a strong advocate of active intervention to treat all kinds of illnesses, including mental illness, through

bleeding. The Hippocratic approach was long forgotten in the Middle Ages and into the modern era. In the US, the Hippocratic philosophy was resurrected in the late 19th century by Oliver Wendell Holmes and William Osler.

Based on their writings, two rules can help clinicians engage in Hippocratic psychopharmacology.

Osler's Rule	Holme's Rule
Treat diseases, not symptoms.	All drugs are guilty until proven innocent.

Osler's Rule

The first rule is derived from the father of modern medicine, William Osler, who urged in 1895: "A man cannot become a competent surgeon without a full knowledge of human anatomy and physiology, and the physician without physiology and chemistry founders along in an aimless fashion, never able to gain any accurate conception of disease, practising a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which."

Osler emphasized that we need to learn first about diseases before we can do much about treatment. Osler's Rule is that we should treat syndromes (based on underlying diseases), not symptoms. Symptoms are not what need to be treated; they are signs which point to the disease (or diagnosis), which is what needs to be identified and treated. If clinicians followed this rule, they would avoid using drugs for multiple symptoms, which leads to a haphazard polypharmacy. In treating bipolar illness, for

example, patients often receive antidepressants for depressive symptoms, antipsychotics for manic symptoms, anxiolytics for anxiety symptoms, sedatives for insomnia, and mood stabilizers for mood swings. This symptom-oriented approach to treatment is prescientific rather than scientific, 19th century-based rather than up to date, and anti-Hippocratic. The Oslerian approach would be to focus on the diagnosis (not the symptoms), namely bipolar illness, and emphasize mood stabilizers, as much as possible by themselves, as the only class of treatment that treats the whole illness (acute depression, acute mania, and prophylaxis of mood episodes). In cases where the disease is not well-identified, or where perhaps no disease exists, treatment is symptomatic, of a band-aid nature, and the risk-benefit ratio for medication treatment would become more unfavorable to extensive prescription of such treatments. Such is not the case with bipolar illness, however, a diagnosis that has been well described since the Roman physician Arataeus of Cappadocia (2nd century AD) and whose biological basis is well-established.

"...practising a sort of popgun pharmacy, hitting now the malady and again the patient...."

This need not mean that we should never use medications merely to relieve symptoms. It does mean that this approach goes against the Hippocratic view of medicine, and we should take it only in the short-term, reluctantly, and for immediate relief of symptoms. In psychiatric populations where diseases are either poorly understood (as in children and the elderly), there is rampant symptomatic polypharmacy. And many psychiatrists consider this state of affairs to be acceptable. Osler's Rule would give us pause.

Holmes' Rule

The second rule is derived from the physician and writer Oliver Wendell Holmes Sr, who said in 1861: “Presumptions are of vast importance in medicine, as in law. A man is presumed innocent until he is proved guilty. A medicine...should always be presumed to be hurtful. It always is directly hurtful; it may sometimes be indirectly beneficial. If this presumption were established...we should not so frequently hear...that, on the whole, more harm than good is done with medication. Throw out opium, which the Creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it were foreseen that wherever there is hunger to be fed there must also be pain to be soothed; throw out a few specifics which our art did not discover, and is hardly needed to apply; throw out wine, which is a food, and the vapors which produce the miracle of anesthesia, and I firmly believe that if the whole *materia medica*, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, – and all the worse for the fishes.”

“A medicine...should always be presumed to be hurtful....”

Thus, Holmes’ Rule is that there must be empirical proof that a treatment is effective so as to outweigh the presumption against the use of a medication. If clinicians followed this rule, they would avoid treatment with medications whose efficacy has not been proven. As Osler put it, all medications are toxic; it is only the indication and the dosing that makes them therapeutic. Before using any medication, one must presume harm; the burden of proof is on the medication to be shown effective, not on anyone to show that the medication isn’t harmful. Risk-benefit calculations should begin, not on the risk side, but on the

benefit side. Otherwise we end up with a kind of “ gabapentin syndrome”—giving people safe, though ineffective, drugs (or alternatively, widely using drugs effective only for a few conditions).

For example, in the case of antidepressants for bipolar illness clinicians have been breaking Holmes’ rule egregiously. They have engaged in the extensive long-term use of antidepressants despite two decades of randomized maintenance data demonstrating that they are ineffective, at best, and harmful, at worst, in bipolar illness.

Often clinicians say they want more evidence to *stop* using antidepressants. If they were practicing Hippocratic medicine, and following Holmes’ rule, they would want evidence to *start* using medications, not to stop them. The burden of proof isn’t that medications should be used unless proven ineffective and unsafe, but that they shouldn’t be used unless proven effective and safe.

With antidepressants, and with amphetamines as well in ADD, many clinicians have gotten it backwards.

The PL Bottom Line

- The Hippocratic approach is not about general conservatism of treatment.
- Hippocrates never said: “First do no harm.”
- The Hippocratic approach is about avoiding treating symptoms without disease, but also about identify and treating diseases.
- Treat diseases not symptoms.
- All drugs are guilty until proven innocent.

Current Study of the Month: *Treatment response in first-episode depression*

Effects of patient preferences on outcomes in the predictors of remission in depression to individual and combined treatments (PReDICT) study. BW Dunlop et al, American Journal of Psychiatry. 2017; 174:546-556

All treatments are similar

The holy grail has long been sought: Prove that one treatment for depression is better than another. The STAR*D trial was funded by NIMH in large multi-center style to prove that one drug is better than another, or that combination of antidepressants might be more effective than a single agent. STAR*D found they were similar.

This trial reluctantly reaches the same conclusion.

In this NIMH-sponsored study, the special feature was supposed to be that all patients would be treatment-naïve, having never been treated for depression before, and most would be in their first depressive episode. In practice, it's quite difficult to identify and treat the actual first depressive episode of many patients, since most people don't seek treatment immediately. Rather, such "first episode" studies really reflect "first treated episode." In this study of the first treated episode, in fact about one-half of patients were in their first depressive episode. The other half had one or more prior depressive episodes.

This study is unique in that there are few if any prior first episode depression studies (in contrast to numerous first episode mania studies in bipolar illness and first episode psychosis studies in schizophrenia). To find first episode subjects, the researchers, centered in Atlanta at Emory University, had to resort to advertising for subjects. They also recruited from a large inner-city public institution, Grady Hospital, at a Spanish-speaking clinic where subjects were

identified who hadn't been previously engaged by the healthcare system.

A reasonably large sample of 344 patients was obtained, blindly randomized for 12 weeks of acute depression outcome to one of three arms: a pure SRI (escitalopram), a SNRI (duloxetine), and cognitive behavioral therapy (CBT). There was no placebo control, which is an unfortunate weakness. (One should prove, not assume, that these treatment-naïve patients wouldn't have improved by natural history or based on nonspecific psychological factors).

The main outcome was the Hamilton Depression Rating Scale (HDRS) score, which reduced similarly in all groups (10.2 improvement with CBT, 11.1 escitalopram, 11.2 duloxetine). The one point difference between

CBT and medications was clinically small and not statistically significant. However, at each week by week visit, CBT was slightly less effective than the medication options. Despite the vaunted marketing of "dual-action" on norepinephrine reuptake as well as serotonin, duloxetine was exactly the same in efficacy as escitalopram. This result contradicts the neuromythology that affecting two neurotransmitter systems produces more efficacy than affecting one....."

The researchers had wanted to find means to support "personalized medicine," a popular phrase these days. But they found nothing, or very little. In effect, it didn't matter if patients received a

pure SRI, a SNRI, or CBT: the result was more or less the same. Differences were minor.

In an accompanying paper, the same researchers report neuroimaging results that differentiate the antidepressant medication response groups from the CBT response groups. These distinctions involve the subcallosal cingulate cortex (SCC) connectivity to other areas of the brain. These findings may be important, but they were not the primary hypotheses of the study, and could reflect post-hoc false positive statistical findings. Nonetheless, they are interesting, suggesting that different regions of the brain may predict CBT response to medication response. However, again, no distinctions were found in comparing one kind of antidepressant medication to another.

Another aspect to understanding this study is the overall response rates, defined as 50% or more improvement in depression symptoms. Those response rates were 42% for CBT, 47% for escitalopram, and 55% for duloxetine. These response rates do tend to support somewhat increasing efficacy in moving from psychotherapy to single neurotransmitter effects to multi-neurotransmitter effects. But again, the effect sizes are relatively small, and not statistically significant.

Lastly, overall, as with STAR*D, only about one-third of patients had remission, meaning resolution of almost all depression symptoms. This is the same result as STAR*D, where most patients had recurrent episodes and prior treatment. Here in the PReDICT study, we have half the sample in its first episode, and none ever treated previously. And still the results of this treatment-naïve sample are the same as in STAR*D. In other words, the poor results in

*“...still the results of this treatment-naïve sample are the same as in STAR*D.”*

STAR*D didn't reflect a treatment-refractory sample.

These results aren't terrible. Half the patients improved short-term. But they aren't overwhelming either. Further, for those who interpret the limited benefits of antidepressant medications as implying a need to use more psychotherapy, the CBT results in this study indicate that psychotherapy isn't any better.

Perhaps because the treatment efficacy results weren't very exciting, this primary paper for this study emphasizes in its title the question of whether patient preferences for randomization influenced outcome. Before randomization patients were asked whether they preferred one of the three options; they were randomized irrespective of their preferences. The Hispanic subgroup had a preference against medication, while the African-American subgroup had a preference for CBT, and the white subgroup had no overall preference. These stated preferences didn't predict any differences in treatment outcomes, though. Instead, a mismatch of preference to randomized treatment (i.e., getting medication if you preferred CBT) predicted less treatment adherence, as expected.

The PL Bottom Line

- Antidepressant response in a treatment-naïve, partly first-episode depression population was not better than in the treatment-refractory STAR*D study.
- Duloxetine was only slightly more effective than escitalopram, if at all.
- Except for neuroimaging possibly, predictors of treatment response couldn't be identified

Drug of the Month: Fluoxetine (*Prozac*)

Once weekly dosing, ideal for cross-taper off other SRIs

Biological mechanism

Fluoxetine is the classic serotonin reuptake inhibitor (SRI), the first marketed in the US in the late 1980s. It is not a “selective” SRI, contrary to popular marketing, but instead has notable norepinephrine reuptake inhibition, similar in potency to medium-dose venlafaxine.

Clinical efficacy

Fluoxetine is FDA indicated for acute and maintenance treatment of major depressive disorder, bulimia nervosa, obsessive-compulsive disorder, and panic disorder. Combined with olanzapine it is FDA-indicated for acute depressive episodes in bipolar illness, and for treatment-resistant depression.

Besides these mood effects, fluoxetine and all SRIs have direct and immediate anxiolytic effects, especially at low doses. Patients with anxiety symptoms feel “better” but this effect can be misinterpreted as depression benefit. It may underlie the “better than well” phenomenon.

Dosing

The standard dose is 20-40 mg/d, with a maximum of 80 mg/d. The half-life is very long, being 4-6 days for fluoxetine, and 16 days for its active metabolite norfluoxetine. Given this very long half-life, it only needs to be dosed once weekly, and a trade Prozac Weekly formulation is proven effective in MDD at 90 mg/weekly.

Side effects

Nuisance side effects are nausea, diarrhea, apathy syndrome, and sexual dysfunction. Medically risky side effects include akathisia, which can lead to suicidality, which has been shown repeatedly to occur with fluoxetine, especially in children and young adults. As with all antidepressants, mania occurs with fluoxetine, though less given with dopamine blockers.

Serotonin withdrawal syndrome occurs after stopping this agent after long-term use, but it is less severe than with other SRIs. In fact, fluoxetine is useful as a cross tapering agent to allow for taper off other SRIs with less serotonin withdrawal syndrome.

Fast Facts: Fluoxetine

Typical dose: 20-40 mg/d

Biological mechanism: Serotonin and norepinephrine reuptake inhibition

Typical side effects: sexual dysfunction, akathisia

Medically important side effects: suicidality

Clinically proven efficacy: FDA indication for major depressive disorder, OCD, panic, bulimia

The PL Bottom Line

- Fluoxetine is not a pure SRI but has noradrenergic effects.
- It is a powerful immediate anxiolytic, more so than an antidepressant.
- The half-life for its active metabolite is 2 weeks. It need only be dosed once weekly.
- It causes akathisia and suicidality in young adults and children.
- It is useful as a cross-tapering agent with other SRIs for serotonin withdrawal syndrome.

Concepts and History of Psychiatry

Aubrey Lewis: Between guesswork and certainty in psychiatry - 1958

[In this issue of PL we are beginning a Concepts and History of Psychiatry section in the newsletter, seeking to provide readers with primary source material access to thinkers in psychiatry, along with commentary and context from PL.]

We begin with Sir Aubrey Lewis (1900-1975), who was the most prominent figure in British psychiatry through most of the 20th century. He was the leader of the Institute of Psychiatry at the Maudsley Hospital for much of the middle of the 20th century. That institution in London was the most influential educational center for psychiatry in the nation. Through his leadership there, Lewis was extremely influential. His articles and essays are masterpieces of psychiatric thinking in English prose. Their style and clarity are impressive, even where the reader might not agree fully with the content. PL hopes to present other articles and essays by Lewis in future issues too.

In this 1958 essay, Lewis addresses the general question of the extent to which psychiatrists know anything. This article, published in the *Lancet* (Volume 1, pages 171-5 and 227-30, 1958), was directed toward a medical audience that was skeptical about the professional credibility of psychiatry. The original text follows.]

It is the common state of reflective and inquiring minds to be somewhere between untrammeled guesswork and certainty....We [psychiatrists] are, however, sometimes suspected of luxuriant speculation and of invincible faith in our tenets: and I propose to soldier how this reputation has arisen.

More than most branches of medicine, psychiatry can be regarded as an art. One of its distinctive procedures - psychotherapy - manifestly depends on subtle relationships and incommunicable qualities of personality....Psychiatry in this is like the rest of medicine, combining moral and

personal principles of action with those arrived at by the methods of science, and depending on the last for any increase in its power to prevent and control disease....'

It would be easy to pile up instances showing that psychiatry is not the only branch of medicine - or of knowledge - to be pilloried for lax thinking and complacent dogmatism. It has, however, troubles which seem peculiar to itself, and some ministrants who seem peculiarly indifferent to the scientific method as understood by the rest of the world....

The aims of medical treatment are ordinarily to remove or lessen disabilities and pain, to put an end to morbid changes in the patient's body of which he may not be aware but which must sooner or later cause disability, and thirdly, to enable him to live satisfying a life as possible, in spite of persistent disability and morbid process. Applied to mental illness, all this becomes equivocal. The patient will often be unaware of disturbances very plain to others; he may not complain of his symptoms; he may even cherish them.

He may lead a less satisfying life when his symptoms have been got rid of than when he had them. The morbid process often has no physical substrate that we know of: and the psychopathology may be obscure and inaccessible. The criteria of recovery are therefore hard to specify, and like the criteria of improvement, depend on an assessment of the patient's happiness, competence, and well-being which involves moral and social values as well as plainly medical ones....

A rather silly but often repeated truism says that the aim of psychiatric treatment is to promote mental health. It is hard to tell what the latter phrase means. Mental health is an invincibly obscure concept.... [It] is an abstraction which is very loosely interpreted....

[Lewis goes on to criticize our ability to know if our treatments work, whether they be physical, like insulin coma or drugs, or psychotherapeutic]

...the medley of 'tranquilizing' drugs may pass... into the like chiaroscuro of approval and rejection. But the doubts which attend physical methods of treatment are dwarfish alongside the giant misgivings and disputes which envelop psychotherapy in dust and fog. The trouble is of long standing, and has divided psychiatrists bitterly... Psychotherapists are seldom skeptical or, as one might say, ambivalent about the treatment they give, and 'philosophic doubt' is not in keeping with their metier.... Here then is a great domain of psychiatric practice in which there has been an excessive proportion of guesswork and rather a lot of subjective certainty....

There are some awful warnings of what a craving for certainty can lead to. You may remember the philosopher Cratylus who, as Aristotle tells us, decided never to say anything but what was certainly true, and so he ceased to talk at all and confined himself to wagging his finger. Psychiatry suffers much from hopeful illusions and cliches used as incantations, just as a few decades ago it suffered, even more, from pessimistic and resigned inertia.... It is easy to lay failings like those at the door of psychiatrists, blaming their lack of scientific training, their loose habits of thought, their incuriosity, their passion for psychoanalysis or for physical methods of treatment, their preoccupation with the fascinating art of understanding other people. To think this seems to me facile and unjust. More important than the deficiencies of doctors are the inherent complexity of the problems.....

I have not enlarged on the attainments of psychiatry, its solid groundwork of detailed, minute, and orderly observations, its empirical successes, its accretions thorough application so the basic medical sciences to clinical problems....

Clearly we are a long way from certainty, and when we meet anyone who is sure that he knows how to tackle the problems of mental disorder and to remedy the failings of psychiatrists and psychologists, we may recall Lord Lansdowne's remark: 'I wish I could be as sure of anything as Tom Macaulay is of everything.' Guessing, too, has its perils and is arduous: it takes unkindly to the discipline which is good for it. Yet between those who are nearly certain and those who guess much there is the bond which Isaac Newton spoke of: 'I doubt not we have one common design: a sincere endeavor after knowledge, without valuing uncertain speculations for their subtleties, or despising certainties for their plainness.'

PL Comment:

In his analysis, Lewis places the limitations of psychiatry in context. Our knowledge in psychiatry, Lewis asserts, lies somewhere between guesswork and certainty. It is not pure guessing, nor is it certain knowledge; yet much of medicine and science is the same. Lewis emphasizes the extent to which psychiatrists can feel overly certain about their theories, and how much they can be deeply unscientific, failing to test those theories. Lewis concludes that the largest part of the problem is the complexity of the nature of psychiatric problems. We know so little, and our most basic concepts, like mental health, are inscrutable.

PL appreciates Lewis' frankness, but he veers too far at times toward his own version of excessive skepticism. Yet there is much to learn from his clear thinking, which future issues will explore.

PL Reflection

Disease has a plurality of forms and a plurality of cures.

Hippocrates

Case of the Month

A first depressive episode at age 18

An 18-year-old male has a first depressive episode. For the last two months, he reports decreased interest, energy, concentration, and appetite. Two weeks ago, his parents took him to his primary care doctor, who diagnosed depression, and began treatment with fluoxetine. The patient had no prior psychological problems or treatment, and has done quite well in school. A few days after starting fluoxetine, the patient reported some suicidal ideation, but denied any intent or plan. He also admitted to drinking some alcohol with friends. He has no other medical problems, no allergies, and is taking no other medications. There is no history of trauma, and he was raised in an intact and supportive family. He has multiple family members with depression, and one aunt diagnosed and treated for bipolar illness.

PL consultation was obtained. The observation was made that the course of illness and genetics of this case are more consistent with bipolar illness than major depressive disorder (MDD). The occurrence of suicidal ideation after treatment with fluoxetine was noted and a causal relationship implied. It was observed that the whole concept of MDD was associated with a lack of bipolar genetics and an age of onset around 30, as opposed to bipolar illness which began around age 19 and had bipolar genetics. The concern was raised that this depression may be the first episode of bipolar illness (with future mania), or at least cannot be the first depressive episode of MDD, given bipolar genetics and course of illness. The PL recommendation was to discontinue fluoxetine and begin lithium.

The patient saw a psychiatric nurse practitioner who concurred with the diagnostic and historical

assessment, but concluded that lithium was a "third line" treatment for more severe illness than this patient possesses. In contrast, fluoxetine was a less intensive and more conservative treatment. Fluoxetine treatment was continued, with a plan to consider lithium later.

The PL perspective is that fluoxetine is not a more conservative treatment than lithium in this case. Fluoxetine increases suicidal ideation and suicide attempts by about 70%, whereas lithium reduces completed suicides by about 90%, as discussed in a prior PL issue. Thus lithium is a more conservative treatment than fluoxetine from the perspective of suicide risk. Since this patient has suicidality, this issue is important. Further, the increased risk of suicidality with fluoxetine specifically occurs in patients in this young adult age group. Finally, the bipolar genetics of this patient raises the possibility that the patient may have bipolar illness, or at least does not have straightforward "MDD." Lithium is proven effective for both unipolar depression and bipolar illness, and is the only drug proven to reduce suicide risk. The psychiatric nurse practitioner's concern may have had to do with the perception that there are many more side effects with lithium than with fluoxetine, especially medical risks like kidney impairment. But, as discussed previously, lithium's kidney risk occurs in a 20-year time frame, and is irrelevant to treatment for an acute depressive episode. Also, even though lithium has a long list of side effects, most patients don't experience any of them, and they are dose related. Fluoxetine has its own list of concerning side effects as well, besides suicidality (which is bad enough), including severe sexual dysfunction and serious long-term serotonin withdrawal syndrome risk.

Curbside Consults

Questions and cases from you

Question: A 34-year-old woman with severe bipolar illness is prescribed lithium 900 mg/d, aripiprazole 20 mg/d, and hydroxyzine 50 mg BID for anxiety. She stopped taking aripiprazole for a month or so and then reported increasing anxiety. Her sleep is good when her family (child age 3 and husband) are away, but impaired when they are home. How should her anxiety be managed?

PL: Aripiprazole is a complicated medication. It is more effective for depressive symptoms at lower doses (<10 mg/d) and for manic symptoms at higher doses (>15 mg/d). In this case, it isn't clear what her current or recent mood symptoms have been. If she has been mostly depressed recently, then it would be reasonable to reduce aripiprazole to 5-10 mg/d to see if she is willing to take it, assuming she doesn't have akathisia or some other important reason why she can't take it. If she has had akathisia, or was recently or currently manic, then it likely makes sense to replace aripiprazole with a different dopamine blocker, like asenapine or risperidone. Despite her current anxiety, quetiapine would have the disadvantage of weight gain and metabolic syndrome, unlike asenapine. Another option could be to add divalproex to lithium, since divalproex has direct anxiolytic effects. It can cause weight gain, but it doesn't cause metabolic syndrome.

Question: To follow up on a prior PL curbside consult, I am sure I'm not alone in wanting PL's opinion about when/how to treat the painful symptoms of grief with medication when there is no prior history of depressive episode.

PL: The general recommendation made by PL was to differentiate grief from depressive illness

by the course of illness. If there are past depressive episodes, then this recurrent condition would be seen as an illness. The setting of grief could be seen then as a trigger, not a cause, of the current depressive episode.

The question seems to be whether and how and when one might consider medication treatment when grief is diagnosed, not recurrent depressive illness. In other words, the patient never had a prior depressive episode, but is currently experiencing severe grief.

Should such patients receive medications, like SRIs? The PL view is that in such settings the use of medication would be symptom-based, not disease-based. Symptom-based treatment is discouraged by PL, but this is a matter of emphasis not prohibition. One should prescribe medications less frequently, at lower doses, and for shorter durations, when such treatment is purely symptomatic.

So in this case of pure grief that is severe, a clinician might decide that some medication could be given if the patient refuses psychotherapy, or if the latter is not available, or if psychotherapy is not helpful enough. Any SRI could be used, such as citalopram or fluoxetine or sertraline, but PL would recommend as low a dose as possible, for as short a time as feasible. Thus, one might give sertraline 25 mg/d and if the patient remained symptomatic, increase to 50 mg/d. If there was sufficient benefit, it might be continued for 3-6 months, and then stopped.

Cultural considerations are relevant. A colleague in Egypt asked about treating grief there. In Muslim countries, grief is valued, even when severe. However, the clinician should keep an eye on patients so that suffering doesn't become extreme. Suicidality, if present, could be treated with low dose lithium 150-300 mg/d.

Upcoming Courses/Seminars

by PL Editor Nassir Ghaemi MD

July 2017 - Cape Cod, MA

Becoming a Master Clinician: Diagnosis, Drugs and Existential Psychotherapy,

New England Educational Institute,

July 24 - 28, 2017, Cape Cod, MA.

www.neei.org

August 2017 - Martha's Vineyard, MD

Clinical Psychopharmacology: Principles and Practice,

Harvard Medical School CME series

August 21-25, 2017, Martha's Vineyard, MA

www.capecodsummerseminars.com

October 2017 - Santa Fe, New Mexico

Becoming a Master Clinician: Diagnosis, Drugs and Existential Psychotherapy,

New England Educational Institute,

October 25 - 28, 2017, Santa Fe, NM.

www.neei.org

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THE PSYCHIATRY LETTER

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course in October 2017
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Bipolar or borderline?

In this issue, PL examines the classic debate about whether patients have bipolar illness or borderline personality. There are proponents that one or the other condition is under diagnosed relative to its opponent. Some claim that the two can't be distinguished in many cases, or that comorbidity is very common. The PL review concludes that they can be distinguished, as long as we focus on what differentiates them, as opposed to their overlap. Specifically sexual trauma, self-harm and dissociative states occur with borderline personality but much less so with bipolar illness. True comorbidity is much less common than what is claimed using DSM definitions.

The Article of the Month describes a new study which finds that stress in older persons leads to cognitive decline, possibly increasing the risk of dementia. The Drug of the Month is duloxetine, an SRI used for pain syndromes as well as depressive states. A curbside consult question is discussed regarding the use of low-dose SRIs for anxiety in persons with stable bipolar illness.

Last week, the July CME course was completed with excellent discussion and interaction in Cape Cod. There is still time to register for the late August course in Martha's Vineyard, which will provide a complete review of psychopharmacology. The October Santa Fe course will be broader and aimed at advanced clinician skills in scientifically sound diagnosis and treatment, with a special emphasis on existential psychotherapies. Both courses are taught by me, and will provide an extensive opportunity for PL readers to interact with me and with other clinicians about many of the ideas discussed in PL, as well as a good opportunity to receive extensive CME credits.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Bipolar or Borderline

Ignore mood swings and anger

Introduction

The differential diagnosis of bipolar illness and borderline personality is important, controversial, and difficult. Some claim that bipolar illness is overdiagnosed and that borderline personality is underdiagnosed. Others claim the reverse. Those who argue that bipolar illness is overdiagnosed often assert that those patients instead have borderline personality. Others claim the reverse. The most common approach to this controversy is to focus on the overlap between the syndromes and then to assert that one merely represents the other. It also would seem to make sense to focus on areas of difference, if indeed these are different conditions.

Borderline personality and bipolar illness have features in common, just as schizophrenia and anxiety conditions can also have symptoms in common (e.g., insomnia). One question is whether the similarities between borderline personality and bipolar illness are central to those conditions, or peripheral and secondary features.

In this clinical overview, PL gives a clinical and conceptual examination of how they are similar and how they differ.

Diagnostic validators

The classic diagnostic validators used in psychiatric nosology research are: symptoms, genetics, course, treatment response, and biological markers. The scientific literature on borderline personality and bipolar illness can be examined for these features. These are summarized in the table and are presented based on the diagnostic validators of symptoms (mood

lability, impulsivity, parasuicidal self-harm, mania), genetics, course (sexual abuse), treatment response, and neurobiology.

	Bipolar	Borderline
Symptoms	Euphoric mood, increased activities	Dissociative symptoms Parasuicidal behavior
Genetics	Very strong	Nonspecific
Course	Severe recurrent mood episodes	High prevalence of sexual abuse
Treatment	Biological cure in 1/3	Modest drug effects
Biology	Hippocampal atrophy Amygala enlargement	Nonspecific

Mood lability

The diagnostic validator of symptoms or phenomenology can also be examined regarding the most common psychopathology discussed in the literature on bipolar versus borderline differential diagnosis: mood lability. Mood lability is here defined as rapid alternations or fluctuations in mood over minutes to hours. . It should be noted that mood lability is a DSM-5 criterion for borderline PD, but not for bipolar illness. It is common in bipolar illness, however.

One study of 29 subjects reported being able to distinguish mood lability between these two

conditions, based on type and intensity of mood shifts; it was small and based on self-report, however. Another study of 55 subjects did not have a bipolar illness alone group (only one comorbid with personality disorders) and thus could not address the question.

In sum, small differences in intensity or frequency may exist, but mood lability is common in both conditions, and is not a strong distinguishing feature between them.

Impulsivity

The symptom of impulsivity is closely allied to mood lability, and is often seen as manifesting as sexual impulsivity in these two conditions, although it can also be physical or aggressive or financial. There are many studies demonstrating high impulsivity in both conditions separately, but very few have directly compared the two conditions, and in most of those studies, adequate comparison was not made between subjects who met only criteria for one or the other condition, as opposed to comparing one diagnosis versus a comorbid control group. Thus, as with mood lability, impulsivity seems to be common in both conditions and has not been shown to be distinctly different in one condition versus the other.

Parasuicidal self-harm

Another key differentiating feature is parasuicidal self-harm. A recent systematic review of 51 articles found that self-mutilation is common in borderline personality (50 to 80% of cases) and is frequently repetitive (41% of patients have more than 50 self-mutilation acts). The largest study of parasuicidal behavior in bipolar illness, and the only such study in an unselected non-clinical population (i.e., a general population sample) is

"...mood lability is common in both conditions, and is not a strong distinguishing feature between them."

found in the National Comorbidity Survey ($n = 5,877$). In that study, the prevalence of self-harm among patients with type I bipolar illness was only 0.9%. The importance of the NCS data is that they are epidemiological, not clinical. They are based on determining prevalence of parasuicidal behavior in persons with bipolar illness who are in the community, not those who seek treatment in clinicians' offices. By using clinically-selected samples, higher rates of parasuicidal behavior are seen, even in bipolar type I illness, in some studies, but these samples involve a selection bias of those who seek help and do not generalize to the entire bipolar population. Even with this limitation, the highest parasuicidal behavior rate reported in clinical studies is 36%, which remains two-fold less frequent than in borderline personality. In contrast, the NCS study does generalize to the whole bipolar population and is probably the most valid data on which to base judgments about parasuicidal self-harm prevalence. In the general population, self-mutilation is reported to occur in only about 4% of non-clinical samples, compared with 21% of clinical samples (patients with psychiatric diagnoses of varied types). Hence, the rates of parasuicidal behavior in the NCS non-clinical sample of bipolar illness is similar to the general population, even slightly lower, and comparable to other clinical samples of psychiatric conditions (excluding borderline personality).

In sum, compared to bipolar illness, borderline personality involves at least a two-fold increased relative risk of parasuicidal self-harm in clinical samples. In the general population, this difference is immense, about a 50-80 fold higher rate in borderline personality. This difference compares favorably to the classic association of cigarette

smoking and lung cancer, in which a 5-8 fold effect size has been considered to be quite large and convincing. Given the literature reviewed above, similar judgments would seem to be reasonable in the case of parasuicidal self-harm and borderline personality.

Manic symptoms

The most straightforward diagnostic validator may be symptoms. A few studies have assessed whether the presence of manic symptoms or manic/hypomanic episodes can distinguish bipolar illness from borderline personality. The largest study (n= 5635), which assessed an unselected mood population with depressive episodes, examine mixed states, defined as the presence of three or more DSM-IV defined

manic symptoms, of any duration, along with a major depressive episode. This definition of "mixed depression"

differs from the DSM-IV definition of a full manic episode lasting at least one week in duration, co-occurring with a full depressive episode. This definition of "mixed depression" included patients who would meet DSM-IV defined bipolar disorders, type I or II, or DSM-IV defined major depressive disorder (MDD). In other words, "mixed depression" reflects a mood disorder population. The question was whether manic symptoms in this mood disorder population were also found in subjects who met DSM-IV criteria for borderline personality disorder. Using this broad "mixed depression" definition, DSM IV-defined manic symptoms occurred much more frequently in "mixed depression" than in borderline personality. In contrast, borderline personality had more of the following DSM-IV features than did patients with "mixed depression": fears of abandonment,

"...manic symptoms distinguish bipolar illness from borderline personality."

identity disturbance; recurrent suicidal or self-mutilating behavior, and dissociative symptoms.

In sum, the literature on presence or absence of manic symptoms supports the view that manic symptoms distinguish bipolar illness from borderline personality.

Genetics

The most definitive review of the immense genetic literature on bipolar illness compared to personality disorders and other conditions is a systematic review of twin studies of genetic heritability. In that systematic review, bipolar illness was found to be one of the two very heritable mental illnesses, along with schizophrenia, both having about 80% heritability, similar to Alzheimer's dementia. This rate is about twice as much as found in that systematic review for

borderline personality or other personality traits or disorders, which tend to have about 40% heritability. For instance, in a study of 2794 Norwegian twins, the genetic heritability of borderline personality was only 37%; in fact, all DSM-IV defined personality disorders fell into the 20-41% heritability range, with the highest being for antisocial personality disorder. Environmental heritability, in contrast, was 63-79%, indicated that it was the major causative feature for these conditions. These studies use personal clinical interviews to assess personality disorders using DSM-IV criteria. It has been reported, using the same Norwegian sample, that the addition of self-report evaluations leads to higher heritability assessments, reaching 69% for borderline PD, and generally in the 60-70% range for all personality disorders. Whether it is legitimate to add self-report to clinical interview in assessing personality disorders is a methodological question that remains to be

answered. But if one accepts clinical interviews as the gold standard, and thus compares personality disorders using that method which is the standard approach in genetic twin research, then the genetic heritability of borderline PD is much lower than bipolar illness.

It should be noted that 40% heritability is not zero; it indicates a modest genetic effect. But it is half as much as 80%, which is similar to the heritability of traits that are widely accepted to be mostly genetic, such as physical height.

In sum, using currently accepted standards of genetic twin research, bipolar illness is almost completely genetic in causation, with a small environmental component. In contrast, borderline personality is mostly environmental in causation, with a small genetic component.

“...bipolar illness is almost completely genetic...[while] borderline personality is mostly environmental in causation...”

Course of illness

A key course feature that potentially could differentiate bipolar illness from borderline personality is a history of sexual abuse. In a commonly cited meta-analysis of 21 studies, 50-76% of patients with borderline personality disorder had experienced sexual trauma. In contrast, sexual abuse occurs in less than 30% of bipolar subjects. These prevalence rates are based on a number of different studies with large samples, including systematic reviews. For instance, a recent systematic review including 3407 bipolar patients found a 24% prevalence of sexual trauma in bipolar illness. According to one of the most extensive national studies of the topic, the US Department of Health and Human Services reports a prevalence of childhood sexual abuse in the general population of 9.2%.

In sum, there is a consistent frequency of sexual abuse in bipolar illness that is similar to the general population rate in some studies, or possibly higher than the general population. Yet the frequency of childhood sexual abuse is consistently at least two-fold higher in borderline personality than in bipolar illness or the general population.

It has been noted the average effect size for the association between childhood sexual abuse and borderline personality is only moderate ($r = 0.279$), but this way of assessing the data does not contradict the frequency noted above. It merely addresses the fact that other causative factors also exist for borderline personality. In this setting, the question is whether this specific risk factor is common in borderline personality, not whether other risk factors also might be common.

Neurobiology

In bipolar illness, a number of consistent neurobiological changes are reported in dozens of studies. Although a range of abnormalities is found, two of the most consistent abnormalities found are hippocampal atrophy and amygdalar enlargement. These differences are shown in studies which compare bipolar illness both to normal controls and often to other psychiatric conditions, like schizophrenia.

In contrast, there are fewer studies of neurobiological changes in borderline personality, and some abnormalities found compared to normal controls, such as deficits in integration between cognition and emotional processing stimuli, are not unique to borderline personality but are also found in other neuropsychiatric

syndromes, including schizophrenia and bipolar illness.

Treatment response

Treatment response has generally been seen as the most nonspecific diagnostic validator, as medications can affect varied diagnoses. However, certain treatment effects may be diagnostically specific. Regarding bipolar illness versus borderline personality, there is a strong consensus after a century of practice and research, that psychotherapies alone are not effective in bipolar illness. They may be effective adjunctively with medications, but not by themselves. In contrast, there is a similar strong clinical consensus for decades that psychotherapies are central to the treatment of borderline personality; many experts in borderline personality see medications as adjunctive treatments for that condition. Many randomized clinical trials (RCTs) of bipolar illness exist, and demonstrate good efficacy with various agents, like lithium, in prophylaxis of that condition, sometimes with complete remission. In contrast, fewer RCTs exist of treatment with medications for borderline PD, and they tend to demonstrate modest symptomatic benefits with psychotropic medications.

In sum, it would seem to be a fair reflection of a long-held clinical consensus that treatment response in bipolar illness versus borderline personality tends to be inverse: in bipolar illness, appropriate psychotropic medications are necessary, with psychotherapies being adjunctive; in borderline personality, appropriate psychotherapies are seen as necessary, with psychotropic medications being adjunctive.

“...these conditions appear to be different in a number of major diagnostic validators.”

Discussion

Reviewing the empirical evidence on classic diagnostic validators, it appears that bipolar illness and borderline personality are distinguishable and different. The most clear differentiating features appear to be a family history of bipolar illness, parasuicidal self-harm, and past sexual abuse, each of which is at least twice more frequent in one condition versus the other. Treatment response also appears to differ markedly, with medication efficacy much stronger and central to treatment of bipolar illness, whereas psychotherapies are not effective alone; in borderline personality, medication effects are modest at best, while psychotherapies are central to its treatment. Symptom features do not differentiate between these conditions as clearly as the above genetic, course, and treatment validators. Mood lability and impulsivity not different in any clearly proven and replicated manner between these conditions; manic symptoms and manic episodes may differentiate between them but direct comparative studies

are few. A large neurobiological literature also exists that finds abnormalities in bipolar illness to a more consistent and definitive degree than in borderline personality. A number of direct comparisons exist which demonstrate more neurobiological abnormalities, and often of different kind, in bipolar illness than borderline personality.

In sum, these conditions appear to be different in a number of major diagnostic validators. To summarize: bipolar illness is a very genetic condition with a large amount of neurobiological abnormalities that requires medication treatment as central to its management. In contrast, borderline personality is a mostly environmental

condition with fewer neurobiological abnormalities that requires psychotherapies as central to its management.

One way of summarizing the proposed interpretation given in this review is that while there are superficial similarities between bipolar illness and borderline personality, there are profound differences. The comparison is between red apples and red skies; redness is shared, but these are two very different entities.

“Comorbidity”?

Even if borderline personality and bipolar illness can be distinguished, it may sometimes be the case that they can occur together. For instance, since bipolar illness is a genetic and biological condition, persons who are genetically predisposed to it are also likely at higher risk of sexual impulsivity being present in family members with bipolar illness; sometimes this may lead to sexual trauma that can derail personality development and eventually lead to borderline personality. This kind of co-occurrence of different conditions is what was

meant by the introduction of the term “comorbidity” by Feinstein in 1970. In contrast, as the leadership of DSM-IV has explicitly stated, the DSM psychiatric nosology has been set up allowing for extensive overlap in diagnostic criteria so as to encourage diagnosis of multiple conditions at once. This “comorbidity” could rationally be attributed to our DSM system, rather than nature. Hence the application of DSM criteria and report of high comorbidity rates between bipolar disorder and borderline personality disorder does not imply that those conditions are highly similar.

“...comorbidity could rationally be attributed to our DSM system, rather than nature..”

A final historical point is that bipolar illness is derived from manic-depressive illness, which has been well-defined in the scientific literature for over a century, if not much longer dating to ancient Rome. Borderline personality, in contrast, was first clearly defined in the psychoanalytic literature in the late 1960s, and thus is a more recent construct. Bipolar illness is based on standard medical methods: observation of signs and symptoms and course of illness. Borderline personality is partly based on such standard medical observation, and DSM criteria are not specifically psychoanalytic in nature, but the most prominent borderline experts emphasize that this condition is also centrally determined by certain psychoanalytic concepts, such as splitting and projection and countertransference. Hence, the evaluation of the empirical literature here is consistent with historical and conceptual differences in how these conditions have been came to be conceived and continue to be understood.

Affective temperaments misinterpreted as borderline personality

Historically, it should be noted that the concept of manic-depressive illness as used by Kraepelin included depressive and manic episodes as part of the same illness, merely as gradations of severity, rather than as two separate illnesses. It can further be added that Kraepelin and Kretschmer held the view that even milder versions of mania and depression, namely hyperthymic and cyclothymic temperaments, were also part of manic-depressive illness. Recent clinical and genetic studies find high rates of these temperaments in persons with bipolar illness and their relatives. Since hyperthymia and cyclothymia are seen as mood temperaments, part

of personality, they can appear to be similar to clinical features that are often viewed as borderline personality traits, such as mood lability and impulsivity, which this review found to be nonspecific diagnostically. If the concept of mood temperaments is scientifically valid, it would require even more caution in making the borderline personality diagnosis in such persons who may not have bipolar illness type I or type II (i.e., full manic or hypomanic episodes) but have hyperthymic or cyclothymic temperament along with other features of manic-depressive illness (such as a family history of bipolar illness and severe recurrent depressive episodes).

Often it is emphasized that bipolar illness involves severe episodes. If symptoms are constant or chronic, borderline personality is presumed. But this conclusion ignores the concept of affective temperament. If sexual trauma and self-cutting are absent, then

cyclothymia often is misdiagnosed as borderline PD, since DSM-criteria easily diagnose the latter in persons with constant mood swings and anger.

The PL Bottom Line

- Borderline personality and bipolar illness are distinguishable clinically and diagnostically.
- Bipolar illness can be seen as a genetically-based biological disease, while borderline personality can be interpreted as a psychosocially-caused clinical picture.
- The two illnesses should be treated distinctly, with appropriate medications emphasized for bipolar illness and psychotherapies emphasized in borderline personality.
- Borderline personality may be misdiagnosed in persons with cyclothymic or hyperthymic affective temperaments.

PL Reflection

Psychiatry's motto is not the one Dante put over the gates of Hell: "Abandon all hope ye who enter here." Psychiatry abounds in hope....But the proper words to put over psychiatry's door are still not ones to quicken every pulse. For we must write there: "Accept uncertainty within, or do not stay"...Psychiatry is the part of medicine furthest away from settled maturity, as strong as any in observation (perhaps even the richest, considering that social observations are much better accepted in psychiatry than in most of medicine), and weakest in correlations and calculations. It is like an adolescent, disputatious, alternately arrogant and humble, strong, full of promise, inconsistent, able to see what others can't, even preoccupied with sex.

Leston Havens

A Safe Place

Current Study of the Month: *Does stress cause dementia?*

Perceived stress and cognitive decline in different cognitive domains in a cohort of older African Americans. AD Turner et al, American Journal of Geriatric Psychiatry. 2017; 25:25-34

It seems so

Does stress cause dementia? We know that stress is bad for the body and the brain. When you are stressed, and in your fight and flight mode, the hypothalamic pituitary adrenal (HPA) axis is in overdrive. Steroids get produced, go directly into the brain, directly into the neurons, stimulate neurons excessively, and kill them (excitotoxicity). Stress is bad.

But does it cause dementia directly? Or is the effect mediated by depression or inflammation or some other mechanism.

In this study, part of the Minority Aging Research Study, older African Americans without dementia (mean age 73 years) were given a battery of 19 cognitive tests every year for a mean of 4 years (up to 9 years maximum). Stress was measured using a 4 item scale (Cohen's Perceived Stress Scale, PSS).

Higher stress on the PSS correlated with decline in global cognition as well as episodic memory and visuospatial ability. This effect was present even after correcting for age, gender, education,

presence of depression, and vascular risk factors (like diabetes or hypertension).

In sum, if you follow healthy older African Americans in their early 70s, they are more likely to have cognitive problems by their mid to late 70s if they have a lot of stress.

This finding is stronger than might otherwise be the case because they have corrected for other possible reasons for developing cognitive impairment, like depression or hypertension or diabetes. There could be other confounding factors that were not measured in this observational study, which could be the real explanation for the changes observed. But, it could be that stress does have an independent effect on cognitive decline in older persons.

The PL Bottom Line

- Stress is an independent predictor of cognitive decline in older persons in this study.
- Besides depression or hypertension or other risk factors, stress is an important remediable risk factor for dementia.

PL Reflection

We haven't got the money, so we will have to think.

*Lord Earnest Rutherford
physicist*

Drug of the Month: Duloxetine (*Cymbalta*)

Souped-up Prozac

Biological mechanism

Duloxetine is similar to fluoxetine, from which it is derived, having serotonin and norepinephrine reuptake blockade. Both agents share the same mechanism; the only difference is in potency. While fluoxetine has mild norepinephrine reuptake inhibition and strong serotonin reuptake inhibition (and thus has more SRI than NRI effects), duloxetine has moderate norepinephrine reuptake inhibition and strong serotonin reuptake inhibition. They are thus more similar than different, and duloxetine still is primarily an SRI (not a "NRI", contrary to its marketing).

Clinical efficacy

Duloxetine is FDA indicated for acute depressive episodes in major depressive disorder (MDD). It also has FDA indications for generalized anxiety disorder, fibromyalgia, chronic pain, and diabetic neuropathy. It has been shown to help pain in depression, and tends to be used by clinicians for pain syndromes. It has never been shown to be more effective than any other monoamine agonist (antidepressant) for depressive episodes.

Dosing

The standard dose is about 20-60 mg/d, with a maximum of 120 mg/d, given once daily at night. For MDD, doses above 60 mg/d have not been shown to be more effective. The half-life is about 12 hours.

Side effects

Nuisance side effects involve sexual dysfunction, diarrhea, and apathy, as with all SRIs. Medically important side effects are uncommon, though, as with all SRIs, there is some risk of osteoporosis and gastrointestinal bleeding (due to inhibition of blood clotting).

The main problem with this agent is that it has a very severe serotonin withdrawal syndrome. This syndrome tends to happen after about one year of constant use. Since this agent is used long-term in

many persons for chronic pain, the serious withdrawal syndrome means that if clinicians give this medication long-term, they are committing patients to indefinite treatment, as it will be very difficult to

come off it ever. If needed, direct taper is almost impossible. In that case, cross-taper with fluoxetine is the best option.

The PL Bottom Line

- Duloxetine is a SRI with somewhat stronger norepinephrine reuptake blockade than its cousin, fluoxetine.
- It is effective in pain syndromes, like fibromyalgia.
- It has typical SRI side effects like sexual dysfunction.
- It has terrible serotonin withdrawal syndrome, complicating long-term treatment.

Fast Facts: Duloxetine

Typical dose: 20-60 mg/d

Biological mechanism: Serotonin/norepinephrine reuptake blockade

Typical side effects: sexual dysfunction

Medically important side effects: severe serotonin withdrawal syndrome

Clinically proven efficacy: FDA indications for MDD, GAD, fibromyalgia, diabetic neuropathy, chronic pain

Curbside Consults

Questions and cases from you

Question: Sometimes, patients have severe anxiety all their lives, which persists even when the bipolar illness is under control and offending agents like amphetamine stimulants are discontinued. I've seen a person who was a complete nervous wreck all her life until Viibryd 40 mg was added. Lithium, Viibryd, Latuda 120 mg and Ativan 1 mg bid have gotten rid of 90% of her anxiety. If successfully treating the bipolar disorder still leaves severe anxiety, do you think sometimes it is okay to use SSRI medicines in that the pros and cons lean towards the pros of using SSRIs and then there will be cases where it will not destabilize the person's mood? I usually use 1/4 of the depression dose of the SSRIs to treat the anxiety so as not to destabilize mood. 20 or 40 of Viibryd is my go-to medicine now for severe anxiety and I have 40 people who every month say this is very helpful.

PL: The March 2015 PL issue described how anxiety is a symptom, not usually a disease or "disorder" itself. If someone has bipolar illness, and they are adequately treated such that they no longer have definable mood episodes of any notable severity, then the continued presence of anxiety would rule out the idea that the bipolar illness itself caused the anxiety. However, two other options exist.

One possibility is that the anxiety is part of the personality trait of neuroticism, as described in the May 2015 PL issue; the person just is highly anxious as part of her personality, just as some people are tall or short, and some people are introverted or extroverted. That's not a disease that can be taken away with medication. It's not an illness to improve. However, you could make the argument that such personality traits can be

modified modestly with medications, and that one can "take the edge off" the anxiety as part of the personality trait, and that some benefit would ensue functionally or subjectively. Another possibility, which is often ignored, is that the mood episodes may not be causing anxiety, but the person may have an affective temperament which could be causing the anxiety.

As reviewed in the June 2016 PL issue, affective temperaments are quite common, occurring in about 50% of persons with bipolar illness or unipolar depressive illness, and in many of their relatives. In other words, in between mood episodes, these persons have constant mild mood symptoms. They are either always manic (hyperthymia), always depressed (dysthymia), or always both (cyclothymia). Especially in the cases of the manic temperaments (hyperthymia and cyclothymia), it is common to have a good deal of anxiety (and often distractibility), leading to misdiagnoses of GAD or adult ADD.

These possibilities need not be mere speculations. Affective temperaments can be measured using the 50 item TEMPS scale. On the PL website, we will make available the TEMPS scale along with a scoring sheet for it. The cut-off PL recommends is that if 75% or more of the items are endorsed, then an affective temperament is present. Sometimes, 50% or more of items may be sufficient given the clinical history. If someone has cyclothymia or hyperthymia, then those temperaments could explain constant anxiety, even if full mood episodes are managed with the standard mood stabilizers. In that case, low dose SSRIs would not be recommended by PL, since those agents can worsen the manic symptoms of hyperthymia or the mood lability of cyclothymia.

If the TEMPS scale is negative, the NEO scale can be used to measure neuroticism. If the score is high, then in that case, it may be that the

person has the personality trait of high neuroticism. Low dose SRIs can “take the edge off” anxiety in that case. Such low doses may not destabilize bipolar illness in terms of causing mood episodes, especially if the personality is otherwise normothymic (ie., no affective temperaments). In that case, such judgments as our colleague makes here may be relevant. However, even there, one is committing the patient to life-long treatment without the option of coming off SRIs, due to severe serotonin withdrawal syndrome. One wonders whether low dose benzodiazepine might not be a better alternative. There is withdrawal there too, but

usually not as severely as with SRIs. There is tolerance and a very small addiction risk of course, which is higher in persons with substance abuse. Either way, whether with SRIs or benzodiazepines, the treatment of neuroticism with medications is a low risk, low yield proposition. Such symptomatic treatment has modest benefit at best, so even with small risks, the benefit-risk ratio is questionable, especially long-term. In the prior PL issue on Hippocratic psychopharmacology, such symptom oriented treatment was discouraged since in the long run, more harm than good occurs.

Upcoming Courses/Seminars

by PL Editor Nassir Ghaemi MD

August 2017 - Martha's Vineyard, MD

Clinical Psychopharmacology: Principles and Practice,
Harvard Medical School CME series

August 21-25, 2017, Martha's Vineyard, MA

www.capecodsummerseminars.com

October 2017 - Santa Fe, New Mexico

Becoming a Master Clinician: Diagnosis, Drugs and Existential Psychotherapy,
New England Educational Institute,
October 25 - 28, 2017, Santa Fe, NM.
www.neei.org

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THE PSYCHIATRY LETTER

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Summer Double Issue

This issue is a summer double issue, consisting of a longer newsletter. In this issue, we review some of the discussions in the summer seminars taught in Cape Cod and Martha's Vineyard.

The Article of the Month has two separate articles from the same issue of the American Journal of Psychiatry recently. They both address suicide, with one showing that suicides occur commonly in the year following a suicide attempt, and the other showing that lithium, but not valproate, prevents suicide attempts. The Drug of the Month is clozapine, a uniquely effective and uniquely harmful antipsychotic. The case of the month addresses the problem of stopping antidepressants when clinicians don't realize they are ineffective. A curbside consult question is discussed regarding the combination of an antidepressant and an antipsychotic, the "poor man's mood stabilizer."

The Concepts and History column follows up on the May 2017 PL issue with a second installation of writings from the British psychiatrist Aubrey Lewis on how psychiatrists should be educated. His comments apply to all mental health clinicians.

The October Santa Fe course remains open for registration. It will be broad and aimed at advance clinician skills in scientifically sound diagnosis and treatment, with a special emphasis on existential psychotherapies. For those PL readers in the Midwest or Western states, this course will be an opportunity for interaction on PL themes.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Summer Seminars

Clinical discussions about PL themes

Introduction

This year's summer seminars on Cape Cod and Martha's Vineyard provided an opportunity for the PL editor to interact with colleagues about clinical themes that are the topic of discussion in PL. Among these themes, the following topics generated special interest and here PL reports on some of the discussions that occurred.

ADD validity

A frequent topic of controversy in the PL summer seminars, especially among child psychiatry colleagues, is the validity of the concept of ADD. As reviewed on the PL website and in a prior PL issue, the viewpoint held here is that ADD in some children represents a temporary developmental delay in cortical maturation, not a permanent disease. In other children, apparent ADD is not ADD at all, but rather the mistaken diagnosis of cognitive effects of other diseases, such as affective illness (bipolar or unipolar) or anxiety conditions (like OCD). The PL view is that the ADD diagnosis in adults is not a valid disease either. Commonly, it again represents a mistaken diagnosis of cognitive effects of other diseases, such as affective illness (bipolar or unipolar) or anxiety conditions (like OCD) or anxiety symptoms (themselves caused by another illness, like bipolar or unipolar conditions). In some people, apparent ADD in adults represents the extreme of the normal psychological trait of attention.

Further, in the summer sessions, we reviewed recent large prospective studies of children followed into adulthood. One study followed 8-year-old children until they were 41 years old.

“...80% of these apparent adult ADD cases are not ADD at all.”

Another study followed teenagers into their 20s. In both cases, about 80% of children with ADD did not have ADD any longer in adulthood. Further, about 80% of adults with ADD did not have it as children. Keep in mind these are prospective data, with prospective controlled groups. It isn't a matter of faulty recollection, or of not having been diagnosed in the past because it wasn't assessed. They were assessed and followed carefully as cases and controls from childhood into adulthood.

These results throw major doubt into the concept of the validity of “adult ADD” in particular, since the DSM criteria require that such adults who meet ADD criteria would have met it also as children. This assessment is done retrospectively usually in clinical practice. But these prospective long-term data show that 80% of these apparent adult ADD cases are not ADD at all (since they were followed prospectively from childhood when they were assessed and found not to have ADD).

A reaction seen by some child psychiatry colleagues is that they might be applying DSM criteria strictly in a 7-year-old, and they obtain collateral verification from teachers and parents. They then continue to confirm the ADD diagnosis into adolescence or even adulthood. This clinical approach is legitimate, colleagues will say, and contradicts the PL perspective.

The PL view is that these clinical colleagues are applying our current diagnostic definitions for ADD correctly. The real question is whether those definitions themselves are correct. In other words, there is no criticism implied here about

how child psychiatry or adult psychiatry colleagues practice. There is no “misdiagnosis” in the sense that they should have known better to diagnose otherwise. The PL critique rather is that the DSM system-based ADD diagnoses which are being implemented may be invalid themselves, and thus their accurate usage is the fault not of clinicians but of the DSM system itself.

Invalidity of maintenance studies in psychiatry

The summer sessions examined the maintenance clinical trials used in psychiatry. The designs used are called “enriched” because they preselect treatment responders, before the study begins, and then they randomize only the responders to enter the study, in which they either continue the study medication, or get taken off (and put on placebo or another control medication). By selecting only treatment responders for treatment response studies, this design is tautologous and invalid, in the PL view. The dopamine blocker data in bipolar illness and monoamine agonist data in MDD were analyzed and the evidence for this invalidity was reviewed. (See PL website for a brief summary and for linked papers).

Clinicians were impressed by this analysis but felt confused about what it means? In the case of dopamine blockers, the PL view is that those agents are not “mood stabilizers,” i.e., they should not be used by themselves in the long-term treatment of bipolar illness. They are not replacements for lithium and anticonvulsants; they are adjuncts at best. In the case of SSRIs and other monoamine agonists in so-called MDD, the PL view is that the jury is out. These agents are not proven to be effective in prevention of mood episodes in “MDD”, for the reasons given above, nor is there counter proof that they are

“...dopamine blockers are not ‘mood stabilizers’...”

ineffective. There just isn’t sufficient data on which to make a clear judgment. In this setting, the PL recommendation is to be cautious and certainly not to routinely prescribe these agents for all or most patients with MDD long-term. Some patients may receive these agents long-term, but not all need do so. Lithium is proven to prevent mood episodes in unipolar depression, and is a proven alternative. Lamotrigine has not been studied in prophylaxis of depressive episodes in unipolar depression, but PL hypothesizes that it may be effective. Potential benefits with valproate and carbamazepine are unknown.

When would you use antidepressants?

The summer sessions also reviewed the acute efficacy data with monoamine agonists in MDD, both the FDA database of pharmaceutical industry studies as well as the classic NIMH-

sponsored STAR*D study. Both analyses show, in the PL interpretation, that monoamine agonists are not effective in most patients with acute depressive episodes diagnosed with “MDD.” They are effective for a subgroup of those patients. Based on subgroup analyses, the PL view is that antidepressants are ineffective in mixed states and mostly in melancholia. They improve mild depression that likely represents neurotic depression, but not pharmacologically, since placebo produces similar benefit. They also likely are less effective in vascular depression. Thus, there is no reason to use monoamine agonists in the majority of apparent cases of MDD: mixed depression, melancholia, vascular, and neurotic depression. The remaining patients, whom one could call “pure” depression, may respond to monoamine agonists, but mainly for severe episodes, and mainly short-term as opposed to long-term. The latter point is based

on the STAR*D finding that about one-half of patients who respond to a monoamine agonist for an acute depressive episode will lose their response, and relapse into another depressive episode, within a year, despite continuing the same agent which had helped them. The PL view is that this observation is not “tolerance” but rather poor maintenance efficacy (prevention of future episodes) as opposed to acute efficacy (treatment of a current episode).

Is existential psychotherapy scientific?

The PL summer sessions at times included a discussion of existential psychotherapies, which are the least appreciated in the US. These approaches, which have varied forms, generally involve the method of empathy as central. There is no attempt to impose a theory (psychoanalytic, cognitive-behavioral), but rather to try to experience what the patient experiences. This sharing of experiences not only leads to more accurate understanding of what is happening, but it can be therapeutic itself.

One way of understanding it is the axiom of Elvin Semrad: To acknowledge, bear, and put perspective on affect.

Participants in the seminars wondered how this approach could be studied scientifically. How do we know it works?

This good question applies also to psychoanalytic therapy, which is very individualized, as is existential therapy. One cannot standardize a person's dreams or free associations, just as one cannot standardize empathy. In this respect, CBT can be studied scientifically more effectively. However, one can assess the outcomes of treatment, as has been done for psychoanalytic therapy, showing benefits in various ways. There

are fewer studies on existential therapies, but there are a few, showing similar benefits in outcomes in various settings (such as improved quality of life scores, or improvement in function).

Pessimistic or optimistic?

The perspectives presented in the summer seminars contrast with many aspects of establishment psychiatry: the DSM ideology, the frequent diagnosis of ADD, the common use of amphetamines and antidepressants. Some participants wondered whether the presentation of this alternative approach to psychiatry was too pessimistic. So often, the emphasis was on the various ways in which contemporary psychiatry resisted or ignored some of the ideas proposed.

An alternative approach would be to emphasize the benefits to be seen with this alternative approach to psychiatry, that we can treat patients better and get better results, if we put aside DSM, and if we are more critical and cautious in some diagnoses and treatments (like ADD, amphetamines, antidepressants). One could state the case more optimistically. Perhaps this approach would convince more clinicians.

One of the reasons PL was created was to create a community of clinicians who could think differently together, to create a place where it would be acceptable to challenge the status quo, and to provide reasons for thinking about psychiatry in a way that might be different than conventional assumptions.

Not all will be attracted, but some will.

The question is legitimate, though, about how to influence the recalcitrant.

There's an old anarchist saying from Mikhail Bakunin (popular in the 1960s student uprisings): Destruction is also a creative destruction.

To make room for new ideas, old ones need to be removed. Usually this process is resisted, and the change can be painful. There is likely an inevitable aspect of negativity, which will seem pessimistic to some. To be solely positive may not be possible, as new ideas will be ignored as long as the older ones are unchallenged.

This is a dilemma for all those who want progress in a profession.

And ketamine?

There is no doubt that there will be continued attraction to ketamine as a new treatment for depression, as shown in a recent Time magazine cover article. The most common misconception appears to be that clinicians and patients appear to think that ketamine is a long-term solution, whereas it only is shown to provide benefit for a few weeks. People will then say that it can be repeated monthly, but there are no randomized data that prove such efficacy. It's the same story as with ECT.

So if you want to feel better for a few weeks, and then get worse again, take ketamine. If you want long-term improvement, there are no scientific data to go to ketamine.

A nasally inhaled version of ketamine likely soon will obtain FDA indication for treatment-resistant depression, and major marketing will follow. PL will try to help readers stay on top of the hype behind the marketing, and focus on the science.

Instead of "treatment resistance," the PL view, based on data such as the STAR*D study, is that

*"To make room for new ideas, old ones
need to be removed."*

the common inefficacy of monoamine agonists has to do with the diagnosis of "MDD", which may be itself invalid, rather than the need for more effective "antidepressants." Instead, the diagnostic subtypes of depressive illnesses need to be better identified and treated with the correct agents (often dopamine blockers or second messenger modifiers/mood stabilizers).

The PL Bottom Line

- ADD and amphetamines remain a major source of clinical controversy. This issue is perhaps the most important clinical theme that needs clarification. The PL view is that the DSM definitions are either misleading or invalid.
- Adult ADHD may be misdiagnosed in persons with cyclothymic or hyperthymic affective temperaments.
- Long-term treatment with monoamine agonists in MDD is based on assumptions, rather than strong scientific evidence, given the likely invalidity of maintenance research designs of those agents in psychiatry.
- Be careful about ketamine: its benefits, if present, are short-term only. It is not a long-term solution to "treatment-resistant depression," which instead reflects, in the PL view, the invalidity of DSM-defined "MDD."

PL Reflection

Our wretched species is so made that those who walk the trodden path always throw stones at those who are showing a new road.

Voltaire

Current Study of the Month - I: *Suicide after a non-fatal suicide attempt*

Suicide following deliberate self-harm. M Olfson et al, American Journal of Psychiatry. 2017; 174:765-774

The risk is high in the next year

Suicide isn't the same thing as a suicide attempt. Clinicians often say something along these lines to argue that even if someone makes a suicide attempt, they aren't necessarily at high risk of eventually committing suicide. The same claim is made regarding the data showing an evidence of increased suicidality with SRIs in children and young adults. This increased suicidality reflects more suicidal ideation and suicide attempts; thankfully, in these 2-month trials where patients are selected so as not to have suicidal ideation, completed suicide does not happen. However, it is questionable to claim that since patients don't kill themselves in the first 2 months, they may never kill themselves. In fact, suicide attempts are important predictors of later suicide. This new study quantifies this relationship.

“...0.4% of the sample committed suicide in the following year.”

The other aspect to this debate is the question of parasuicide, or self-harm without intent to kill oneself, such as superficial cutting. Usually, such patients are thought not to be at high risk for later suicide. This study provides data on such patients.

The study examines a Medicaid database in the US. Patients were identified who had been recorded to have engaged in “deliberate self-harm”, meaning suicide attempts or self-cutting or similar parasuicidal self-harm. The sample size was over 61000 patients. Medical charts were examined for diagnoses of repeated self-harm or eventual suicide. Data were obtained for the first year (12 months) after the identified non-fatal self-harm event.

Overall, 80.4% of the sample did not make any repeated self-harm attempts in the year after the initial attempt. 19.7% made at least one repeated non-fatal attempt in the following year. 243 persons, or 0.4% of the original sample, committed suicide in the following year.

This completed suicide rate that occurred in the following one year was 37 times higher than a matched general population cohort. This is a huge effect size, multiple folds larger than the association between cigarette smoking and lung cancer.

If the initial self-harm was violent, such as the use of firearms, the risk of eventual suicide was even higher, with a 15 fold greater risk in those using firearms versus those who did not use firearms. The use of guns in the initial attempt predicted a high likelihood that eventual suicide would occur using guns as well.

Looking at clinical risk factors, among diagnoses, the condition with the greatest predictive effect of repeated nonfatal self-harm was a diagnosis of a personality disorder. Recent inpatient treatment also was a predictor of both nonfatal self-harm repetition and of completed suicide. Other diagnoses were not much more predictive compared to each other, but these Medicaid medical chart diagnoses were not made systematically and are of dubious validity for research purposes. Cutting was common equally among non-fatal attempts and completed suicide. Use of firearms was a major predictor of

completed suicide, occurring in 13% of suicide cases versus only 1.3% of non-fatal attempts.

The study confirmed standard risk factors for suicide, with the rate being higher among males than females, among whites than non-whites, and in older adults (age 45-64) than younger age groups.

It is important to discuss the overall finding about the absolute frequency of suicide in those who make suicide attempts. The rate was about one half of one percent (0.4%) completed suicide in this sample of people who have made suicide attempts. Other studies have reported that the rate of eventual suicide in persons with past suicide attempts approximates about 10% of persons over a lifetime. Usually those follow-up studies examine about 10-20 years. That finding is consistent with the result in this study. If we round up the number to about 0.5% per year, then the eventual overall figure would be about 5% in 10 years or 10% in 20 years, assuming equal risk per year. This 5-10% rate is consistent with other longer term studies of suicide rates in persons with past suicide attempts.

It also is important to note that it is reported that about one-half of persons who commit suicide do so on their first attempt. In other words, suicide attempts are a major risk factor for the other half, but one half of persons who kill themselves never made prior attempts. All the more reason to pay attention when someone makes a suicide attempt, and survives.

The above discussion is not exactly the same for less violent or less risky parasuicidal behavior. In these cases, the occurrence of completed suicide does seem to be low, as shown in this study.

A clinical conclusion from this study is that clinicians should be very concerned when patients make suicide attempts with any potentially lethal means, especially firearms. Clinicians should know that about 10% of those patients will kill themselves eventually. Efforts should be made for heightened intervention for prevention of suicide in this population of patients with serious suicide attempts. The most effective intervention may be treatment with lithium, even at low doses, as discussed in prior PL issues, and in the second Current Article in this double issue.

The PL Bottom Line

- A suicide attempt will lead to completed suicide in the next year in about one half of one percent of persons.
- This risk is 37 times higher than the general population.
- It adds up to an overall long-term risk of about 10% in 20 years of follow up.
- The use of firearms in a prior suicide attempt is a major predictor of eventual completed suicide.
- Clinicians should make extra effort to prevent future suicide in patients who have made serious past suicide attempts.

PL Reflection

There are foolishnesses that are respected if they concern respectable things.

Voltaire

Current Study of the Month - II: Preventing suicide

Suicidal behavior during lithium and valproate treatment.
J Song et al, American Journal of Psychiatry. 2017; 174:795-802

Lithium but not valproate prevents suicide attempts

A number of studies have assessed suicide risk with lithium versus other anticonvulsants (valproate and carbamazepine) in the past. Those analyses repeatedly have found that lithium prevents suicide while those anticonvulsants, despite being mood stabilizers, do not. In other words, it's not the case that mood stabilizers in general prevent suicide; rather, there seems to be something unique about lithium.

Those prior analyses were both large epidemiological studies (e.g., US, Denmark) or randomized clinical trials. This new study comes from Sweden and adds to this literature with another large nationwide epidemiological analysis. In this sample, analysis was made of over 51000 persons in Sweden diagnosed with bipolar illness between 2005 and 2013.

Lithium was given to 41% of the overall population, while valproate was given to 16%. About the half the diagnosed bipolar patients were never treated with either lithium or valproate. The analysis of lithium versus valproate effects in the same persons was conducted in 4405 persons.

What is unique is that these over 4000 individuals received both agents at some point in treatment, and thus the effects of lithium versus valproate were compared in the same individuals, not in different persons. This "within-individual" analysis reduces many of the confounding factors that can bias observational studies.

In that nearly decade time frame, about 9% of the analyzed sample ($n=4405$) made a suicide attempt or committed suicide. Since those attempts were repeated, there were over 10000 suicide-related adverse events (defined as suicide attempts or completed suicide) in this sample.

Completed suicide occurred in 1.1% of the total sample, and was equally common in lithium-treated (1.1%), valproate-treated (1.2%), and never lithium or valproate-treated (1.2%) groups.

This increased suicidality was reduced by lithium by 14% (Odds ratio 0.86, 95% confidence intervals 0.78-0.95). Valproate

did not reduce this suicidality, having a neutral effect (Odds ratio 1.02, 95% confidence intervals 0.89-1.15). Taking into account time on medication, it was estimated that about 12% of the suicide-related adverse events seen could have been prevented if lithium had been prescribed and taken during the entire 8-year follow up period. The beneficial effect of lithium was present even when corrected for use of other concomitant psychotropic medications.

Substance abuse was a major predictor of suicide attempts, but lithium still reduced suicide attempts even in those with concurrent substance abuse.

Interestingly, the lithium benefit was seen even if the medication was used for less than one-month, although it was greater in longer term use.

The study also compared its within-individual analyses to the standard between-individual

“...lithium still reduced suicide attempts even in those with concurrent substance abuse.”

analyses. In other words, it compared lithium versus valproate effects in the same persons (who received both at some point), as well in different persons (in those who received one but never the other). Overall, the analyses were similar in both groups: lithium prevented suicidality while valproate did not.

How should clinicians interpret this study?

First, it is highly representative of actual treated patients, since it represents all people with bipolar illness in actual treatment in Sweden. It is not a selected randomized clinical trial sample.

Lithium reduced suicide attempts in this study, while valproate did not. This lithium benefit was present even in brief one month treatment, as well as in those with the highest risk, such as substance abusers.

What is somewhat different than other reports is that lithium did not prevent completed suicide in this study, which occurred in about 1% of subjects. This rate of 1% in about a decade is not low, when compared to epidemiological studies of suicide, such as the first Current Article in this issue. In that study of suicide frequency in the US, it was found that the rate of suicide in persons who make suicide attempts is 0.5% per year. In a decade this would be about 5% of persons. Since this bipolar sample involved 9% who made suicide attempts in 8 years, the completed suicide rate of 1% would be about 10% of those who made suicide attempts (1% divided by 9% = 11%).

In other words, lithium reduced suicide attempts, but for some reason it did not translate to prevention of completed suicide in this study, in contrast to other epidemiological and randomized studies.

What is clear is that there was no benefit with valproate in any way for suicide attempt or suicide

prevention. Again, there seems to be benefit with lithium, and this suicidality benefit appears to be unique to lithium.

PL Reflection

In 1896, in the reshuffling of file cards that produced the fifth edition [of Kraepelin's textbook]...dementia praecox [schizophrenia] was now a 'metabolic disorder' set, to everyone's astonishment, next to thyroid psychosis and neurosyphilis. Yet what gripped his readers' attention most was his declaration in the preface that he was tired of grouping disorders according to their symptoms; he wanted to get to the inner nature of the illness, 'as manifest in their course and outcome.' 'I have abandoned any effort to classify on the basis of clinical presentation.' This was the decisive statement of Kraepelin's shift from studying the presumed causes of psychiatric illness, such as genetics, brain biology, and so forth, to concentrate on classifying illness in a way that would let one predict outcome. Prognosis, not cause, is the single most important word in understanding Kraepelin....

He was not denying the validity of biological psychiatry, but simply decrying himself agnostic: 'As long as we are unable clinically to group illnesses on the basis of cause, and to separate dissimilar causes, our views about etiology will necessarily remain unclear and contradictory...' As Kraepelin said in 1899, 'The doctors' first task at the bedside is being able to form a judgment about the probable further course of the case. People always ask him this. The value of a diagnosis for the practical activity of the psychiatrist consists in letting him have a reliable look at the future.'

*Edward Shorter
A History of Psychiatry*

Drug of the Month: Clozapine (*Clozari*)

The most effective, most harmful, and most mysterious antipsychotic

Biological mechanism

Clozapine has mild blockade of dopamine and serotonin receptors. This effect is mild, much less than with other antipsychotics. It has no other effects that are known to be associated with clinical efficacy for psychosis. It has many other mechanisms that produce side effects: it is highly anticholinergic, antiadrenergic, and antihistaminic.

Clinical efficacy

Clozapine is FDA indicated for schizophrenia. It is the only antipsychotic proven more effective than other antipsychotics for refractory psychosis. It also has FDA-approved language for prevention of suicide attempts, based on a single randomized clinical trial. It did not prevent completed suicides in that trial better than its comparator, olanzapine. It is used for mania and bipolar illness, but it has no randomized trials for affective conditions.

Dosing

The standard dose is about 300-600 mg/d, with lower doses used for depressive episodes in bipolar illness, down to 200 mg/d. Doses below 100 mg/d likely have no clinical efficacy. Above 300-400 mg/d, clozapine reduces the seizure threshold, which may be related to its efficacy and to risk of seizures.

Side effects

Nuisance side effects involve sedation, constipation, impaired cognition, and weight gain.

Clozapine has major anti-insulin receptor effects, which cause cardiac harm and markedly increase the risk of diabetes. In some early studies, mortality was about 1% per year, from cardiac events. Diabetes rates were 30-50% in a decade. These medical harms occurred in schizophrenic

patients in their mid-30s. At older age, and with more cardiac risk factors, the risks likely are higher. Clozapine causes marked increase in cholesterol.

Clozapine also has a notable seizure risk at medium to higher

doses.

It causes agranulocytosis in about 0.8% of patients, leading to the need for weekly CBC checks, later reduced to biweekly or monthly.

The PL Bottom Line

- Clozapine is the most effective available antipsychotic agent.
- The biological mechanism of its strong clinical efficacy is unknown.
- It is also the most harmful available antipsychotic, with major cardiovascular and diabetes harms, along with seizure risk and notable agranulocytosis risk.

Concepts and History of Psychiatry

Aubrey Lewis: Learning psychiatry

Introduction: In these three lectures, Lewis provides his detailed analysis of how best to teach and learn psychiatry. His focus is on medical students and psychiatric residents, but similar considerations would apply to all mental health clinicians, including social workers and psychiatric nurse practitioners. As you read these excerpts, mostly from the 1940s to the 1960s, think about how much of his experiences still apply today.

Source: *The State of Psychiatry*, Sir Aubrey Lewis, 1967, New York, Science House, pp 113-162.

From "Psychiatric Education: Background and History" (1963):

The history of psychiatry is full of paradoxes. One of them is the change in the attitude of clinical teachers towards the psychological element in illness during the nineteenth century....at the beginning of that century the important thing for the doctor and for his students was not the pathology or the physical signs of the illness but the symptoms and what the patient thought about the illness.... [He then contrasts this early 19th century humanism with a later 19th century shift to scientific concepts of disease.] The changes in psychiatric education that occurred during the last century and in the first half of this century have been gradual, sometimes imperceptible, and never dramatic... the story can be a somewhat tedious record of intermittently large aims and meagre achievements.

From "The Education of Psychiatrists," 1946:

Who are to be taught, and to what end are they to be taught?...Eloquent appeals; arguments, however useful and true, enticements, whether in the form of material prospects in pay and promotion or as alluring chances for doing good and advancing knowledge - all these will, I believe, have little (or only adverse) effect in enlisting good recruits unless medical students see for themselves that psychiatry is an absorbing field of medicine, one which gains the devotion of people whom students respect and would emulate.

Though the outlook of medical students is already becoming more favourable, not doubt in response to effective teaching, it is still commonly asserted in this country that medical students form a poor opinion of psychiatry and psychiatrists....[He then reviews a survey of medical students about their opinions on psychiatry]. To one question, the answers were chastening: 22 [of 75] of these keen young observers were fairly certain, and 21 others inclined to think that there are more odd and peculiar people in psychiatry than other medical specialties; only 2 considered that there are fewer oddities in our ranks than in the other specialties....

"...a somewhat tedious record of intermittently large aims and meagre achievements."

You may be disposed to quarrel with my frequent use of the word 'training', as though a psychiatrist were an athlete or a circus elephant: and to remind me that I had chosen to speak of education. By the time a man enters on the postgraduate study of psychiatry, his general education should be able to look after itself and should gain from all his experience: if it cannot, the horse is out, and it will be idle to close the stable door by formal teaching. John Locke said, on a similar occasion, 'I have seldom or never observed anyone to get the skill of reasoning well, or speaking handsomely, by studying those rules

which pretend to teach it.' The whole of the psychiatrist's postgraduate studies should train him in reasoning and understanding - what Thomas Lewis called the vital flame in education. And surely example and steady guidance, rather than precepts and 'a course', are the best corrective for defect in that general education which should fit a man to combine the scientific and the humane temper in his studies, as the psychiatrist needs to.

Coming from this high ground to the uneven plain where doctors are tight to be competent specialists, I see only two methods as essential there: well-supervise practice (in hospital, laboratory, school, or clinic), and contact with more informed minds wherever the may be found - in books, seminars, educational films, lectures, and case-discussions, and on less formal and didactic occasions....

Clinical teaching must be the core of the psychiatrist's education: 'taking cases', studying and treating individual

patients, arranging and digesting the findings, formulating the problem relating it to what may be learnt elsewhere than in the company of the patient - this is the body of psychiatric opportunity....There is much proper emphasis nowadays upon preventive psychiatry, extramural psychiatry, social psychiatry, psychiatry apart from the patient who wants to be treated for an illness: it is clearly necessary that these aspects shall be studied and pursued vigorously. But if they are not to become chimeras fed on catchwords and flight pretensions, buzzing in a vacuum, then psychiatrists who follow them need clinical training with patients of every sort, just as much as do those of us who pursue more familiar therapeutic aims....

"...they used to suppose that they trained people by imparting to them not the art but its products."

Child psychiatry and psycho-analysis - igneous topics these. As for child psychiatry, I see no valid division in the training of psychiatrists which could depend on the age of the patient, and I have no doubt that presently the psychiatry of the old will likewise become a prominent part of our branch of medicine....Psycho-analysis is an older and thornier educational problem....it is unseemly that a postgraduate institute, if it holds that psychoanalysis may be valuable in the training of some psychiatrists, should shut itself off from that work, or profit by it without taking responsibility for it, as we have profited - and how much we have profited - by the bold and enlightened education effort of American and European centers of psychiatric training, at which so many of us, in the last thirty years, have been nourished or polished....

It is hard to tell how soon it will be possible to come at the full means of realizing aims now generally agreed upon by all of us. To realize these aims I think we must get away from the D. P. M. [Diploma in Psychological Medicine] outlook, as I may call it, in psychiatric education. At its worst this attack has created psychiatrists who are bare empirics, and teachers of psychiatry who are like the sophists that Aristotle denounced - 'they used to suppose that they trained people by imparting to them not the art but its products.'

What are its outstanding faults?...The psychiatrist has been encouraged to nibble at many branches of knowledge instead of study them, and has often come to regard the experts in these - for example the psychologist - as rivals or subordinates, as technicians, as academic playboys, as masters of orange and efficacious arts, as anything but scientist and collaborators on who he intelligently depends. His training has not saved him, in

psychopathology, from a weak syncretism. Therapeutic effort has prospered at the expense of therapeutic discrimination....

But, mindful of much public misunderstanding of what psychiatrists can do and what psychiatry stands for, we can heed the assurance of a Victorian, 'Depend upon it, there is only one way of really ennobling any calling, and that is to make those who pursue it real masters of their craft, men who can truly do that which they profess to be able to do.' If the education of the psychiatrist does that, and produces men capable of adding to the knowledge that will advance psychiatry, then, whatever its shortcomings, it will have deserved well of our generation.

From "Psychiatric Education and Training," 1961:

Psychiatry, which may in many respects fairly be regarded as in much the same state as medicine was at the end of the eighteenth century, cannot be presented to the medical student as an adequate theoretical system or as a body of established and classified facts about causes, pathology, course and treatment of mental diseases. If it were to be so presented the intelligent, sophisticated student, well educated in other branches of medicine, would be puzzled or repelled, and might scorn it; the mediocre student might accept what he is told uncritically, and be thereafter at the mercy of every subsequent swing of the pendulum of psychopathological or therapeutic fashion. Equally, however, psychiatry cannot be presented as just a holistic point of view, as a commonsense appraisal of salient personal and environmental facts about the patient, since this ignores the wealth of observational data, in longitudinal or dynamic terms as well as in cross-section, which has been amassed by the labors of psychiatrists,

"Therapeutic effort has prospered at the expense of therapeutic discrimination...."

psychologists, and social investigators. Whether the happy mean can be found, avoiding the extreme of the system-maker, the empiric and the self-sufficient manipulator, must depend on the policy of the medical school and its climate of educational effort, as much as on the psychiatric teachers....

Some writers have frankly expressed the view that the chief purpose is to 'humanize' the future doctor, to induce him to see each patient as a person, rather than as the assembly of organs and functions which his scientific studies might have made him contemplate.... With this may go a lessen concern for detailed knowledge of the phenomenal and course of illness (dismissed rather contemptuously as 'descriptive psychiatry') and there may be also an aversion for physical methods of treatment, districts of physiological explanations of the pathology of mental illness, and denial of the part played by heredity in determining the recurrence, form and course of such an illness...

But it would be unrealistic to suppose that a boorish, unsympathetic, tactless student will be converted by some psychiatric lectures and demonstrations into a man well-fired to practice medicine, or the mollifying and civilizing effect of psychiatric teaching will be greater than that produced by the example of kindly and humane teachers of the other branches of medicine. A decent regard for the feelings and needs of sick people is one of the products of all medical education. Psychiatry contributes to this end, but cannot arrogate to itself primary responsibility for it....

The aim of psychiatric education, according to a representative American group, is to develop in the medical student ability to interview; ability to

diagnose...; and finally understanding of was the physician who is not a psychiatrist can and should do, and what he cannot and should not do....this is a series of practical objects. What they omit is as significant as what they include: they do not mention ability to evaluate critically theoretical and practical issues affecting mental health.... [They] sum up the basic aim of the teaching as 'to equip the stone with a reasonably adequate knowledge of the facts of human nature'. Unfortunately, we are still ignorant of much we should like to know about human nature, and we are at intervals exposed to waves of enthusiasm of new methods of treatment. It should therefore be a further aim of psychiatric education to cultivate and train in the student a capacity for weighing evidence and examining speculations about the intangible material of psychiatry, which can be so much more elusive and deceptive than somatic phenomena....

Extreme views have been the bane of psychiatry. They certainly can become the bane of psychiatric training. One group of extremists holds that psychodynamics is the alpha and the omega of the subject. Another group insists, with bigoted sincerity, that physiological interpretations, chemical and tissue pathology, and physical method of treatments are the only proper meat and drink for the fledgling psychiatrist. A third maintains that in the training of psychiatrists of a particular complexion, psychiatry as Esquirol and Kraepelin, Bleuler and Maudsley and Adolf Meyer understood it need play not part at all: it is boldly urged that the psychiatrist of childhood, for example, need be only a pediatrician who has qualified as a psychoanalyst [as Winnicott argued]. These are ill-advised and harmful views. A broad training is essential...

"Extreme views have been the bane of psychiatry."

The practice of psychiatry makes demands on a doctor which are in some respects different from those of...other branches of medicine. It has not been possible, however, to determine what sort of doctor can best meet these demands. Some doctors who are attracted to psychiatry are themselves in need of psychiatric treatment. It is generally assumed that these should be steered away from the specialty, since their mental conditions may disturb their clinical judgment and expose their patients to risk. The kind of risk will depend on what sort of mental disturbances the doctors in question are prone to and the kind

of psychiatric work they are going to undertake....On the whole, however, it is sufficient if the would-be psychiatrist has the intelligence, integrity, and balance that one would like in every doctor.....

Prominent among the obligations of those who provide postgraduate education is the duty to recognize and further whatever talents for research their students possess. The fields within which psychiatric research is cared on are so wide that there is scope for many kinds of interest and ability; the complexity of the problems is so daunting, however, that it is profitless, and can be unkind, to encourage competent clinicians to attempt scientific investigations beyond their powers...

Though there can be no substitute for personal enthusiasm and ability in the student and the corresponding qualities in teacher or exemplar, much can be accomplished by a steady insistence, in all clinical work, on recognizing problems that planned inquiry might illuminate, or even solve, and by guiding the student in the design and execution of a manageable investigation which he himself has chosen....

Case of the Month

Stopping antidepressants for “depression”

A 30 year old female has been diagnosed with major depressive disorder (MDD) since age 21. She initially was treated with sertraline, which helped, and then she got worse again about a year later. Bupropion was added, which helped, and then she stayed well for three years on both agents. She finished college and got a job. She then relapsed into another depressive episode around age 25, and the doses of sertraline and bupropion were increased. She improved, got married, and then just had another depressive episode that began about 2 months ago. She has remained on sertraline and bupropion this entire time. She has been treated by her primary care doctor although she had a psychiatric consult when she started bupropion.

Her family history is significant for bipolar illness in a sibling and in a cousin.

She has no medical illness, no allergies, no substance abuse, and works as a podiatrist. She is happy in her marriage and has many friends.

There is no past trauma of any kind.

There was no major trigger for her current depression, although she has more anxiety at work when she is depressed because she feels less capable of functioning. She has managed to continue to work despite her current depressive episode. Her symptoms involve decreased sleep and interest and energy and concentration, but no suicidal ideation. She never had manic or psychotic episodes.

She describes her baseline personality as “bubbly, high energy, very active.” She exercises a lot, and is very extroverted.

The PL consultation diagnosis was recurrent unipolar depressive episodes with bipolar genetics and hyperthymic temperament. This clinical presentation is typical for the classic diagnosis of manic-depressive illness (MDI), which means both recurrent unipolar depression and bipolar illness. Bipolar genetics was supposed to be absent in unipolar depression, as a rationale for the legitimacy of unipolar depression as being a valid independent diagnosis separate from bipolar illness. Otherwise, they both are part of the same illness - MDI.

In this scenario, the patient is a squared circle, and illogical and supposedly rare phenomenon: unipolar depression with bipolar genetics almost never should occur. The PL consultant states: There are only two alternatives; either the textbooks are wrong, or you don't exist. Since the patient exists, the textbooks are wrong.

The PL consultant concludes that sertraline and bupropion may have had acute efficacy but the history repeatedly shows that they do not have maintenance efficacy in prevention of future depressive episodes.

The consultant recommends that the patient taper off both agents, with cross taper of fluoxetine for sertraline to manage serotonin withdrawal syndrome. Lithium or lamotrigine are recommended for maintenance prevention of future depressive episodes. Hyperthymic temperament puts the patient at some risk for future depressive episodes, and low dose lithium and valproate appear to help it, but lamotrigine

likely does not help hyperthymia since this agent has no acute antimanic effect. Thus, low dose lithium (300-600 mg/d) was the consultant's recommendation.

The patient went to her primary care doctor, whose reaction was: "You have depression. There's no way I'm taking you off antidepressants!"

This is like saying, after penicillin failed repeatedly: "You have an infection. There's no way I'm taking you off antibiotics." The mistake is to view the drug class as equivalent: antidepressants are not "antidepressants" because they don't work for all kinds of depression. Similarly, not all infections respond to antibiotics. But the primary care doctor, who can be logical and scientific about infections, is illogical and unscientific about affective illness. It's not his fault. It's DSM's fault, because that is how DSM is set up. The doctor is just following the instructions of the profession.

The consultant recommended that the patient change her treating clinician, which she agreed to do. A psychiatric nurse practitioner agreed to implement the recommended changes, with gradual improvement over months.

PL Reflection

One lash of affliction will sooner convert a man than many courses of philosophy.

*Robert Burton
paraphrased*

Curbside Consults

Questions and cases from you

Question: A 43-year-old male has been diagnosed with psychotic depression, schizoaffective disorder, and OCD. He had a first episode of depression with acute catatonia and psychosis at age 25. He was treated with paroxetine and risperidone and subsequently attempted suicide by drowning leading to a one-week hospitalization where he was treated with paroxetine, olanzapine, and ziprasidone. He eventually tapered off olanzapine a few months later, and then paroxetine 6 months later. He had a relapse of psychotic depression treated with olanzapine and paroxetine, and again went off both agents about 6 months later. Between episodes he demonstrates hyperthymic temperament. His OCD symptoms mainly occur when he is depressed. He is a gifted musician, and teaches as a mathematician, and is generally outgoing and creative sometimes taking on more projects than his wife feels he can cope with. He is happy with his current medications and feels he is doing very well.

Family history is relevant for the fact that his paternal aunt committed suicide. Diagnoses in siblings include severe depression, treated with medications, and anorexia nervosa.

He has never been treated with any mood stabilizer. Is the diagnosis bipolar illness? Should he be treated with a mood stabilizer?

PL: This is a classic case of using the "poor man's mood stabilizer", namely an "antidepressant" plus an "antimanic" agent. Clinicians and patients believe that the combination is mood-stabilizing because one moves your mood up and the other moves your mood down, stabilizing you in the middle. These metaphors have no scientific basis to them. It's not about "stabilizing in the middle," and it's not about moving your mood up

or down. This patient has repeated depressive episodes; they go away and come back; they recur. This is classic Kraepelinian recurrent affective illness. The main treatment is prophylaxis: a medication that prevents the recurrence of future depressive episodes. If we wanted to use the word "mood stabilizer," that's what it should mean, not moving the mood up or down. The question is whether the combination of a SRI like paroxetine along with an antimanic agent like olanzapine has ever been shown to prevent mood episodes in recurrent unipolar depression. The answer obviously is no. There never have been such data on the combination; it's never even been studied.

What has been proven? Lithium has been proven to prevent depressive episodes in unipolar depression. One might argue that SRIs alone have been shown to do so, but the problem of the invalidity of enriched maintenance designs throws doubt on such claims, as discussed above. Olanzapine alone only has such data in bipolar illness, with the same problem of the likely invalidity of the enriched maintenance designs upon which such efficacy claims are based.

So purely from a scientific perspective, the claim of efficacy with this combination is not supported by valid evidence.

We can turn to two other aspects of the case: 1) the patient's preference, 2) the likely diagnosis and recommended treatment.

Regarding the patient's preference: the patient is happy now, likely because he is in a phase of remission. The medications now likely are not keeping the patient well. They are neutral, probably ineffective. Nature, by giving this illness phases of remission, is keeping the patient well, and the patient is crediting the medications. Since the patient has hyperthymia, it could be also that the constant SRI use feels good to the

patient, that it makes him a little more manic, which he enjoys. These aspects of the case could be explained to the patient. It could be explained that hyperthymia puts the patient at increased risk of future depressive episodes, and that the current medications, especially the paroxetine, do not decrease that risk, but actually increase it by potentially worsening manic symptoms of hyperthymia. Patients with manic symptoms often lack insight into those symptoms. This seems to be worse, paradoxically, the milder the manic symptoms. Thus, there is lack of insight in about one-half of patients with severe manic episodes, but it is higher in mild hypomanic episodes, where about 2/3 of patients lack insight into their hypomanic states. It likely is even worse in hyperthymia, since the manic symptoms are mild and constant, and thus patients generally do not see them as abnormal because they have no normality with which to compare their experiences. Thus, it may be difficult, but if the patient can receive some psychoeducation on these matters, he may begin to understand the nature of his condition.

Regarding the diagnosis and treatment, the patient has manic-depressive illness (MDI) defined as recurrent depressive episodes along with hyperthymic temperament. The fact that his depressive episodes have psychotic features makes it more likely that he has MDI because psychotic depression is much more common in bipolar illness than unipolar depression. The "diagnosis" of psychotic depression is meaningless, even though it is in DSM, because this is clinical acute state, like an acute depressive episode. This is not a longitudinal diagnosis, but a cross-sectional picture. There is no such thing as "psychotic depression" as a diagnosis, just as severe fever is not a diagnosis. The patient has recurrent depressive episodes, with psychotic features, which is the diagnosis of recurrent unipolar

depression. In between these episodes, he has constant manic symptoms, which is the diagnosis of hyperthymic temperament. Put together, that's a common presentation of MDI. Family history of suicide confirms the genetics of a severe mood disease, which is what MDI is.

The PL recommendation would be to taper off paroxetine, which has terrible serotonin withdrawal syndrome, by replacing it with fluoxetine and then gradually tapering over 6 months. Olanzapine could be stopped. The main treatment for hyperthymia is low dose lithium or divalproex, increasing doses if needed for breakthrough mood episodes. PL would recommend starting with lithium since he has genetics for suicide, at a dose of 300-600 mg/d, to see if it agreed with him. If it was sufficient, that dose could continue. If he became doses, standard doses and levels of about 0.8 could be used. If not tolerated, then Depakote could be used but very

low dose lithium (150-300 mg/d or less) would still be recommended for suicide prevention and for long-term cognitive benefits of dementia prevention. With these agents, it is possible he would not need other treatments, but if needed, other safer dopamine blockers could be used, without risk of worsening heart disease risk, like risperidone or aripiprazole or asenapine or lurasidone.

PL Reflection

Though held to be out of season,
speaking the truth is always in season.

Nietzsche

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by PL Editor Nassir Ghaemi MD

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Pregnancy and drugs

In this issue, PL publishes a special article on pregnancy, medications, and lactation. The difficult decision-making processes that are involved in that setting are discussed. There also is a review of the basic available knowledge regarding the range of psychotropic medications and their use during pregnancy and lactation.

The Article of the Month is a classic study, BALANCE, which is a recent maintenance trial of lithium versus divalproex in bipolar illness, showing more benefit with combination than monotherapy, but also showing special benefit with lithium in depression episode prophylaxis. The Drug of the Month is risperidone, a classic dopamine/serotonin blocker with excellent efficacy in mania and acute psychosis. The curbside consult questions involves a case of antidepressant use in bipolar illness.

Through our collaboration with PeerPoint Inc, we continue to provide Continuing Medical Education (CME) and Continuing Education Units (CEU) to psychiatrists and nurses and psychologists.

This issue likely will be the last that will reach readers before the October Santa Fe CME program, so please do attend the program if you are able. It will be a chance to discuss these kinds of topics in person and in detail.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Pregnancy and drugs

To continue or discontinue?

Many experts in psychopharmacology tend to recommend continuing psychotropic medications, especially SSRIs and dopamine blockers, during pregnancy. However, this judgment of safety is based on immediate effects that can be observed during or soon after pregnancy is over. In other words, the judgment of safety is based on presence or absence of birth defects. This assessment does not tend to entail effects that can happen a few years after delivery. For instance, it has been found that some medications, like divalproex, can have long-term effects 3 to 5 years after birth, involving some evidence of low IQ or neurodevelopmental delay. Thus, the judgment of safety should be understood to be short-term only. Long-term safety is unknown for most psychotropic medications.

It is difficult also to make causal judgments about the safety or lack thereof of psychotropic medications during pregnancy since there are very few if any randomized trials of medications during pregnancy. Due to the special nature of pregnancy, most of the research on this topic is observational, and not randomized. Thus the potential problem of confounding bias exists with almost all research studies on pregnancy.

One of the questions raised during pregnancy has been the clinical lore that women during pregnancy have less psychiatric symptoms than before afterward. Some women report a sense of subjective well-being during pregnancy that is higher than their baseline. Some clinicians have judged that depression is less likely during pregnancy, due to this subjective improvement in mood. The theorized biological basis for this pregnancy effect has been the idea that estrogen

“...the judgment of safety should be understood to be short-term only...”

is markedly increased during pregnancy, and estrogen is thought to have an antidepressant effect. The clear clinical problem of postpartum depression is hypothesized to be related to the sharp decline in estrogen that happens at and after delivery.

This clinical opinion has been studied in some observational studies in which it has been found that relapse rates into depression during pregnancy do not appear to be notably different than relapse rates before or after pregnancy. These observational studies suggested that the clinical lore of enhanced well-being during pregnancy may not be the case or at least may not protect against depressive relapse. This is one reason why some perinatal psychiatry experts recommend continuation of antidepressants during pregnancy on a routine basis.

Trimesters

It is important to divide pregnancy risks into the three major trimesters. During the first trimester, major organ formation is occurring, and thus any harmful drug effects will lead to major organ malformations. These tend to be rather serious results such as anencephaly or somewhat less serious but clear abnormalities such as Ebstein's anomaly associated with lithium. Unless pregnancy is planned, it is usually the case that a woman would not realize she is pregnant until she is well into her first trimester. Thus, with any medications they can potentially have first trimester effects, it is difficult to fully prevent first trimester harm.

Most medications of concern in psychiatry have second trimester effects. These include anticonvulsants and benzodiazepines which can cause neural tube defects. During the second trimester, one of the major processes that occurs is brain development. During this trimester, there is migration of cortical neurons, for example, and general maturation of the brain. Other organs in the body had been fully formed, but final maturation of those organs tends to occur in second trimester. The only organ that is not fully developed until the third trimester is the lungs, and the third trimester is mostly devoted to lung maturation.

Thus, when considering the effects of psychotropic medications on fetal development, it is relevant to think about which trimester is being discussed and which effects could occur. Usually, the first trimester is already underway by the time pregnancy is discovered, and in the third trimester there is no

major organ effect that is important. Hence the main trimester of concern tends to be the second trimester. Since benzodiazepines and anticonvulsants are the main medications that have effects in the second trimester, these tend to be the medications that are stopped during pregnancy. It should be noted that the main anticonvulsants that have been associated with neural tube defects are divalproex and carbamazepine. It appears that lamotrigine does not have notable neural tube defects based on its pregnancy registry.

Looking at the major drug classes, the above considerations explain the usual recommendations that are given during pregnancy. Antidepressants tend to be continued;

"Most medications of concern in psychiatry have second trimester effects..."

anticonvulsants except for lamotrigine tend to be stopped, as are benzodiazepines. Lithium tends to be continued past the first trimester.

Regarding dopamine blockers, there is a great deal of experience with haloperidol and with some other older dopamine blockers such that many clinicians continue those agents during pregnancy. Many of the second-generation dopamine blockers have been studied in pregnancy registries, and generally are reported to be safe by their manufacturers. Again however, this judgment of safety is observational and based on short-term effects only.

FDA categories

Many clinicians focus on FDA category assignment given to different medications. It should be kept in mind that these category assignments are based on poor outcomes reported to the FDA, which are purely observational

and can be affected by many confounding factors, including non-report based on unpredictable factors. Thus these category assignments are not the most valid measures of safety during pregnancy from a scientific perspective. Nonetheless, there may be at least medical-legal reasons to pay attention to some category assignments from the FDA regarding pregnancy. The FDA categories are as follows: Category A refers to drugs thought to be safe with no known adverse effects. Category B refers to drugs that are not known to have any risks in humans. Category C refers to insufficient research to be able to make a judgment regarding safety. Category D refers to adverse effects having been found in humans. The American College of Obstetricians and Gynecologists guidelines on

psychotropic drugs lists benzodiazepines as category D. Other agents used for sleep, such as eszopiclone (Lunesta) and Zaleplon (Sonata) are category B and zolpidem (Ambien) is category C.

Divalproex and carbamazepine and lithium are all listed as category D, while lamotrigine is listed as category C. This categorization is not clinically accurate since lithium has much fewer risks than divalproex or carbamazepine.

All antidepressants are listed as category C except for bupropion (category B). All amphetamines, including methylphenidate and its variants, are listed as category C. It is interesting that bupropion is an amphetamine but it is listed as category B. All dopamine blockers are listed as category C except for clozapine (category B).

“...make decisions regarding continuation of psychotropic medications during pregnancy in relation to the natural history of the illness in that person...”

Consider natural history

What guidelines can be given clinicians regarding decision-making about continuing or discontinuing psychotropic medications before during and after pregnancy, given the above considerations? One approach would be to make decisions regarding continuation of psychotropic medications during pregnancy in relation to the natural history of the illness in that person. The most difficult decision making would involve chronic severe illnesses, such as schizophrenia or epilepsy, in which discontinuation of medications completely would not seem to be a viable option. For other illnesses that are mild, but chronic, such as generalized anxiety or affective temperaments, it may be reasonable to come off medications during pregnancy, since symptoms are not severe naturally otherwise. For other illnesses that are severe, but episodic, like bipolar illness and

recurrent unipolar depression, it may be reasonable to come off medications if the natural history of the illness would suggest that remission could persist for nine months or longer. This last scenario may be feasible if the illness is well treated, and the patient has been in remission for some time before a planned pregnancy. For example, suppose a woman with bipolar illness has been treated with divalproex for 10 years and has not had any mood episodes for the prior five years. If she has been completely stable for five years, it is unlikely that she will relapse into a mood episode immediately upon discontinuation of her divalproex. It is likely that she will have at least a few months or longer of natural remission.

The natural history of the patient can inform the decision-making. Suppose in this case, the patient had had three episodes of her lifetime, one at age 17, another age 20, a third at age 25. Now she is 30 years old, and considering pregnancy. Her natural history is such that she tends to go three years in remission before having an episode. Since she has been five years in remission, it is likely that discontinuation of divalproex will not lead to mood episode relapse in the following nine months of pregnancy. Thus she and her clinician could potentially make the judgment that it would be reasonable to come off divalproex a few months before planning pregnancy, and continuing to stay off of it throughout pregnancy as long as she does not have a relapse into a mood episode. A backup plan should be put into place such that other medications could be instituted should a mood episode occur. For instance, a dopamine blocker could be given if a manic episode were to occur, and an antidepressant could be given if a depressive episode should occur. In contrast, if a patient had rapid cycling

bipolar illness, and had mood episodes every 2 to 3 months, then discontinuation of divalproex or any other psychotropic medication would likely lead to a mood episode relapse during pregnancy. This fact would not necessarily mean that divalproex should be continued during pregnancy, given its clear risks, but the decision-making would at least be informed with a high probability of relapse should divalproex be stopped, and other effective medications not given.

In other words, the decision whether to continue or discontinue medication during pregnancy is a contextual one. There is no general rule that words absolutely prohibit or absolutely ordain the use of psychotropic medications during pregnancy. Some perinatal psychiatry experts contend that medication should be continued and the vast majority of cases during pregnancy, albeit using ones that have lower fetal risks, but the above considerations would suggest that this general rule does not apply and that decision should be made contextually in relation to the natural history of the illness and the patient's specific response to medications prior to pregnancy.

If this approach were taken, the general perspective would be that all other things being equal, it would be best to take as few medications as possible during pregnancy, and preferably none. This approach could be feasible in patients with milder episodic psychiatric illnesses which are well-controlled for a long period of time before pregnancy. It would not be recommended in patients with severe chronic psychiatric illnesses or with those with highly episodic or relatively uncontrolled symptomatology prior to pregnancy.

“...all other things being equal, it would be best to take as few medications as possible during pregnancy, and preferably none...”

Impact of psychopathology

Another aspect that is relevant to possible psychotropic medication discontinuation before or during pregnancy is the viewpoint that if psychotropic medications are discontinued, then increase in anxiety or depressive symptoms or relapse into mood episodes or psychosis are harmful experiences not only for the mother but also for the fetus. It is held that these psychopathological states lead to over activation of the hypothalamic pituitary adrenal axis which results in increased steroid hormone production. The steroid hormones tend to cross the blood brain barrier easily, and cross the placental barrier easily. They would then cause direct damage to

the fetus, in various ways. The perspective here is that continuation of medication, even with a small amount of possible harm, outweighs the potential harm of the marked psychopathological worsening of the underlying psychiatric illness, including its physiological effects via the hypothalamic pituitary adrenal axis. This perspective may be correct, but it does not obviate the approach of making decisions regarding possible medication discontinuation based on the natural history of the illness of the patient. Where there is a reasonable likelihood of natural remission lasting six months or longer, then the continuation of medications just may not be necessary. However if there is a serious risk of relapse that is probable based on the natural history during the six to nine-month period of pregnancy, then the considerations given here would argue for continuation of medication treatment in some way to minimize the pathological harm of psychiatric illness relapse not only for the mother but also for the fetus.

If medications were discontinued just before pregnancy, it should be appreciated that a full nine months without medication use is not absolutely necessary. The most important trimesters are the first and second trimesters as described above. Thus, in women who might be in remission but in whom there is some risk of relapse that increases after six months, it may be reasonable to come off medication only during the first and second trimesters and then to resume medications in the third trimester. Also, since the highest risk is postpartum, at least for the mother, then it is important to resume medications in the third trimester, or just before, at, or after delivery. This resumption of medication will

be very important in terms of reduction of risk of postpartum depression. Some women have the experience of postpartum mania with or without psychotic features, and sometimes postpartum psychosis occurs without a clear manic or depressive episode. In these cases, pregnancy can be seen as a trigger of mood episodes in a person with bipolar illness, just as many other triggers exist. Since postpartum depression is so common in bipolar illness, it is very important to resume mood stabilizing medication at or around delivery.

Breast-feeding

The resumption of medications at delivery raises the question of breast-feeding. On this topic, there have been a number of studies assessing the extent to which psychotropic medications of various kinds cross the placental barrier and cross into the milk and thus are transmitted to the baby. In general, researchers have suggested that an infant serum level 10% or higher than the mother's level could be a potential clinical

“...the smaller the molecule the more likely it will be transmitted into the milk...”

concern. Another rule of thumb is that the smaller the molecule the more likely it will be transmitted into the milk. Therefore, lithium, which is an ion, crosses the milk barrier easily and is transmitted in notable amounts from the bloodstream of the mother into the milk supply of the baby. It is estimated that about one half of the serum levels of lithium in the mother is transmitted into the breast milk and exposed to the baby. Medications which are highly plasma protein-bound do not tend to diffuse into the breast milk. For example sertraline is 98% plasma protein-bound and does not transfer into the milk readily. Venlafaxine is much less plasma protein-bound and will diffuse into the milk more than would be the case with sertraline.

Other SRIs are generally reported to pass into the breast milk at low levels, and small studies of infants tend to report that there are no observable behavioral or clinical harmful effects of those SRIs in those infants. Carbamazepine is not highly plasma protein-bound, and is found in notable amounts in breast milk, but divalproex is highly plasma protein-bound and is found at relatively very low amounts in breast milk. Among dopamine blockers, the traditional dopamine blockers are thought to have low amounts of transmission into the maternal milk supply, and small studies have indicated no observable harmful clinical or behavioral effects in the infant. Similar results have been found with most of the second-generation dopamine blockers, except for quetiapine where there are very limited data, and for clozapine where there is some evidence of accumulation of that medication in the breast milk and occasional cases of agranulocytosis in the infant.

A key factor in minimizing the infant's exposure in breast milk to medications is pharmacokinetics and timing of dosing of medication. Thus if a mother is taking lamotrigine in the evening, it would be preferable to breast-feed the baby before taking the evening dose. Furthermore, she can pump and dump breast milk after the evening dose, and feed the baby with milk the next day in the morning or preferably in the afternoon. She can try to pump and store her breast milk long after the half-life of the last dose of the medication.

This approach is more effective with drugs with shorter half-lives.

In the example just given for instance, lamotrigine has a half-life of about 29 hours, and thus it will remain in the bloodstream even when breast milk is pumped long after an evening dose. Nonetheless, the longer one waits, the lower the amount of the medication in the bloodstream, and the less that will enter the milk supply.

It is also relevant that drug metabolism in the infant is somewhat slow in the first three weeks of life, but then increases and becomes more rapid than adults by about 12 weeks of life. Hence infants are able to metabolize and excrete psychotropic medications after a few months, and appear to do so even more efficiently than adults.

Lactation categories

Categories also exist for lactation risk based on FDA recommendations. These categories are as follows: L1 is safest meaning that the medication has been taken by a large number of people without observed harmful effects. L2 is safer meaning it has been studied in a limited number

"A key factor in minimizing the infant's exposure in breast milk to medications is pharmacokinetics and timing of dosing of medication"

of people without any observed adverse effects. L3 is moderately safe meaning there are possible or minimal adverse effects noted. New medications tend to be put at this level until they are studied more carefully. L4 is possibly hazardous meaning that there is evidence of some adverse harm, but the benefits of breast-feeding may outweigh that harm. And L5 is contraindicated meaning that there is evidence of harm which exceeds benefits of breast-feeding or there is clear evidence of high risk of damage to the infant. Most benzodiazepines and GABAergic agents are categorized as L3. Among anticonvulsants, lamotrigine is categorized as L3, while carbamazepine and divalproex are categorized as L2, and lithium is listed as L4. Most SRIs and modern antidepressants are listed as L2, except for citalopram which is listed at L3, as are bupropion, mirtazapine and venlafaxine. Dopamine blockers are listed as L3 or L4, notably with quetiapine and ziprasidone listed as L4. The only commonly used agents listed as L2 are haloperidol and olanzapine.

The PL Bottom Line

- Decisions regarding drug continuation in pregnancy are contextual.
- Natural history of the treated illness is key to such decisions.
- "Safety" in pregnancy is based on short-term data, not long-term.
- Lactation can be managed partly by timing of drug ingestion and half-life.

Classic Study of the Month: *BALANCE study*

Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. JR Geddes et al. *Lancet.* 2010;375:385-95.

The best recent maintenance study of bipolar illness

The most important feature of this study is that it is a throwback to the old prophylaxis study design in bipolar illness. It is not a relapse prevention study. Patients did not have to respond to lithium or valproate to enter it. They only had to tolerate those agents for a brief time (4-8 weeks), after which they entered the maintenance study. There was no requirement for a recent acute episode of mania or depression either. By abjuring a relapse prevention preselection of drug responders, it sets a far higher standard for maintenance efficacy than the relapse prevention designs in the pharmaceutical company-sponsored trials of dopamine blockers and lamotrigine.

The BALANCE researchers designed the study to be practical, large, and simple.

Hence the lack of blinding and absence of placebo. One benefit of this simple approach, besides generalizability, is that 60% of the sample completed the 2-year study, while in most bipolar maintenance trials 90% of the samples have dropped out by the end of one-year studies. 330 patients were recruited over 40 sites in 6 years. BALANCE was headquartered at the University of Oxford, part foundation-funded and part pharmaceutically funded. This kind of research – conducted by academic researchers, with primarily government or foundation funding – is uncommon.

Patients entered the study stable and in remission. They were randomized to receiving

"Overall the combination of lithium plus valproate was more effective than either agent alone."

lithium alone, or divalproex alone, or the combination in up to two years of follow-up. The outcome was either hospitalization or the need for new medication intervention for worsening symptoms. Overall the combination of lithium plus valproate was more effective than either agent alone. Subgroup analyses found that this effect was driven mainly in mania prevention. For depressive episode prevention, though, lithium alone was equally effective as the combination, and more effective than divalproex alone.

This result indicates that lithium is effective to a high degree in prevention of depressive episode relapse in bipolar illness, contrary to mistaken judgments made from the lamotrigine studies, which were enriched and preselected for lamotrigine responders, and thus were biased against lithium. The BALANCE study, which was not preselected for lithium responders, proves that lithium has excellent benefit in depressive episode prophylaxis. It also proves, with the largest available randomized sample, that the strategy of combining mood stabilizers is more effective than either alone, after failure of mood stabilizer monotherapy.

The PL Bottom Line

- Lithium has excellent benefit in depression episode prophylaxis in bipolar illness.
- The combination of lithium plus divalproex is more effective than either alone.

Drug of the Month: *Risperidone*

A classic dopamine/serotonin blocker

Risperidone is FDA-indicated for schizophrenia and mania. It does not have appreciable data of benefit for bipolar depression, nor FDA indication for prevention of mood episodes in bipolar illness.

Biological mechanism

This agent is a dopamine and serotonin blocker. It was the first of the modern class of such agents, developed as a combination of haloperidol (pure dopamine blocker) and ritanserin (pure serotonin blocker). It was created in the 1980s by Dr. Paul Janssen, who had previously created haloperidol in the 1960s.

Side effects and dosing

Extrapyramidal symptoms are its major side effects, mainly akathisia but also parkinsonism, and sometimes rigidity and dystonia. It has some weight gain, but much less than olanzapine or quetiapine, yet it is not weight-neutral. It can increase triglycerides, but does not cause the metabolic syndrome (i.e., does not cause diabetes or hypertension or worsen other lipid profiles). It has few medically serious side effects, although an association with stroke in the elderly has been reported, with FDA black box warning.

It has a wide dose range, from 0.5 mg/d to 6 mg/d, and is typically effective for mania or schizophrenia at 2-4 mg/d, with higher doses needed in severe cases. It can be effective at very

low doses of 0.5-2 mg/d in older persons or for mild manic symptoms. Its half-life is 20 hours and needs only to be dosed once daily (not BID).

Clinical efficacy

Risperidone can be thought of as haloperidol with somewhat less EPS. Like its parent compound, it is very effective for manic symptoms and for acute psychotic symptoms. Hence it is useful in severe acute exacerbations of schizophrenia or mania. For bipolar depression, it has been studied less, but it appears to have less benefit than with some other dopamine blockers. It also has not been as well studied for long-term prevention of mood episodes in bipolar illness, although it likely is effective, especially as adjunct to standard mood stabilizers.

Fast Facts: Risperidone

Typical dose: 2-4 mg/d

Biological mechanism: Serotonin/dopamine blockade

Typical side effects: akathisia, parkinsonism

Medically important side effects: potential stroke in older persons

Clinically proven efficacy: FDA indication for acute mania and schizophrenia

The PL Bottom Line

- Risperidone is a classic effective dopamine-blocking agent for psychosis and mania.
- Its main limitation, which it shares with all dopamine blockers, is EPS like akathisia.
- It has some weight gain, but does not cause metabolic syndrome.
- Its wide dose range allows for benefit with very low doses in some settings.
- It need be dosed only once daily, not BID.

Case of the Month

A functional young adult with intrusive suicidal thoughts

A 23-year-old woman is admitted to the hospital with intermittent suicidal thoughts that come and go multiple times in the course of the day. She also has a current depressive episode with decreased interest, energy, appetite, and concentration. Duration of these symptoms is three months. When admitted to the hospital, the admitting psychiatric team prescribed fluoxetine. The patient denies prior depressive episodes, but describes depressive symptoms lasting up to two days but not longer in the past. During those two days of depressive symptoms though, she would experience the intrusive suicidal thoughts. These thoughts consisted of images of hanging herself, or of otherwise dying. These few day periods of depressive symptoms with suicidal thoughts began around age 15. She had never been diagnosed with or treated for any psychiatric condition, nor had she sought help for the symptoms until recently. She was able to function throughout high school and in college, with good academic achievement. After graduation from college, and beginning work for the first time, she felt unable to tolerate these symptoms and function in her employment in the medical field. Past medical history is negative. There is no history of substance abuse, and family history of psychiatric illness is unknown. She feels it is likely that she has relatives with psychiatric conditions, but due to stigma details are unknown. She has no history of trauma. In PL evaluation, manic symptoms were explored. She denied manic or hypomanic episodes in the past, but she reported that her moods would fluctuate up and down in the course of the day many times. When asked about her baseline personality, she reported that she was an "always on the go person." She was

always very active, busy, and productive. After some reflection, she also reported that she would have 1 to 2 week periods of up-and-down moods, with the brief depressive days and suicidal impulsivity. And then she would have 2 to 3 weeks where she felt "normal like myself." The PL diagnosis was recurrent mixed episodes, with possible cyclothymic temperament. The patient clearly does not have only "depression". The use of fluoxetine doubles the risk of suicidality in this age group, and that medication was discontinued. Low-dose lithium was recommended both for her mixed states and cyclothymia, as well as for direct suicidal benefit.

PL Reflection

Frank Ayd was one of the first psychopharmacologists in American psychiatry, a leader in introducing the profession to psychotropic drugs in the 1950s and 1960s. He later recalled early reaction to the drugs:

At the New York Academy of Sciences, I gave a paper on chlorpromazine and my experiences with it. The discussant of my paper was a past president of APA, who used to be at Yale. He thought my paper was very erudite, interesting, and informative. And, then, he got to the punch line, and said, "I have one word of advice to you people in the audience. Hurry up and prescribe this stuff while it still works."

*Frank Ayd MD
Oral History, conducted in 2001 by
Thomas Ban MD*

Curbside Consults

Questions and cases from you

Question: A 64-year-old married male first reported depression with associated anxiety at age 45. The initial episode of depression was attributed to metoclopramide, which had been initiated for new-onset GERD, and improved with paroxetine for 3 months. A second episode of depression occurred in a year later, treated with Effexor (venlafaxine) 150 mg/d which was partially effective but dose was limited by urinary frequency. Interestingly, during this time of residual depressive symptoms, he did have short one to two-day periods of notable normality. He was switched to paroxetine 20mg qd and two weeks later felt "more back to my own self" but also developed some manic symptoms: volunteering for everything, being very active, and participating in many communal events. Paroxetine dose was increased gradually to 60 mg/d over a year, with reports that his mood continued to go up and down. Lithium was added at 900 mg/d for augmentation, after which his wife noted he was "the best he had been in last few years." Due to polyuria lithium dose was reduced to 600 mg/d. He later tried fluoxetine and nefazodone and eventually lithium was reduced even further to 300 mg/d due to restless legs syndrome. He did well after a time and lithium was stopped because lithium levels were subtherapeutic and it was thought perhaps he didn't need it. Within two weeks it was restarted for manic symptoms, followed by more depressive symptoms. Since then, he has remained on Lithium 450 mg/d and fluoxetine, which is increased when more depressed and decreased when hypomania occurs, within a range of 30-60 mg/d. His mood fluctuates every month or so.

After reviewing this chart, I think the patient has bipolar illness with evidence of mixed states. The Prozac may be inducing more mood episodes and

having little impact on depression although I'm not sure. The patient definitely benefits from lithium, but dose is limited by side effects. Restless leg syndrome perhaps secondary to lithium is requiring 1 mg clonazepam qhs which is not helpful for depression. Plan: Taper off Prozac. Add divalproex perhaps before tapering Prozac. Eventually, consider tapering off Lithium if divalproex proves effective. This might improve RLS enough to stop clonazepam. Any input on chart summary and management plan would be much appreciated.

PL: The case presented is typical of the scenario where bipolar illness is misdiagnosed, and antidepressants have been tried without success. Paroxetine has been tried over and over again. There may have been some anxiolytic benefit at times, or even possible short-term depressive symptoms benefit. It's also possible that natural recovery was misinterpreted as response to the repeated administration of paroxetine. In any case, what is clear is that there was not long-term benefit. This led to the addition of stabilizing agents like lithium. However, antidepressants never were stopped. The addition of lithium as "augmentation" is a misinterpretation of what is needed. The SRI is ineffective long-term, therefore there is no augmentation of benefit with lithium. Rather, lithium is simply effective or not by itself. In fact, the SRI is, if anything, interfering with long-term benefit of lithium by its potential mood destabilizing effects. The side effect of restless leg syndrome with lithium is unusual. Use of other SRIs, like Prozac, does not provide any more utility than paroxetine. In fact, Prozac clearly seems to be causing manic symptoms in this case. It is therefore destabilizing. The concept of mixed states may indeed be relevant to this case, especially since antidepressants worsen mixed states. PL would

agree with the plan to taper off Prozac, and add a different stabilizing agent. Divalproex is a reasonable choice, and lamotrigine could potentially be reasonable as well. However, if the patient has mixed states, divalproex is likely more effective than lamotrigine. Obviously, there are more side effects from the former than the latter, but the benefits may outweigh those harms.. Given potential RLS, a low dose of lithium

might still be worth while continuing if only for potential dementia prevention. The prevalence of dementia in individuals in their late 60s with either unipolar depression or bipolar illness is about 20%, reduced by lithium to less than 5% of treated patients.

PL Reflection

The process of new drug development in psychopharmacology is a fundamentally conservative and empirical process that appears to overvalue principles of drug action established or proposed for known agents. This process results in searches for more drugs with similar effects and limitations. For example, it remains hard to imagine investing tens or hundreds of millions of dollars in developing a potential antipsychotic agent that has no antagonistic action on central dopamine or serotonin receptors, or an antidepressant that does not limit the inactivation of serotonin or norepinephrine. Following such conservative models derived from the pharmacology of older, successful, agents may be an effective business model, but is hardly likely to provide highly innovative or truly unique means of achieving desired clinical ends. More fundamentally, the process of psychopharmaceutical drug development over the past half century reflects the severely limiting effect of a lack of knowledge of etiology of psychiatric disorders, and only fragmentary and unconvincing notions about their possible pathophysiology. Even the pathophysiological hypotheses that have been proposed are logically circular and based largely on known actions of available treatments. In short, drug development for psychiatry has been empirically effective, if basically repetitious, for several decades but true innovation remains extraordinarily elusive.

Ross Baldessarini,

Chemotherapy in psychiatry, 2013

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THE PSYCHIATRY LETTER

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Cardiovascular disease and antidepressants

In this issue, PL publishes a special article on cardiovascular disease and antidepressants, reviewing a number of important randomized studies which fail to find medical benefits. The Article of the Month is a meta-analysis of two decades of research on dopamine blockers and cortical atrophy, finding evidence that a causal association likely exists. The Drug of the Month is mirtazapine, an agent which achieves monoamine agonism through a unique combination of receptor blockade effects. The curbside consult section addresses the question of new pharmacogenetic testing for treatment of depressive episodes with SRIs. An Update on discussion at the recent Santa Fe conference is provided.

This is the first issue of PL published since the Editor began employment this month with the Novartis Institutes for Biomedical Research in Cambridge, MA, in addition to his teaching and research activities at Tufts and Harvard universities. The Novartis position involves leading clinical research for early new drug development in psychiatry. Despite being a research position, since it is a branch of a pharmaceutical company, it is important to make this disclosure to readers. The overall approach of PL will not change, with the exception that if any Novartis agents are discussed (like clozapine or carbamazepine), the Editor will remind readers of this disclosure. The Editorial Board of PL will continue to review content to ensure that all discussion is fair-minded and scientifically sound.

We recognize there has been some delay in CME availability in recent months, and will rectify that matter soon so that CME questions will be available soon after each issue is published. As PL nears its third year of existence, we thank our readers and subscribers for their continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Cardiovascular disease and antidepressants

Are they helpful? Are they safe?

It's well known that depression increases the risk of cardiovascular disease. It's also known that depression can occur as a result of having medical illnesses, like cardiovascular disease. The arrow of causality goes in both directions.

Given that depression can cause or worsen heart disease it would seem to make sense that treatment of depression should improve cardiovascular outcomes. Besides that aspect, clinicians are faced with the question of how to treat depressive symptoms in cardiovascular disease.

Of course the standard approach would be to seek to provide symptomatic improvement with the "antidepressants," or monoamine agonists.

In this article, we'll review the scientific evidence about the efficacy of SRI agents in depression in cardiovascular disease, both for mood and for cardiac outcomes.

There have been four major RCTs of monoamine agonists in the treatment of depressive states in cardiovascular disease: the Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, the Sertraline against Depression and Heart Disease in Chronic Heart Failure (SADHART) trial, the Myocardial Infarction and Depression-Intervention (MIND-IT) trial, and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial.

ENRICHD involved 2482 patients who had experienced myocardial infarction, randomized to cognitive behavioral therapy or usual care. If their

Hamilton Depression rating scale scores were above 24, meaning mild to moderate severity, they received SRIs. The primary outcome was mortality or recurrence of myocardial infarction, with secondary outcomes for depression symptom scores. Overall, there was no benefit with treatment for the primary cardiovascular outcomes in the study, with a mean follow-up of over two years (29 months). There was improvement in depression symptoms of 1.5 points, which is a small effect, compared to the control group.

SADHART involved 469 patients with heart failure randomized to sertraline versus placebo. The primary endpoint was a composite outcome of cardiovascular status at 12 weeks. There was no

meaningful improvement in that outcome with sertraline versus placebo. Also, there was very little difference between sertraline and placebo in

depression symptom improvement in the three months of treatment. The medication was said to be safe from a cardiovascular perspective, although in a posterior analysis, it was notable that there was a slightly increased overall mortality with sertraline versus placebo (7.7% versus 6.8%, RR= 1.25, 95% CIs 0.62, 2.33), and greater cardiovascular death rates with sertraline treatment versus placebo (6.8% versus 4.3%, RR =1.60, 95% CIs 0.74, 3.47). These differences are not statistically significant, but the study was not large enough to be able to detect statistical significance for these differences. Rather, as discussed in September 2015 issue, when assessing studies with low statistical power, effect estimates and confidence intervals are more meaningful. Reanalyzing these data, the relative risk indicates

"...there was no benefit for the primary cardiovascular outcomes..."

a 60% increase cardiovascular mortality with sertraline, with confidence intervals suggesting that this increase is more likely than not to be real effect. Other cardiovascular outcomes did not differ appreciably between groups, except for the observation of a small but notable increase in risk of cerebrovascular stroke and sertraline-treated patients versus placebo (4.3% versus 1.7%, RR = 2.51, 95% CIs 0.80, 7.89). In other words, sertraline more than doubled the risk of stroke, with the possibility of even higher risk based on the confidence intervals. Thus, this reanalysis cannot support the conclusion made by the authors and commonly cited from this negative trial that sertraline was shown to be safe in cardiovascular disease. Rather, allowing for infrequent outcomes and low statistical power, the available evidence suggests some increased risk of harmful cardiovascular and cerebrovascular outcomes with sertraline in this heart failure population. A later analysis examined inflammatory markers in the study and reported benefit with sertraline versus placebo in reducing the prevalence of C-reactive protein, Interleukin-6, and fibrinogen.

These two studies are both negative in their outcomes but provide some insights that raise some questions regarding the nature of the association between depression and cardiovascular disease. The ENRICHD trial showed some benefit for depressive symptoms, but this benefit did not translate into cardiovascular outcomes, despite long-term follow-up over greater than two years. This finding may mean that depressive symptoms may predispose to cardiovascular disease, but their treatment does not improve cardiovascular outcomes. On the other hand, the improvement

seen with the CBT treatment arm in the study was small compared to placebo, and thus perhaps specific treatment benefits for cardiovascular events would be difficult to observe even with long-term follow-up.

The SADHART study only lasted three months, and an expectation of notable cardiovascular benefits in a short timeframe was probably misplaced. Further, the medication just failed were completely even to improve depressive symptoms in the study, and thus the association between depression improvement and cardiovascular outcomes could not be tested. The failure to have even depressive symptom benefit in this trial also raises the question whether antidepressants may simply be less effective in treating depressive symptoms and cardiovascular disease. In other words, like vascular depression, it may be that depression in the setting of cardiovascular disease confers poor prognosis and nonresponse to antidepressants.

The SADHART study results also provide a suggestion that improvement in inflammatory markers may not translate into improved cardiovascular outcomes. In fact, cardiovascular outcomes seemed somewhat worse with sertraline than with placebo, and this appeared to be the case especially for a doubling of risk of cerebrovascular stroke with sertraline treatment.

Turning to the other two randomized trials, MIND-IT was a study of 331 patients with myocardial infarction randomized to mirtazapine or citalopram versus treatment as usual. They were followed for a meeting of 18 months. In the primary outcome of depression symptom

"The ENRICHD trial showed some benefit for depressive symptoms, but this benefit did not translate into cardiovascular outcomes..."

improvement, there were no notable differences between groups. Cardiac event rates were essentially identical between the two groups as well (14% vs 13%). It was observed that if patients improved for depression, they had fewer cardiac events. Treatment nonresponders for depression had more cardiac events. No differences were seen between the two groups of antidepressant treatment versus treatment as usual.

In the CREATE trial, 284 patients with coronary artery disease were randomized to citalopram versus placebo for 12 weeks of outpatient treatment. Improvement in depression was seen with a mean difference of 3.3 points on the Hamilton Depression rating scale, but no improvement in cardiovascular outcomes was seen. No depression symptom benefit was seen with interpersonal psychotherapy versus clinical management. There was a 2 ms increase in the QTc interval with citalopram versus placebo.

Interpreting these latter two studies, the MIND-IT trial was long and able to assess cardiac outcomes, and confirmed the findings from the ENRICHD trial that no long-term cardiovascular benefits can be seen with antidepressant treatment. The observation that depression symptom improvement in general correlated with better cardiovascular outcomes is important though, and may be more meaningful than the opposite finding in the much shorter SADHART trial.

The CREATE trial was interesting in that depression symptom improvement was shown, in contradiction to the SADHART trial, but again cardiovascular benefits were not seen, with short-term treatment. The observation of no depression

symptom improvement with interpersonal psychotherapy raises the question whether patients with depression and cardiovascular disease may be less responsive to psychotherapies as well. This finding is somewhat consistent with the ENRICHD trial, in which only a small benefit was seen with CBT for depression symptoms.

In sum, these large randomized trials of depression and cardiovascular disease generally suggests limited benefit with either monoamine agonists or psychotherapies both for depression symptoms as well as for cardiovascular outcomes. There may be a disconnect between improvement for inflammatory pathophysiology and clinical mood and cardiac outcomes. In fact, there is some evidence that some SRIs, like sertraline, may in fact increase risk of poor cardiac or cerebrovascular outcomes.

"There may be a disconnect between improvement for inflammatory pathophysiology and clinical mood and cardiac outcomes..."

This interpretation of these results complicates standard recommendations regarding the use of SRIs in depression for coronary artery disease. The recommendation of the UK national health service is that sertraline should be a first line treatment, based on the reported safety results of the SADHART trial. This conclusion is put into some doubt based on this analysis. Other SRIs tend to be avoided due to drug interactions, in the case of fluoxetine and paroxetine, and due to increased risk of cardiac arrhythmias for citalopram and escitalopram. Venlafaxine should be avoided due to evidence of increased risk of sudden cardiac death in individuals with coronary artery disease and history of cardiac arrhythmias in particular. It also increases coronary risk factors such as high blood pressure. Sertraline also is excluded based on the poor outcomes for

cardiovascular and cerebrovascular safety described here, then almost all SRIs would be avoided in the treatment of depression and coronary artery disease. In the past, bupropion tended to be recommended, due to absence of drug interactions, but it has the pharmacological properties of the amphetamine class, which are known to increase risk of cardiac arrhythmias. Bupropion has been shown to increase blood pressure. Hence, there may be reason to avoid bupropion in this population as well.

The PL Bottom Line

- SRIs are not proven reliably effective for depressive symptoms or episodes in cardiovascular disease.
- Psychotherapies, like CBT and IPT, also appear to have little to no benefit for depressive symptoms in cardiovascular disease.
- Sertraline, contrary to common claims, appears to have some cardiovascular risks, increasing mortality in the SADHART study, and more than doubling risk of stroke.
- Although SRIs may improve inflammatory markers in cardiovascular disease, notable clinical benefits are not seen for cardiovascular outcomes.
- In short, SRIs do not appear to be effective notably either for depressive symptoms or for cardiac outcomes. Their safety also is questionable.
- A conservative conclusion is that SRIs should not be given routine for depressive symptoms in cardiovascular disease.

PL Reflection

We have heard the outcry: Science destroys faith....These critics doubt the eternal truth which shines forth in modern science. They deny the dignity of man which is today no longer possible without a scientific attitude. They attack philosophical enlightenment, which they associate only with the flatness of the understanding and not with the breadth of reason. They turn against liberalism, seeing only the congealed liberalism of laissez faire and superficial faith in progress, not the profound force of liberality. They attack tolerance as heartless indifference, and fail to recognize the universal human readiness for communication. In short, they reject our foundation in human dignity, in the power to attain knowledge, in freedom, and advocate philosophical suicide.

In opposition to these beliefs, we are certain today that there can be no integrity, reason, or human dignity without a true scientific attitude....Where science is lost man falls into the twilight of vaguely edifying sentiments, of fanatical decisions arrived at in self-willed blindness. Barriers are erected, man is led into new prisons.

*Karl Jaspers
Way to Wisdom*

Current Study of the Month: *Brain effects of dopamine blockers*

Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. P Fusar-Poli et al. *Neuroscience and Biobehavioral Reviews*, 2013, 37:1680-1691

A review finds that medications cause cortical atrophy

There has been some debate for some time whether antipsychotic medications cause or worsen cortical atrophy in the brain in patients with schizophrenia. It has been known from a range of studies that schizophrenia itself is associated with brain changes. Hippocampal atrophy has been reported, and ventricular enlargement (which reflects atrophy of midbrain structures such as the caudate and putamen) is a well-replicated finding in middle and later stages of schizophrenia in particular.

The question has then arisen as to the effects of use of dopamine blockers for long-term treatment of schizophrenia, in a setting of possible underlying neurodegeneration which occurs as part of the disease. Are dopamine blockers protective in any? Or are they neutral? Or do they hasten or worsen the degenerative process in the brain in schizophrenia?

Until recent decades, these questions couldn't be answered partly due to insufficient duration of treatment to assess long-term effects, partly due to the inherent expense and difficulty of conducting such long-term studies, and partly due to inadequate technology to measure brain structure and function. Beginning with some studies in the 1990s, MRI studies have been conducted. This review paper is a systematic review and meta-analysis of this topic.

30 longitudinal MRI studies were identified, 104 patients with schizophrenia versus 780 controls. They were followed for an average of about 1.5 years (72 weeks). Brain volumes before and after

"After treatment with antipsychotic agents, there was new reduction in gray matter volume...."

antipsychotic treatment were examined. Duration of exposure to treatment was recorded as a primary predictor. Researchers also assessed duration of illness, as well as a measure of severity of illness, along with other clinical and demographic variables included in the 30 studies.

Baseline evaluation, *before* treatment with antipsychotic medications, showed that the patients with schizophrenia had smaller whole brain volumes and enlarged lateral ventricles, compared to controls. This finding confirms the general view, dating back to Kraepelin, that schizophrenia involves a neurodegenerative

process such that there is loss of neurons in various parts of the brain. Overall gray and white matter volume did not differ between schizophrenia and controls. Most of the baseline changes were likely driven by smaller mid brain structures.

After treatment with antipsychotic agents, there was new reduction in gray matter volume, and the lateral ventricular enlargements also worsened. These results were observed in patients with schizophrenia, but not in controls. These worsened outcomes correlated inversely with duration of antipsychotic exposure. The longer antipsychotic treatment was given, the worse the neurodegenerative outcomes of gray matter volume reduction and ventricular enlargement.

When other possible factors were examined, such as severity of illness or duration of illness, these other illness factors did not influence the finding of greater gray matter cortical atrophy and further ventricular enlargement.

In other words, the worsened neurodegenerative results seemed to be associated with dopamine blocker treatment, and could not be accounted for by severity of illness or duration of illness.

In sum, schizophrenia itself is a neurodegenerative disease, mainly with midbrain cortical atrophy producing lateral ventricular enlargement. Over time, antipsychotic treatment appears to worsen this midbrain atrophy, and also seems to be related to causing or worsening generalized gray matter cortical atrophy.

These results could be interpreted as providing evidence that antipsychotics do not have beneficial disease-modifying effects long-term in schizophrenia. This conclusion does not take away from their symptomatic benefits short-term for acute exacerbations of schizophrenia.

The PL Bottom Line

- Dopamine blockers (antipsychotics) appear to worsen the neurodegenerative process in schizophrenia in long-term treatment.
- Their main benefit is for symptomatic improvement of acute psychotic exacerbations.

Drug of the Month: *Mirtazapine*

Same result by different means

PL Reflection

Amid an eternal heritage of sorrow and suffering our work is laid, and this eternal note of sadness would be insupportable if the daily tragedies were not relieved by the spectacle of the heroism and devotion displayed by the actors. Nothing will sustain you more potently than the power to recognize in your humdrum routine, as perhaps it may be thought, the true poetry of life - the poetry of the commonplace, of the ordinary man, of the plain, toil-worn woman, with their loves and their joys, their sorrows and their griefs....Hilarity and good humor, a breezy cheerfulness, a nature 'sloping toward the southern side', as Lowell has it , help enormously both the study and in the practice of medicine. To many of a sombre and sour disposition, it is hard to maintain good spirits amid the trials and tribulations of the day, and yet it is an unpardonable mistake to go about among patients with a long face.

William Osler
The Student Life

Mirtazapine (Remeron) is FDA-indicated for acute depressive episodes in major depressive disorder (MDD).

Biological mechanism

This agent produces increased serotonergic and noradrenergic activity indirectly, unlike standard SRIs or other antidepressants. It does so partly by blocking the negative feedback loop at synapses for norepinephrine. This loop is mediated by the alpha-2 adrenergic receptor, which is a presynaptic receptor located on the dendrite (not the axon, where most antidepressants act). The alpha-2 receptor, when stimulated by norepinephrine in the synapse, sends a message back inside the presynaptic neuron, informing it to stop producing norepinephrine. By blocking this signal, norepinephrine continues to be released into the synapse, instead of stopping.

Another effect of mirtazapine is direct blockade of the serotonin 2 and 3 receptors. Blocking serotonin receptors might seem to be the opposite of what SRIs do. But the theory is that by blocking the 5HT-2 and 5HT-3 receptors, more serotonin is left to stimulate the 5HT-1 receptors, which are thought to mediate depression symptom benefit. The other receptors are thought to be related to side effects of serotonin activity, such as sexual dysfunction. This mechanism is thought to be why mirtazapine does not have sexual dysfunction, unlike SRIs.

The other class of medications that are serotonin blockers are the modern neuroleptics, and this effect may mediate their weight gain. Mirtazapine shares this side effect. Alpha-adrenergic blockade also tends to cause sedation and cognitive impairment.

Side effects and dosing

As noted above, mirtazapine has the benefit of not having sexual dysfunction, but it has notable weight gain and sedation/cognitive impairment. In all these side effects, it differs from SRIs.

Fast Facts: Mirtazapine

Typical dose: 15-30 mg/d

Biological mechanism: alpha 2 and serotonin 2 receptor blockade

Typical side effects: weight gain, sedation

Medically important side effects: none known

Clinically proven efficacy: FDA indication for acute depressive episodes in unipolar depression

Its dose range is 15-45 mg/d, with 30 mg/d being a typical dose. Its half life is 20-40 h.

Clinical efficacy

Its proven efficacy is in depression, though due to its sedating properties, clinicians commonly prescribe it for insomnia. It is not proven more effective than other antidepressants.

The PL Bottom Line

- Mirtazapine is not more effective than other antidepressants.
- Unlike SRIs, it does not have sexual dysfunction, but it does have weight gain and sedation/cognitive impairment.

Update from the Santa Fe conference

At the end of October, the PL editor held a 3-day conference in Santa Fe with a number of colleagues and practitioners. In the course of lengthy discussions, a number of questions and

comments arose. For the benefit of PL readers, the editor provides here a selected report of some of those questions and comments and the discussions that ensued.

Unipolar depression

Q: After reviewing the limitations of monoamine agonists (antidepressants) in randomized studies regarding their efficacy for DSM-defined MDD, the following question arose: What role do you give to SRIs in the treatment of unipolar depression?

PL: In the conference, we reviewed the evidence that modern antidepressants have an overall small effect size of benefit for the acute depressive episode in MDD. We also reviewed the concerns that they may not have true maintenance prevention benefit of future depressive episodes, due to the potential invalidity of the enriched clinical design. That kind of design he selects treatment responders, and then assesses treatment response again. As discussed elsewhere, this issue raises some concerns about whether these long-term studies truly demonstrate benefit. If we accept these concerns for both acute and long-term treatment, then the overall approach taken here in the PL perspective would be to use SRI antidepressants for certain subtypes of acute depressive episodes in unipolar depression, but not for other subtypes, and to be willing to avoid using those drugs long-term. In other words, the routine long-term continuation of those medications is questionable in the PL view. As to what should be done instead, since these questions are not raised for research, the available research literature provides few clues. Nonetheless, it is worth noting that lithium has been proven effective for prevention of depressive episodes in both unipolar depression and bipolar

illness. The question can be raised whether lamotrigine might have similar long-term efficacy, although it has only been studied in bipolar illness and not unipolar depression.

Unipolar or bipolar?

Q: After the discussion of the concept of manic-depressive illness (MDI), and how it is equivalent to both bipolar illness and unipolar depression combined, the question came: How would you treat "unipolar" depression that you say is similar to bipolar illness?

PL: This way of putting the question is part of the problem. The discussion about MDI involves the use of pre-DSM-III language. This way of thinking predates the terms bipolar or unipolar. Hence in the past when some of us use the phrase bipolar spectrum to argue for a broadening of the bipolar concept, this language may have been misleading in that the issue is not so much broadening bipolar illness definitions, it is also about narrowing unipolar illness definitions. More accurately, the issue is about whether any such unipolar and bipolar concepts are valid at all, they simply represent subtypes of one overall illness, namely MDI. So the question is not whether one would treat "unipolar" depression that is similar to "bipolar" illness in some way, but rather whether there is any rationale to distinguishing these two subtypes in any definitive way. Asked to treatment, there may be some differences, but one would also expect many similarities. For instance, it may be that the so-called mood stabilizers are effective in prevention of depressive episodes in both illnesses.

DSM and insurance

Q: After a critique of the legitimacy of DSM, the observation was made that such discussions are great, but clinicians still need to provide an insurance diagnosis for reimbursement. Aren't they forced to then follow and practice using the DSM system?

PL: It is not the case that one has to use DSM-III coding for insurance reimbursement in many settings. For instance, in the past and presently, most insurance reimbursement is done with ICD codes, not DSM. Hence, the claim that one needs to accept the DSM definitions would need to be replaced by the claim that one should study and follow ICD definitions, which most clinicians do not do. Even if DSM or ICD definitions are used, for insurance coding purposes, this does not mean that clinicians should base all or even the majority of their clinical beliefs and judgments on the definitions used in the ICD or DSM systems for coding purposes. In other words, one could use those DSM definitions for coding, but make clinical decisions regarding diagnosis and treatment simply based on the scientific literature, unrelated to the DSM coding. In short, you may have to use the coding which you do not have to believe it, much less limit your clinical thinking to those codes.

Existential psychotherapy: Being yourself

Q: In a discussion of the meaning of existential psychotherapy, a colleague commented that it seems to mean that you have permission to be yourself. Is that true?

PL: It is relevant that empathy has become part of most modern psychotherapies. It is commonly used in discussions about psychotherapy as well as medical care. Part of the importance of the discussion at the conference was to understand

the roots of the concept of empathy in the existential psychiatry literature, and thus to better appreciate it and know how to achieve and use it. It is about being yourself, but the existential tradition provides teaching tools about how best to use and achieve empathy and other aspects of this approach to psychotherapy.

Using lithium

Q: One colleague noted that for over 5 years, for some reason, she has not prescribed any lithium. She just saw it as old and full of side effects.

PL: One of the themes of the conference involved in the many benefits of lithium not only for mood episodes, but also for suicide and dementia prevention. It is unfortunate that this medication has been ignored by so many clinicians in recent decades because of the intense marketing of other new medications. New is not always better. In fact new is almost never better in psychiatry, since our most effective treatments are agents which were introduced in the 1970s or earlier. As to side effects, the harms of lithium are wildly exaggerated, and in many ways certainly not worse than extensively use medications like olanzapine and quetiapine, where the effects of marketing have led clinicians to accept many side effects.

PL Reflection

Women [have]...a subtler understanding of unconscious processes....

*Freud
Psychopathology of Everyday Life*

Curbside Consult

Questions and cases from you:

Question: What is your view on genomic testing for psychotropic drugs? An increasing number of patients, nurse practitioners, and even a few psychiatrists seem to believe that these tests can be used to identify the “right” antidepressant to use in bipolar patients. I think they are confusing metabolic issues with clinical efficacy, and they are not taking into account the adverse effects of antidepressants on the course of bipolar illness.

PL: The perspective provided here is consistent with the PL view. One should not confuse pharmacokinetic factors with clinical efficacy. The matter is complex and deserves some discussion.

The approach of simply using genomic testing to make treatment decisions regarding antidepressants for MDD assumes many things. One of the central assumptions of this approach is that the diagnostic concept of MDD is valid, and that the antidepressant class is an appropriate treatment. These two assumptions are simple, and accepted by the vast majority of mental health clinicians. However, as has been discussed in PL issues, there are reasons to doubt both assumptions. Firstly, MDD consists of many subtypes, some of which actually worsen with antidepressants, like mixed states. Other subtypes, like melancholia, do not respond well to modern antidepressants at all. Further, the SRI class of antidepressants have other issues besides their inefficacy and potential harms in melancholia and mixed states. For instance they are completely ineffective and bipolar depression, and it can cause mania or worsen bipolar illness. Further, they can cause suicidality in young adults

and children, perhaps related to prodromal bipolar illness or undiagnosed or misdiagnosed bipolar illness. Another possibility is that such young adults have mixed states, which worsen with SRIs, leading to suicidality. Lastly, the benefits of SRIs for depressive episodes are much better proven acutely and short-term, rather than in maintenance treatment for long-term prevention of new depressive episodes, due to the potential invalidity of the enriched maintenance design, as discussed above. Hence, it is common for patients to have acute benefit for few months, and then to relapse into new depressive episodes despite continuing the SRI which has helped them initially. In the STAR*D study, about one half of patients who had responded to antidepressants for the acute depressive episode in MDD relapsed into new depressive episodes within six months, despite continuation of the same antidepressant which had helped them initially.

None of these issues have anything to do with pharmacokinetics, the cytochrome P450 system, and whether patients are rapid metabolizers or poor metabolizers. These issues can be relevant in some patients, but they become relevant only if one assumes that an accurate diagnosis has been made, for instance with the patient not having bipolar depression at all. Further it assumes that the subtype of the depressive episode in so-called MDD is not mixed or melancholic. Also, it assumes that the depressive episode which is difficult to treat is not a maintenance relapse as opposed to nonresponse for the acute phase. All of these clinical factors need to be taken into account before any genomic testing can be useful in improving treatment response for depressive episodes.

In the research conducted on genomic testing so far, none of these aspects of clinical diagnosis and treatment are taken into account.

Hence the research studies that claim to support efficacy of genomic testing are questionable in the PL view, and only partially valid at best.

Ten Fallacies of Psychopharmacology

1. More is better. (If a low dose helps a little, a higher dose helps more. Not so.)
2. What gets you well keeps you well. (Happily ever after: but many drugs work acutely but not preventively, and vice versa.)
3. Treat to remission. (If one drug helps somewhat, and two drugs help more, keep going until all symptoms are gone completely; they rarely do, but side effects increase inevitably.)
4. Polypharmacy is good. (A variant on the first fallacy: If one drug helps somewhat, two drugs will help more.)
5. Make one change at a time. (Clinical practice isn't research; one can't go too slowly)
6. 4-8 weeks is a sufficient trial of a drug. (Possibly correct for some acute trials, but not for maintenance trials.)
7. Dose low, go slow. (If common, this approach produces undue suffering).
8. Always taper a drug. (Sometimes very harmful effects call for immediate discontinuation; not all drugs have withdrawal syndromes.)
9. Treat the most severe symptom. (This often has no relation to the underlying disease.)
10. Always incorporate the patient's preference. (The patient can be wrong.)

PL Reflection

Now we scientists are used to this, and we take it for granted that it is perfectly consistent to be unsure, the it is possible to live and *not* know. But I don't know whether everyone realizes this is true. Our freedom to doubt was born out of a struggle against authority in the early days of science. It was a very deep and strong struggle: permit us to question - to doubt - to not be sure. I think that it is important that we do not forget this struggle and thus perhaps lose what we have gained.

Richard Feynman
The Value of Science, 1955

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THE PSYCHIATRY LETTER

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Fallacies of psychopharmacology

In this issue, PL publishes a special article on Ten Fallacies of Psychopharmacology. These are common beliefs that are held regarding how to treat patients with medications for psychiatric syndromes. They each rest on some assumptions which are untrue, and the special article explains why. In the next issue of PL, we will follow up with Ten Truths of Psychopharmacology. Stay tuned.

The Article of the Month examines a meta-analysis on anti-inflammatory medications, like NSAIDs, and makes the surprising discovery that their benefit is quite similar to what is shown with standard monoamine agonist antidepressants, like SSRIs. The Drug of the Month is citalopram, the only truly selective SRI. The curbside consult question addresses the question of how to manage refractory violent agitation in the emergency room setting with patients who have bipolar illness.

We would like to let readers know that some staff changes at PL are in process as we try to improve CME availability in a more efficient manner. We expect to have all CME questions for all months updated within the next few months.

We appreciate your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Ten Fallacies of Psychopharmacology

False assumptions to avoid

In the preceding issue of PL, Ten Fallacies of Psychopharmacology were listed. Here those fallacies are described again, and detail is provided about why they are fallacies, as opposed to truths.

1. More is better.

If a low dose helps a little, a higher dose helps more. Not so.

The first fallacy of psychopharmacology has to do with a belief that is logical, but needs to be proven in clinical practice. Examples abound of useful and effective medications which are harmful at too high of a dose. Aspirin at very low doses prevents heart attacks and strokes, but at average to high doses has no further preventive benefit, and instead causes gastrointestinal bleeding. In low to average doses, lithium is very effective for manic episodes, but at higher doses, it is toxic and can cause kidney failure. Tricyclic antidepressants at average doses are effective for depression, and at higher doses cause cardiac arrhythmias. One could multiply examples for almost every drug class.

The disadvantage of high doses is not always related to toxicity. Some medications are less effective at higher doses. For instance, aripiprazole is more effective for treatment of the acute depressive episode at less than 10 mg per day compared to more than 10 mg per day. It is frequently the case that higher doses lead to a plateau of effects. For example, haloperidol does not produce more benefit above 10 mg per day than below 10 mg per day. Lithium does not

produce more benefit above a level of 1.0 than below that level. Steroids do not produce more benefit for autoimmune diseases above low to average levels.

Certainly more benefit can be obtained with somewhat higher doses in the effective dose ranges of certain medications, but those dose ranges need to be established. It is not a rule in a general sense that increasing doses routinely will lead to more benefit. In fact, it is a much more general rule that after a certain dose range, increasing doses will lead to a plateau of effects, with usually more side effects, toxicity, or harm.

2. What gets you well keeps you well.

“...unfortunately common sense is not consistent always with scientific truth...”

Happily ever after: but many drugs work acutely but not preventively, and vice versa.

This is the happily ever after fallacy. The idea is that if medications are helpful acutely, then they should be continued and the patient will continue to do well, happily ever after. Again, this belief is consistent with common sense, but unfortunately common sense is not consistent always with scientific truth. There are many examples of drugs which work acutely not preventively, and vice versa. For example, sumatriptan is effective acutely for migraine, but does not prevent it. In contrast, propranolol is effective for prevention of migraine, but does not treat it acutely. Penicillin and other antibiotics are generally effective acutely for various infections, but do not prevent infections if continued long-term. Steroids are generally effective acutely for autoimmune disease

exacerbations, such as lupus, but continuation of steroids do not prevent future exacerbations effectively. In short, there is no scientific or biological reason to believe that what gets you well keeps you well. In psychiatry, this is one of the most common and harmful fallacies. SRIs are given acutely for depressive and anxiety symptoms, with some benefit, and then continued forever, for years and decades, with no exit plan, and with the eventual occurrence of very severe withdrawal syndrome if any attempt is made to come off them. Dopamine blockers are continued long-term for schizophrenia, based on short-term benefits, even though their maintenance benefits are limited, and there is evidence now that they cause cerebral atrophy long-term.

3. Treat to remission.

If one drug helps somewhat, and two drugs help more, keep going until all symptoms are gone completely; they rarely do, but side effects increase inevitably.

This fallacy has become the mantram of many psychopharmacology researchers. Clinicians and researchers have been justifiably bothered by the limited benefit obtained with psychotropic drugs in recent years. The early excitement of psychotropic drugs in the 1960s to 1980s has not been sustained. It has been replaced by an inability to obtain equally impressive outcomes compared to those early years. The joke has become that one should hurry up and use a new medication before it stops working. The reaction of many clinicians and researchers has been to increase the dose of medications, as in the first fallacy, and then to combine medications from the same or different classes, as in this fallacy. The view is that if patients are not improving sufficiently, it is simply because clinicians are not trying hard enough. If

“...the underlying assumption behind this fallacy is that our diagnostic system is legitimate...”

we use more medications and at higher doses, we will be able to achieve more benefit. In the absence of new and different medications developed by the pharmaceutical industry, clinicians and researchers have focused on the same classes of medications that have been available for the last few decades, but just use them more aggressively. The problem of "residual" symptoms is to be fixed by more and more medications of the same kind. These clinicians and researchers sometimes don't appreciate that the problem may be that the wrong kinds of medications are being used for the wrong kinds of diagnoses. Or, as a related problem, the diagnoses, often based on DSM, may not be biologically valid enough to improve markedly with certain drug classes. In other words, the underlying assumption behind this fallacy is that our diagnostic system is legitimate and we just need to get better treatments for those diagnoses. This assumption itself is questionable.

A related topic is that even if we have valid diagnoses, and effective treatments for those diagnoses, there may be some benefit to allowing for the occurrence of mild symptoms. Or, it may be that the balance of harms and benefits with medications may be such that lower doses that lead to mild symptoms may be preferable to

higher doses that may lead to zero symptoms. For example, mild symptoms of depression are associated with the positive traits of empathy and realism, and mild symptoms of mania are associated with the positive traits of creativity and resilience. The occurrence of mild manic or depressive symptoms is associated with being more functional in many cases, and with success in the creative arts as well as in politics and leadership. It may not be necessary or even desirable to completely remove all manic and

depressive symptoms in such persons, even if complete remission was feasible.

4. Polypharmacy is good.

A variant on the first and third fallacies: If one drug helps somewhat, two drugs will help more.

Even if remission is not set as the goal, there is the belief that multiple medications will be more effective than any single medication. This approach, call polypharmacy, has been criticized in medical tradition going back to the 19th century, but in recent years it has seen a resurgence in psychiatry. An effort is made to legitimize this approach by changing the name, to terms such as "polytherapy", or "combination pharmacotherapy." These changes in language cannot hide the basic idea, which is related to the first and third fallacies, namely the view that more medication should produce more benefit. Sometimes medications in the same class are combined, and sometimes medication in different classes are combined. In either case, one cannot assume that combinations of medications are more effective than monotherapy. Sometimes they are, but sometimes they are not, and the adjudication has to rely on clinical research that proves the matter one way or the other. For example, it has been shown that about one third of persons with bipolar illness have complete resolution of almost all of their symptoms with lithium monotherapy. Two-thirds may need other medications in combination treatment, but one-third do not. The view that almost everyone should be on combination medications for bipolar illness, which is held commonly, leads to overmedication of one third of that population, who would do well with just one very effective medication such as lithium. Further, in the STAR*D study, it was shown that

"The primary purpose of clinical practice is to improve the patient's clinical state, not to obtain knowledge...."

combination treatment with multiple antidepressants was not more effective than switching to a different antidepressant. Thus, in general, it cannot be claimed that combination treatments are more effective than a single medication. This is an empirical question, not a logical one.

5. Make one change at a time.

Clinical practice isn't research; one can go too slowly.

Sometimes clinicians will say that they like to make one change at a time, because they want to know what is causing what. Although laudable in principle, this approach can lead to an overly slow process of finding the right medication or medication combination in an individual. One can go too fast or too slowly in practice. The rationale

for making one change at a time is not really a clinical rationale. One wants to know what is causing what, but this is only a secondary concern to wanting to get the patient

better. The primary purpose of clinical practice is to improve the patient's clinical state, not to obtain knowledge. The latter is a goal for research. Knowing what is doing what is a knowledge question, and really belongs to the world of research. Getting the patient better is the first goal of the clinician. Even if two changes are made at the same time, or three, what really matters is whether the patient improves. How can you find out which change led to the improvement? Later, when the patient is doing well, the clinician can remove one medication from a mix, to see if the patient's improvement persists. Then clinicians can tell whether a first or second medication led to the change. It is better to make these changes when a patient is well, rather than a patient is ill. The main goal when a patient is ill is to get a patient well. Once a

patient is well, then a slow process of obtaining knowledge about what medication is doing what is feasible. But to go slowly when the patient is still sick, on the grounds that one wants to have adequate knowledge about the effects of medications, is to let the patient suffer excessively, and in a way that is not justifiable given the primary goal of clinical practice.

6. 4-8 weeks is a sufficient trial of a drug.

Possibly correct for some acute trials, but not for maintenance trials.

The opposite problem to the fifth fallacy is the problem of going too fast. Frankly this is the case when multiple medications are tried one after the other, for one to two months in duration. This belief that one to two months is the timeframe for a medication trial is based on clinical research studies, often

for depressive episodes, where acute efficacy is being studied. Many of these research projects are conducted by the pharmaceutical industry, and the eight-week acute efficacy design is based on what is required by the FDA for a marketing indication. This timeframe is not necessarily relevant to clinical practice, depending on what is being treated. Acute indications are emphasized by the pharmaceutical industry because they are cheaper and quicker to obtain than long-term indications. Clinical practice, in contrast, typically involves long-term treatment, not just treatment for 1 to 2 months. Almost always, then, what is relevant for clinical practice is long-term maintenance prevention of symptoms or episodes of illness, not just its acute treatment. As discussed in the second fallacy, one cannot presume that there will be long-term maintenance prevention benefit with a drug which is only been proven effective for acute short-term symptoms.

“...what is relevant for clinical practice is long-term maintenance prevention of symptoms or episodes of illness, not just its acute treatment....”

The duration of the trial that is sufficient to prove long-term benefit depends on the illness being studied, but typically involves six months to one year of treatment or longer for the classic conditions in outpatient psychiatric treatment, like affective illness or schizophrenia. This does not mean that clinicians should wait 1 to 2 years with each trial of every medication, because then they would be going too slowly, as in the fifth fallacy. But one to two months is probably too fast. For example, in a trial of a monoamine agonist for depressive illness, or a mood stabilizer for a bipolar or depressive illness, or even a dopamine blocker for schizophrenia, it probably makes sense to try new medications for about 3 to 6 months, depending on the severity of symptoms and the need to go more quickly or more slowly based on that severity.

7. Dose low, go slow.

If common, this approach produces undue suffering.

This fallacy again relates to going too slow. The first part of this belief has to do with the idea of starting a low dose with every patient. This is not reasonable because many patients present with severe acute symptoms that require medium to higher doses for immediate symptom control. For instance in a severe outpatient acute manic state, medium to high doses of a dopamine blocker should be given quickly so as to prevent possible hospitalization. If risperidone is used, it should be given a 2 to 3 mg per day for that purpose. If given at 0.5 to 1 g per day, it will be better tolerated, but the patient may end up being hospitalized. Going slowly, which is the second part of this fallacy, is not necessarily rational either. In some cases, one may start with a low dose to assess and ensure tolerability, but a relatively rapid increase in dose may be needed for a more severe condition. For

instance, divalproex might be started at 250 mg per night, but in a patient with moderate manic symptoms, it should be increased to at least 750 mg per day relatively quickly, meaning 3 to 7-day intervals between doses, but no longer.

8. Always taper a drug.

Sometimes very harmful effects call for immediate discontinuation; not all drugs have withdrawal syndromes.

The view that medication should always be tapered is restrictive to an excessive degree. There are many medications which do not have withdrawal syndromes, nor any known clear common risks from discontinuation, such that tapering is unnecessary. For instance, bupropion has no withdrawal syndrome, and the claim of rebound risk of seizures is not based on any clear empirical evidence. Unlike SRIs, bupropion can be stopped without the need for slow taper. Especially when one is making more than one change at the same time, as discussed above in relation to the fifth fallacy, it is important to not engage in unnecessary drawing out of those changes, such as with slow tapers of medications that do not have serious discontinuation syndromes. Another example is divalproex, which has no withdrawal syndrome and can be stopped when needed. This fact contrasts with lithium, which has a withdrawal syndrome, and which should be tapered off in a one-month time frame or longer. Again, there is no general logical rule here, but rather a need to ask for empirical evidence and then to decide one way or the other.

9. Treat the most severe symptom.

This often has no relation to the underlying disease.

It is common for clinicians to rely on the concept of "target symptoms." Frequently, the target symptom is the most severe symptom that the patient experiences. This fallacy comes back to the problem of taking a symptom-oriented approach to treatment, as opposed to a disease-oriented approach. It would be like focusing on fever as the most severe symptom, rather than trying to treat the underlying infection. One could give plenty of Tylenol, but only modest symptomatic benefit would be achieved. This scenario may be similar when multiple or higher doses of monoamine agonists are given for anxiety or depressive symptoms, but the underlying affective illness is not treated. It is the case with medical diseases that the most severe symptoms are not related directly to the underlying disease. Many medical diseases have no symptoms at all, such as hypertension or cancer. The severity of symptoms therefore does not correlate at all with the disease, nor does it accurately direct which kind of drug should be selected.

"...the most severe symptoms are not related directly to the underlying disease...."

10. Always incorporate the patient's preference.

The patient can be wrong.

In contemporary medicine, it is no longer acceptable to be paternalistic with one's patients, at least in the United States. This laudable approach to practice, which is consistent with the American emphasis on individual and civil rights, runs into a problem when a clinical profession is supposed to possess specialized knowledge which is unavailable to the general population. In the case of clinical psychiatry and the mental health professions, clinicians are presumed to possess such specialized knowledge, and are held accountable for the application of that knowledge both ethically and legally. They can be the subject

to state board complaints or lawsuits based on the fact that they have specific obligations to know certain things and to apply that knowledge in practice. Hence, the view that the patient's opinion is equally important as that of the clinician needs to be balanced by the reality that the clinician is held to a higher standard than the patient. In short, clinicians need to be aware that they are expected to have knowledge that is not possessed by the patient, and they need to determine how they can apply

that knowledge in a way that is respectful of the patient's individual liberties, but without equalizing their relationship to the patient in a way that is neither factually true nor legally protected.

In psychiatry, we also run into the special problems of stigma and lack of insight. Because of stigma, many patients have culturally influenced attitudes about certain psychiatric diagnoses or medications. Those attitudes are based on insufficient or incorrect knowledge, and it is not appropriate for the clinician to allow such opinions, based on stigma, to hold equal weight to other opinions that are based on more adequate knowledge. In such settings, patients are free to

"In psychiatry, we run into the special problems of stigma and lack of insight..."

have their own opinions; clinicians are also free, and in fact obligated in some ways, to educate patients as best as possible. In the case of lack of insight, clinicians face the problem that it is the nature of some diseases, such as mania or schizophrenia, that patients will not be aware that they have those illnesses. In such cases, it is not a

matter of education or knowledge, but rather it is part of the disease that patients will have viewpoints that may not be correct. In the United States, the clinician's role is to

provide the best advice and knowledge to patients as possible, and then to leave it to patients to decide what to do, within the constraints of the legal system. When symptoms are very severe, and there are risks of self harm or harm to others which is imminent, legal aspects come into play which require clinicians to intervene, at least short-term, to prevent physical harm either for the patient or for others, if feasible. Outside of that extreme setting though, patients are free to make their own decisions; it is important also to realize that clinicians are not obligated to accept or follow decisions of patients that may be mistaken, either based on stigma or lack of insight.

PL Reflection

...[T]he deepest and most widespread of human weaknesses [is] intellectual cowardice, the craven appetite for mental ease and security, the fear of thinking things out.

*H. L. Mencken, Prejudices
The Student Life*

Current Study of the Month: *Are NSAIDs antidepressants?*

Effect of Anti-inflammatory Treatment on Depression, Depressive Symptoms, and Adverse Effects: A Systematic Review and Meta-analysis of Randomized Clinical Trials. O. Kobler et al, JAMA Psychiatry. 2014;71(12):1381-1391.

A meta-analysis finds efficacy, with effect size similar to SRIs

It is known that depression is associated with a range of inflammatory changes in the body. In general, there is an increase in inflammatory cytokines, of which there are many, such as interleukin-1, interleukin-2, and so on. There are other inflammatory markers that are well-known such as C-reactive protein (CRP), tumor necrosis factor-alpha, and others. These inflammatory markers are elevated during a depressive episode, and return to normal after those episodes. These markers are nonspecific, and also are elevated with anxiety states and general stressful states, such as PTSD. Elevations are seen also during psychotic episodes, and in manic states. Hence, inflammation is not specific to depression, but it is associated with it.

The association of elevated inflammation with depression raises the obvious question whether anti-inflammatory medications can be effective treatments of depression. Physiological studies show that monoamine agonists, such as SRIs, decrease inflammatory cytokine activity in persons with depression. This observation also raises the question whether part of the mechanism of antidepressant benefit with these medications may have to do with their anti-inflammatory effects, as opposed to their monoamine agonistic effects. An obvious way to test this hypothesis would be to see if anti-inflammatory agents which are not monoamine agonists have benefits and depression.

“...inflammation is not specific to depression, but it is associated with it...”

The most potent anti-inflammatory agents available are steroids, and it is notable that they are not seen as being pharmacologically helpful in the treatment of depression. However, they do elevate mood, and cause mania, suggesting that they may have antidepressant effects. Nonetheless, they also can cause depression. The most commonly used class of anti-inflammatory medications for clinical purposes are the nonsteroidal anti-inflammatory agents (NSAIDs). These agents are used for pain most commonly, but also are used for a wide range of symptom effects. Their extensive usage has raised questions regarding their safety, as they are known to have some harmful kidney and cardiac effects in high doses and with long-term usage. Nonetheless, some clinicians and researchers have advocated and/or examined their use for depression.

In this systematic review, a meta-analysis was conducted of all the publications of anti-inflammatory treatments for depressive episodes in major depressive disorder (MDD). 14 randomized clinical trials were conducted in over 6000 patients, with 10 trials examining NSAIDs and 4 trials examining cytokine inhibitors. The overall pooled effect size for reduction of depressive symptoms was a standardized mean difference of -0.34 (95% CIs -0.57, -0.11). This difference was statistically significant.

Although the authors of this systematic review do not make this comparison, it is interesting to note that this overall standardized effect size of -0.34 is

nearly identical to the overall effect size of benefit with serotonin reuptake inhibitors in a meta-analysis of over 40 studies, where the standardized effect size was -0.32. As readers of PL know, the widespread belief that there are massive benefits with monoamine agonists for depression is not supported by the randomized clinical trial literature as reviewed in prior PL issues and on the PL website. The overall effect size described here for SRIs is considered small, and this is also the case with the anti-inflammatory agents. Nonetheless, this overall small benefit is equivalent to what is seen with SRIs, and yet the latter agents are widely used in the general population for the treatment of depression.

The overall result of this meta-analysis provides two suggestions and raises some questions. The first suggestion is that anti-inflammatory mechanisms may be important in improvement of depression, even for SRIs and other monoamine agonists, independent of any effects on serotonin or other monoamines in the brain. The second suggestion is that anti-inflammatory treatments already on the market may be useful to treat depression. One question that is raised is whether better anti-inflammatory agents could be developed for more effective treatment of depression.

It should be kept in mind that the NSAIDs have a wide range of biological effects independent of their anti-inflammatory effects. Hence their benefits for depressive symptoms may not be attributable to their effects on inflammation per se. Further, the studies of some of these anti-inflammatory agents, especially cytokine inhibitors like Interferon-alpha, suggest that benefits seen for depression are present more clearly in persons who have evidence of

“...this overall small benefit is equivalent to what is seen with SRIs...”

inflammatory overactivity, such as elevated CRP. In persons with no evidence of inflammatory elevation, as with CRP levels near zero, there was no notable benefit with Interferon for depression. In short, not all depressive episodes are associated with elevated inflammatory activity, and there may be at least two subtypes of depressive states, one that is inflammatory and another which is not. It may be that anti-inflammatory treatments are effective for the inflammatory kind of depression only. Even if so, this possibility raises the interesting idea that a laboratory test may be available that may predict treatment efficacy, namely CRP or other inflammatory markers predicting benefit with anti-inflammatory treatments.

Returning to the meta-analysis, an interesting results found by the authors was that one agent, celecoxib (Celebrex), seemed to have more consistent benefit than other agents. The authors

suggested that this NSAID in particular may be effective for depression. However it should be noted that there is good evidence that celecoxib is associated with increased cardiac side effects, including increased morbidity and mortality in individuals with underlying cardiovascular disease. Hence caution should be in order with this medication. It may be that the consistent benefits seen with this agent had to do with the fact that it was studied more than other agents for depression. This may not reflect any inherent higher efficacy with celecoxib than with other NSAIDs.

Cardiac and gastrointestinal side effects were not observed overall in the meta-analysis based on studies that were conducted.

As a result of this review, should clinicians begin to prescribe NSAIDs for depressive symptoms or

episodes in their patients, either alone or as adjuncts to monoamine agonists? Based on these data, it would seem that this notion would not be unreasonable, but it would be premature also to make this recommendation in a general way. Rather, it may make sense for clinicians to check CRP levels in patients with depression, and where those levels are elevated, the use of NSAIDs could be considered as adjuncts to standard treatments, until further research is available. At this point, the specific agent used need not be limited, and perhaps standard treatments like ibuprofen would be reasonable. It is worth noting though, that the blood brain barrier does limit

penetration of most NSAIDs, including ibuprofen. Nonetheless, it could be that peripheral effects on inflammatory mechanisms could translate to benefits in the brain. This question is still being examined by researchers on this topic.

The PL Bottom Line

- NSAIDs are effective for depressive states, especially in persons with elevated CRP or other inflammatory markers.
- The efficacy of anti-inflammatory agents is similar in size to that seen with SRIs.

PL Reflection

'Undress...your soul at night,' not by self-examination, but by shedding, as you do your garments, the daily sins whether of omission or of commission, and you will wake a free man, with a new life. To look back, except on rare occasions for stock-taking, is to risk the fate of Lot's wife. Many a man is handicapped in his course by a cursed combination of retrospection and introspection, the mistakes of yesterday paralyzing the efforts of today....To die daily, after the manner of St. Paul, ensures the resurrection of a new man, who makes each day the epitome of a life.

The load of tomorrow, added to that of yesterday, carried today makes the strongest falter. Shut off the future as tightly as the past....The future is today - there is no tomorrow! The day of a man's salvation is now - the life of the present, of today, lived earnestly, intently, without a forward-looking thought, is the only instance of the future. Let the limit of your horizon be a twenty-four-hour circle.... [C]ultivate the habit of a life of day-tight compartments.

William Osler
A Way of Life

Drug of the Month: Citalopram (*and Escitalopram*)

The only truly selective SRI

Citalopram (Celexa) is FDA-indicated for acute depressive episodes in major depressive disorder (MDD). It has registration approval in Europe for panic disorder as well. Its left-enantiomer, escitalopram (Lexapro, Cipralex) is FDA-indicated as well for acute depressive episodes in major depressive disorder (MDD), both in children and adults, and also FDA-indicated for generalized anxiety disorder.

Biological mechanism

This agent is a pure serotonin reuptake inhibitor. It does not have any direct reuptake inhibition of any other monoamines, unlike all other SRIs. activity indirectly, unlike standard SRIs or other antidepressants.

Side effects and dosing

Its dose range is 10-40 mg/d, with 40 mg/d being a typical dose. Its half-life is about 35 hours. Previously it was dosed up to 80 mg/d but those higher doses were found to be associated with cardiac arrhythmia leading to FDA instruction to reduce the dosing limit. Its left-enantiomer escitalopram is more potent, and thus dosed 10-20 mg/d. It has a half-life of greater than 24 hours.

Clinical efficacy

Citalopram was the first SRI, preceding Prozac (fluoxetine), as it was introduced in Europe in 1988. However, it was preceded in the US by

fluoxetine and multiple other agents until it received its FDA approval finally in 1998. It has not received sufficient recognition for its more selective SRI effects compared to other agents (fluoxetine, for instance, is noradrenergic). In recent years, its risk of cardiac arrhythmia at higher doses has limited its use as well. At very low doses, though it has pure anxiolytic effects that can be useful. In standard doses, it has benefit for pure depressive states. Like all SRIs, it is ineffective in bipolar depression, proven in a recent randomized clinical trial.

Fast Facts: Citalopram

Typical dose: 10-30 mg/d

Biological mechanism: Serotonin reuptake inhibition

Typical side effects: sexual dysfunction, withdrawal syndrome

Medically important side effects: none known

Clinically proven efficacy: FDA indication for acute depressive episodes in unipolar depression

It is not more effective than citalopram overall though.

The PL Bottom Line

- Citalopram is the only truly selective SRI. It has no other monoamine effects.
- Its left-enantiomer escitalopram is more potent, so that the same effect is achieved with lower dose, but it is not more effective.
- Above 40 mg/d, it causes cardiac arrhythmias.
- It is effective for anxiety at low doses, and for pure depressive states at standard doses.
- It is not effective for bipolar depression.

Curbside Consult

Questions and cases from you

Question: I run an acute inpatient adult unit at a city hospital. I have noticed a subset of bipolar patients that are seemingly impervious to medications. Some of them use synthetic cannabinoids, but others do not use any substances. They are given copious amounts of meds [IM and/or PO] which has a minimal effect for a short duration. When given medicine they fight it and when agitated tend to be provocative and violent. They often end up in restraints. We even have had to send some to forensic units. Is there any medication regimen that you have found to be effective for this type of patient? We have used large doses of Haloperidol, Prolixin (fluphenazine), Ativan, Thorazine (chlorpromazine), Geodon (ziprasidone) IM, as many of the patients refuse to take meds orally. If they take oral medications, we add lithium or valproic acid.

PL: This is a very difficult situation obviously. The medications given above tend to be the ones used in emergency room settings in the last few decades. A classic combination is haloperidol 5-10 mg plus Ativan 1-2 mg IM. Sometimes Benadryl (diphenhydramine) 50-100 mg is added to the above combination. Haloperidol could be replaced with thorazine or olanzapine in this mix. Prolixin and ziprasidone (Geodon) tend to be less effective for acute control of psychotic agitation,

in the clinical experience of some of the PL board. High dose valproate can be used orally, such as valproate loading with 1000-2000 mg (20-30 mg/kg is sometimes used as a guideline). But oral valproate is probably less effective than dopamine blockers. Valproate could be combined with a dopamine blocker, such as with haloperidol or thorazine or olanzapine. Lithium is not effective acutely enough to be helpful in such settings. Generally speaking sedating agents like olanzapine and chlorpromazine are more effective for control of agitated violence than non-sedating agents like risperidone or ziprasidone. Quetiapine is sedating but has little anti-dopamine potency so it is not helpful.

As you noted, sometimes concomitant substances, like amphetamines, can be a factor in such apparent non-response to anti-agitation treatments. But sometimes there are no substances, and the reason for such non-response is unclear. PL does not have special insights into other possible etiologies for these difficult situations. In the hospital, as opposed to the emergency room, intravenous haloperidol at high doses, up to 50 mg/d or more, has been advocated and may be effective, with EKG monitoring for cardiac arrhythmia.

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THE PSYCHIATRY LETTER

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Truths of psychopharmacology

In the last issue, PL published a special article on Ten Fallacies of Psychopharmacology. These were common beliefs that rested on some false assumptions. In this issue of PL, we will follow up with Ten Truths of Psychopharmacology. These are approaches that are established on more solid ground scientifically and humanistically.

The Article of the Month examines a recent study of long-term intellectual/cognitive effects of exposure to antidepressants during pregnancy. A link to some long-term harm is found, although the article's authors downplay the risks. The Drug of the Month is buspirone, a drug in search of an indication. The curbside consult question addresses the concept of nocebo effects, and psychological aspects to side effects.

We are pleased to inform PL readers that now all CME questions for all months updated are available on the PL website. For those of you who had been unable to access CME questions from April 2017 onward, please go to the website where you will now be able to complete questions from April 2017 onward and thus receive CME credits for those issues. We appreciate your patience and are happy that we are now up to date with CME accreditation for all issues.

As this year comes to an end, we'd like to thank our loyal readers for their continued support, and look forward to renewal of your support and engagement with PL in the coming year.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Ten Truths of Psychopharmacology

Guidance for the perplexed

In the preceding issue of PL, Ten Fallacies of Psychopharmacology were described. This issue follows with Ten Truths.

1. Your treatment is as good as your diagnosis.

If DSM is wrong, then treatment fails.

This concept flows out of the general Hippocratic perspective that we should treat diseases not symptoms. So if the disease is unknown or not diagnosed, treatment of symptoms will only have partial benefit at best, often counteracted by many side effects. One of the problems in contemporary psychiatry is that it doesn't pay much attention to diagnosis; many clinicians just treat symptoms. Another way it works is that diagnoses are made using the DSM system, which is mostly invalid, as discussed in prior PL issues. In that case, if the diagnosis is invalid, the treatment will be ineffective. This axiom was told to the PL editor by Dr. Edwin Cassem, former chairman of the department of psychiatry at Massachusetts General Hospital, and also a Jesuit priest.

2. Treat diseases, not symptoms.

Symptomatic treatment is modestly helpful, at best.

As stated above, the Hippocratic principle is that we should treat diseases, not their symptoms. William Osler stated this perspective most clearly at the turn of the 20th century. When a disease is treatable, then effective treatments will manage all symptoms, and even notable side effects will be outweighed by benefits for the overall disease.

...The default position of the clinician should be: Do not prescribe..."

When a disease is unknown, untreatable, or invalidly defined, then treatment of its symptoms may occur to a partial or modest extent, but will never be complete. Further, since all drugs have side effects, as in the following principle below, those side effects often outweigh partial or modest benefits. As an example, Tylenol will never completely get rid of fever, but penicillin will. This is the case, even though penicillin has no direct anti-fever effect, and Tylenol does.

Similarly, in psychiatry, so-called antidepressants will never completely rid patients of depressive symptoms, but a medication to treat the underlying disease that causes depressive episodes, such as lithium, can and will.

3. All drugs are guilty until proven innocent.

The default position of the clinician should be: Do not prescribe; you must have proven benefits that exceed harms to prescribe.

This is the principle that relates to the Hippocratic tradition which the PL editor has called Holmes's rule, given its historical basis in the teachings of Oliver Wendell Holmes Sr. In this perspective, all medications have side effects, and therefore they should not be used because side effects are always harmful. However, if medications are proven effective, and a disease is improved or cured, then those medications can be used since those benefits will outweigh side effects in most cases. This approach relates to the classic risk-benefit analysis of medical treatment. Clinicians know that all treatment involves weighing of risks and benefits.

However, it is quite important to be clear and explicit about whether one starts on the risk side of the ledger, or the benefit side. Many clinicians start on the risk side: they first ask themselves whether a certain medication is harmful or has many side effects. Or when considering a class of medications, they asked themselves which are the safest ones to use, or which are the ones with the least side effects. Then they begin to assess potential benefits among those medications that they deem safest or most benign. Often, the search for efficacy is quite limited or even ignored, and medications are simply used because they are apparently benign. It is important to always remember that no medication is truly benign. All medications have harms, and therefore this approach of using medications which might be ineffective based on the belief that they are safe is itself a dangerous approach. It is well established that, over time, apparently safe medications turn out to have been harmful. The medical profession has had this experience with hormone replacement therapy recently, and with other medications in the past such as aspirin and children or diethylstilbestrol during pregnancy.

The alternative approach is to start not with risks but with benefits. Before thinking about which medications to use, clinicians should focus first on what medications are proven effective, or are deemed to be most effective. Then with that winnowed list, clinicians can assess which ones are safest or have the fewest side effects. Start with efficacy, then assess side effects, not vice versa. This is a truth, taught by Holmes in the 19th century, still as true now as ever.

“...the judgment that a medication is harmful or toxic should never be made in isolation....”

4. All drugs are toxic; only the dosing and indication makes them therapeutic.

Don't judge on abstract risk concepts.

This is another classic teaching of William Osler. It builds on the last few truths above. All medications have side effects and harms, and thus in a sense they are all toxic. However, side effects and toxicities vary with dose. Many times a medication can be quite harmful at high doses, and quite safe at low doses. So dosing is an important aspect of making judgments about the risks and harms of medications. Indication for treatment relates to efficacy and benefits of medications. If a medication is proven effective, as discussed above, for a certain diagnosis or disease or indication, then it can be used even if it has many side effects or toxicities. So the judgment that a medication is harmful or toxic should never be made in isolation. For instance, one often hears that lithium is a “strong” medication, or that it is toxic. But lithium is not toxic at all at very low doses, and its side effects and harms are greatly outweighed by its many benefits for bipolar illness, unipolar depression, and possibly other conditions like dementia.

5. Always have an exit strategy.

Do not prescribe acutely, and assume indefinite treatment. Have an endpoint in mind, or a strong scientific rationale for long-term use.

When patients get better with medications for current symptoms, clinicians and patients should not conclude that those medications should be continued indefinitely. This is not the case in general medicine. One does not go to one's general practitioner with pain, then receives

medication which improves the pain, and then decides to stay on that medication for the next few decades of one's life. It is the case in psychiatry that patients routinely come to clinicians with symptoms of anxiety or depression, for instance, receive symptomatic treatments for anxiety or depression, and then improve over the course of a few weeks to a few months. Often those medications tend to be continued indefinitely, not infrequently for decades. There is no medical or biological rationale for this approach. It can make sense in some cases, where there are recurrent mood episodes, and some medications are proven to prevent those mood episodes. Those medications often are the so-called mood stabilizers, which have less acute benefit for the mood symptoms than so-called antidepressants.

In other words, treating patients in some ways is similar to deciding to go to war. A general should have an exit strategy. Before prescribing the first medication, one should have in mind how long you would continue that medication if it works. Clinicians should tell patients how long that duration of treatment would be, as opposed to waiting to address that decision later. One problem with waiting is that patients are unwilling to stop medications after they have improved. They have a fear that their symptoms or illness will return, a fear which is not medically or biologically sound if the analogy with Tylenol for fever is correct. Patients should be told ahead of time that they will need to come off their medications in three months, six months, or one year, however long is judged by the clinician. Otherwise clinicians will have a hard time convincing many patients to come off medications later.

"A general should have an exit strategy..."

Another reason to discuss how long medication treatment will continue at the beginning is that it may enhance patient compliance among those who are skeptical or nervous about taking medications. If they are told that medication treatment will continue for no more than one year, for instance, they may be more willing to begin medication trials and stick with them for that timeframe. This is important because research shows that by six months of treatment with antidepressants, the vast majority of patients have stopped taking their medications. Another aspect that is important to the exit strategy approach is the problem of long-term withdrawal syndromes. It is now clear that SRIs have very serious withdrawal syndromes after one year of treatment. In the long run, those withdrawal syndromes can cause much more harm than any benefits that were achieved symptomatically in the shorter-term. It is important to avoid such withdrawal syndromes, unless absolutely necessary, and an approach of emphasizing treatment for one year or less with SRIs would make sense in many cases.

6. Most current psychotropic drugs have symptomatic benefits, but are not disease-modifying.

The clearest exception is lithium.

Many clinicians who have come to the mental health professions in the last four decades entered a field which widely accepted the efficacy of most medications. It is important to realize that when the modern classes of psychotropic medications came into existence in the 1950s and 60s, a major factor in the excitement around these agents was the belief that they were not purely symptomatic.

For over a century beforehand, physicians and clinicians had access to many medications with symptomatic benefits, such as sedating agents or tranquilizers. It was believed that the antidepressants were special because they actually removed the whole clinical condition of depression, and not simply because they improved some of its symptoms. It was believed that antipsychotics were special because they remove the whole clinical syndrome of a psychotic episode, taking it away completely, and not just because antipsychotics had some symptom benefits for delusions or hallucinations. It was held that anti-anxiety agents could completely remove anxiety conditions like obsessions. In other words, by the 1980s, it was believed, implicitly or explicitly, that psychotropic medications cured the overall clinical syndromes of depression, mania, psychosis, and anxiety states. In short, it was held that they modified diseases causing those symptoms, and were not purely symptomatic. They were held to be more like antibiotics than Tylenol. Almost half a century later, we have enough clinical and scientific experience to say that these beliefs do not appear to have been confirmed. The majority of psychotropic drugs are symptomatic in their effects, and do not alter or improve the underlying disease process that might be causing those symptoms. This has been proven to be the case with antipsychotics in schizophrenia, which do not improve the course of the illness. It appears to be the case of antidepressants in unipolar depression, where long-term maintenance efficacy is questionable, as discussed in a prior PL issues. It appears to be the case with most anxiety states, where symptom benefits with SRIs are seen but long-term removal of anxiety

"since the 1970s, the wide variety of new psychotropic medications has not produced a single medication that is more effective than medications in prior generations....."

symptoms is less apparent. An exception to the prior statement may involve SRI efficacy in OCD. Another exception to this overall rule is that mood stabilizers like lithium do alter the course of bipolar illness and unipolar depression, and prevent mood episodes in a way that often is curative.

7. Older drugs are more effective than newer drugs.

Newer doesn't mean better.

It is the case that the most effective medications in psychiatry are its oldest medications. The most effective treatment for depression is ECT, which was discovered in the 1930s. The most effective medication class for depression is the monoamine oxidase inhibitor class, which was developed and

discovered in the 1950s. The next oldest class of antidepressants, the tricyclic antidepressants, is more effective than the newest class of antidepressants, the SRIs. The most effective treatment for mania is achieved by neuroleptic medications, without any increased benefit with new agents versus older ones. The most effective treatment for bipolar illness overall is still lithium, which is the oldest agent. The most effective treatment for schizophrenia is clozapine, which was developed in the 1960s and 1970s. In short, since the 1970s, the wide variety of new psychotropic medications has not produced a single medication that is more effective than medications in prior generations.

8. Newer drugs are more tolerable than older drugs.

Newer tends to mean safer.

The flipside of the prior truth is that the newer generation of medications in the past few decades has been developed to have fewer side effects than older medications. This is the case with second-generation antipsychotics versus older antipsychotics, and with SRIs versus tricyclic antidepressants. It also is the case with some anticonvulsants compared to lithium. However, it should be clear that these medications have become popular and widespread in use primarily because of their increased tolerability and fewer side effects, not because they are more effective than older medications. In many cases, they are less effective than older medications, but still effective enough to be used clinically, and with their lower side effect burden, they are more feasible to use. The point is not that clinicians and patients should never use older drugs, nor that they should be satisfied with newer drugs, but merely that they should realize that any benefit with the newer drugs that has been achieved in the last few decades is really related primarily to tolerability rather than efficacy.

“...poor treatment results would follow if the current diagnostic system is simply wrong...”

9. Treatment “resistance” usually reflects either misdiagnosis or an invalid diagnosis.

Better diagnoses, not just better drugs, should be a goal.

The current attention to treatment resistance in psychiatry is a reflection of acceptance of the current diagnostic system as valid, while looking for better treatments for those diagnoses. If the current DSM diagnostic system is only partially valid, then insufficient benefit with medications could reflect the fact that the clinical phenotypes being treated are not real enough to produce notable benefits with treatments that affect biological mechanisms. In addition, a different issue may be that the diagnosis is simply wrong,

and that other valid diagnoses have been missed. For instance, bipolar depression is misdiagnosed as unipolar depression, followed by use of antidepressants which are ineffective in the underlying bipolar depression, unbeknownst to the patient or clinician. This kind of misdiagnosis is still common and quite problematic. However, a larger problem is that even if clinicians do apply diagnostic criteria correctly, and use current knowledge as they have been taught, poor treatment results would follow if the current diagnostic system is simply wrong.

10. Course, not symptoms, reveals the diagnosis.

Course of illness trumps symptoms.

This is an axiom of psychiatric diagnosis based on the tradition of Kraepelin. The DSM system takes an opposite approach, using symptoms to make diagnoses in almost all cases, without reference to course of illness. Since many

different illnesses can have many different symptoms, often overlapping, this symptomatic approach leads to diagnostic complexity that is both unnecessary and harmful. Many illnesses reveal themselves over time by their course, even if they overlap in symptoms to a great extent. This was the classic insight of Kraepelin into the differentiation of schizophrenia from manic-depressive illness. It holds just as well for differentiating mood conditions from anxiety conditions, or from personality states, or from cognitive conditions. In general, clinicians focus too much on current symptoms, as DSM teaches them, and do not carefully assess prior long-term course of illness in making a diagnosis, nor do they carefully assess prospective long-term course

of illness in either confirming or changing their initial diagnostic impressions. Pay attention to the course of illness: it is equivalent to pathology for psychiatry. It tells you which symptoms reflect which diseases, as opposed to assuming that each symptom is its own disease.

Psychopathology

Otto Dorr

Excerpt from "Dialectical thinking in psychopathology," 2013:

[In] the manic-depressive dyad...the polar and dialectical character is evident: mania is the reverse of depression and vice versa. But at the same time each emphatically needs one another so that in some way the one is contained in the other and vice versa. How frequently we perceive,

behind the joy and hyperactivity of the manic, infinite sorrow and, inversely, behind the sorrow and inactivity of the depressive patient, feelings of envy and aggressiveness which are almost impossible to emanate from his weakened and harmless appearance. Additionally, what draws one's attention is the fact that situations triggering the two illnesses would seem to be inclined to produce the opposite effect; they are marked by an inverse sign: what would result in joy for any normal person (a move to a better house, the happy marriage of a daughter, the birth of a child who is wanted, promotion at work, etc.) may trigger a depression, while those precipitating mania generally represent intolerable setbacks (the death of a beloved person, financial bankruptcy, the diagnosis of a serious mortal illness, situations of great pressure, etc.). In other words, the manic develops his mania against depression, while the depressive patient develops his depression against the mania.

PL Reflection

How hard was the battle in this century against the entrenched and stubborn foe!
Listen to the eloquent pleadings of Stokes, pleading as did Sydenham, against authority and angst the bleedings, purgings, and sweating of fifty years ago.
'Though the hair be grey and his authority high, he is but a child in knowledge and his reputation an error. On a level with a child so far as correct appreciation of the great truths of medicine is concerned, he is very different in other respects, his powers of doing mischief are greater; he is far more dangerous. Oh that men would stoop to learn, or at least cease to destroy!'

William Osler

Medicine in the Nineteenth Century, 1901

Current Study of the Month: *Are antidepressants during pregnancy harmful long-term?*

Association of antidepressant medication use during pregnancy with intellectual disability in offspring.
A. Viktorin et al, JAMA Psychiatry. 2017;74(10):981-1084.

A national Swedish study finds increased long-term cognitive harm

This article examines the question of whether antidepressants are associated with intellectual disability long-term after exposure during pregnancy. Usually, questions about whether antidepressants are safe in pregnancy involve immediate birth defects, meaning that delivery. Typically clinicians are not informed or know about later long-term effects of such exposure. Researchers have the problem of the complexities of such long-term outcome analyses as well. In this paper, the Swedish national database of medical information was used to provide a glimpse that such possible outcomes. First, all women who are pregnant were examined for a two-year period in 2006 to 2007, by their medical records. About 5000 women who were pregnant during that timeframe took SRI antidepressants.

They were compared to over 170,000 pregnant women in the same timeframe who did not take any antidepressants. Then medical records and their children followed for about seven years. The outcome of intellectual disability was based on diagnoses in the medical record to that effect. In the seven-year timeframe it was observed that intellectual disability was about twice as common in women who had taken antidepressants during pregnancy compared to children of unexposed control women. The frequency of that outcome of course was low, consisting of 0.9% of the exposed women, compared to 0.5% of the unexposed women. The authors then conducted statistical analyses to adjust for potential confounding factors, and the original increased risk of 1.974 relative risk decreased to 1.64, but the confidence intervals cross the null value one. The 95%

confidence intervals were 0.952-2.83 since the number one reflects the null value, crossing that number implies that one does not have 95% or higher sure to that the results did not happen by chance. In other words the results were not statistically significant. The authors therefore concluded that the study could not be used to demonstrate evidence of an association between intellectual disability and maternal antidepressant medication use during pregnancy.

However, the claim that the study found no such association is something that PL would not support, given that an increased association was still found. In other words the relative risk of 1.64 implies a 64% increased risk. The fact that this increased risk is not statistically significant does not mean that it did not happen. It only means that one cannot be confident that it did not happen by chance with 95% or more certainty. However one can be confident with about 90% certainty. Since this issue is very difficult to study, these important data should not be dismissed simply because one does not have 95% certainty. 90% certainty is better than zero. Thus, if one were to ask what is the best evidence we possess regarding the long-term effects of SRI antidepressants on intellectual impairment based on exposure during pregnancy, this study would not be fairly interpreted as saying there are no such facts. Rather this study should be interpreted as saying that there is about 90% certainty that such intellectual disability effects occur.

Clinical implications

How should PL readers interpret this study's results in terms of how it applies to their clinical practice?

PL doesn't mean to imply that antidepressants are "unsafe" in pregnancy, in some generic way. As discussed in the Third Truth of Psychopharmacology (All drugs are guilty until proven innocent), here is another example of finding out about harms in the long-term, after many years of believing in no or little risk. The implication here is that clinicians should not use antidepressants routinely during pregnancy, with the belief that there are no harms at all. An all-or-nothing reaction is the wrong one. The nuanced weighing of risks and benefits is needed, as always, but this study provides information on risks that was not known before, i.e., that there are long-term risks of cognitive effects in children exposed

to antidepressants during pregnancy. Mothers should be informed of this potential risk, unlike now where they are not informed. The fact that the authors of the study, who are prominent Swedish researchers, downplay the risks is a reflection of the profession's tendency to avoid blaming medications. The data stand on their own, with the excuse of statistical significance being a scientifically mistaken way to try to minimize the results. If the results are accepted as they stand, showing more evidence of risk than not, then those results should be incorporated into the risk-benefit judgments of clinicians and patients.

The PL Bottom Line

- Exposure to antidepressants during pregnancy increase the risk of long-term intellectual disability about 5 years later.

PL Reflection

A science only lays down lines within which the rules of art must fall, law which the follower of the art must not transgress; but what particular thing he shall positively do within those lines is left exclusively to his own genius. One genius will do his work well and succeed in one way, whilst another succeeds as well quite differently; yet neither will transgress the lines.

William James

Talks to Teachers

Drug of the Month: Buspirone (*Buspar*)

A drug in search of an indication

Buspirone (*Buspar*) is FDA-indicated for “for the management of anxiety disorders or the short-term relief of the symptoms of anxiety”. Its benefits, to the extent they exist, have been shown mainly in patients given the diagnostic criteria for generalized anxiety disorder (GAD).

Biological mechanism

This agent has mild agonist effects on the 5HT_{1A} serotonin receptor. It does not have any direct reuptake inhibition of serotonin or other monoamines, unlike all other SSRIs.

Side effects and dosing

Its dose range is 15–45 mg/d, with 60 mg/d being a maximal dose. Its half-life is only about 2–3 hours. Since it is not effective in immediate or pre usage, it needs to be dosed twice or thrice daily for long-term treatment. It has minimal side effects of the typical serotonergic variety, such as nausea and diarrhea. It doesn't seem to have appreciable sexual dysfunction by itself, probably because it is so mild in its serotonergic effects. For similar reasons, it has not been reported to have notable serotonin withdrawal syndrome with long-term treatment.

Clinical efficacy

Buspirone is not effective for acute treatment of panic attacks, or OCD, or other conditions, where it has been found ineffective or little effective. It has been found to have some benefit

as an adjunct to standard monoamine agonists (antidepressants) in MDD, as in the STAR*D study, where it was as efficacious as other commonly used adjuncts, such as bupropion.

Given its limited benefits, and limited harms, this agent has been said to be a drug looking for an indication. After about two decades, it appears that no meaningful indication has been found.

Fast Facts: Buspirone

Typical dose: 15–45 mg/d

Biological mechanism: Serotonin receptor agonism

Typical side effects: nausea

Medically important side effects: none known

Clinically proven efficacy: FDA indication for anxiety symptoms

The PL Bottom Line

- Buspirone is a mild serotonergic agent.
- It has mild anxiolytic effects long-term, but little effect immediately.
- It has mild adjunctive depressive symptom benefits.

PL Reflection

It would be terrible, Socrates used to think, for knowledge to be in someone, but mastered by something else, and dragged around like a slave.

Aristotle
Nichomachean Ethics

Curbside Consult

Questions and cases from you

Question: Please expound on the “nocebo” effect and particularly study participants that have side effect when taking placebo. Is there a delineation of the usual profile of those that are more prone to complaint of side effects, and are there strategies that can help to decrease the frequencies of pseudo-side effects?

A second and related issue is to ask you to comment on what we read about side effects in the FDA package insert or Physician's Desk Reference (PDR). Some of us that have to be in court every week, dealing with a public defender that pulls out information from the PDR, as part of an attempt to convince the judge that a patient refusing medications should be discharged from the hospital, even though he might have "voices" telling him to hurt people, and even though he was brought to the emergency room by the police after he assaulted a person in a shelter.

PL: In some senses, the treatment-intolerant patient is more difficult to treat than the true treatment-refractory patient. In the case of treatment intolerance, two major factors are likely to be relevant. One factor is a possible nocebo effect.

“Nocebo” (Latin for “I shall harm”) was a term coined in 1961, to describe how there are psychological reactions to taking pills. The nocebo effect is basically a reverse placebo effect. In other words, just as the placebo effect can make one feel better due to one’s psychological expectations, the nocebo effect can make one feel worse due to one’s psychological expectations.

In research studies, investigators often conduct what is called a “single-blind placebo lead-in.” In these cases, the investigators know that the patient is getting placebo, but the patient does not know, and this state is maintained for the first week of the study, before the patient is then treated according to the research protocol (e.g., double-blind treatment with either a drug or placebo). Not infrequently, one observes the nocebo effect in the one-week single-blind lead-in, with patients reporting numerous side effects, such as headache, tiredness, nausea, muscle aches, and chest pain. These patients are then dropped from the study as a means of reducing the placebo effect and thus being able to detect true pharmacological benefit with drugs more effectively. In real-life practice, one can only imagine how often this scenario occurs. The nocebo effect is sometimes at play in patients who are quite anxious about taking medications. Perhaps they delayed seeing a psychiatrist for a long time, or they were pushed to come to the appointment by family or friends, but deep down they do not want to be treated with medications. Even if they take medications, their underlying psychological mindset can be so negatively predisposed to medications that numerous side effects are almost guaranteed.

Another factor that may promote the nocebo effect is excessive interest in the side effects of medications. Pharmacists often review medication side effects in some detail with patients, which is usually helpful, but can sometimes promote nocebo side effects. Access to the internet can lead to unreliable or exaggerated information about medication side effect risks and access to the FDA package insert or Physicians Desk Reference (PDR) listing usually heightens fears about taking medications. In general, access to more information rather than

less is beneficial to medical care. If patients are more knowledgeable, treatment is usually more successful. However, in the case of individuals predisposed to the nocebo effect, a little knowledge can be quite dangerous.

In cases where clinicians are concerned about a negative mindset on the part of the patient, they can emphasize a few points. First, they can ask patients to let them know if they have any concerns about taking the medications based on their discussions with their pharmacist. Second, clinicians can direct patients toward reliable internet sites and warn them about possible misinformation in other venues.

Research studies have demonstrated that exposure to too much information regarding side effects can increase the occurrence of side effects.

Third, clinicians should discuss the FDA package insert side effect listing with concerned patients and emphasize that almost any medication has a long list of side effects in the package insert

because it is based on clinical trials, where researchers were obligated by the FDA to include any side effect noted. It is not until clinical experience develops that clinicians can understand the most common and severe side effects. Further, it is important to note that the package insert is not intended to be used by patients, or even as a primary source for doctors beyond the initial introductory period of a medication's use. Rather, the package insert is meant to provide the guidelines within which pharmaceutical companies are allowed to market their drugs. It limits what those companies can say legally.

In short, the FDA package insert of a drug is aimed mainly at pharmaceutical companies for marketing purposes, not at clinicians for prescribing purposes.

This kind of speech, given before the first prescription is written, may help reduce the nocebo effect.

PL Reflection

When a patient says something, you don't always have to give your opinion. It is a long struggle to realize that they come for a search for understanding, not for your opinions.

Jonathan Kolb MD
The Student Life

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THE PSYCHIATRY LETTER

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The classic disease of psychiatry

This issue starts the fourth year of the exist of PL, a timeline that is long enough to say it is no longer new, but not long enough to call it old. We hope readers continue to enjoy the newsletter each month, and we ask that you continue to tell your colleagues about it, and to spread the word, so that there is more attention to the scientific-humanistic approach to psychiatry described here.

A change in the basic format of PL occurs with this fourth year of publication. After 36 issues, PL has described each of the main drugs or drug classes in psychiatry in the Drug of the Month. Future issues will not have a monthly drug, since few remain that have not been described. Instead, new drugs, as they arise, will be discussed in occasional columns.

The Special Article is on the classic disease of psychiatry: schizophrenia, revisited in the light of the most recent treatment and neuroimaging studies, while rethinking its nature based on historical sources.

The Study of the Month examines an analysis of cannabis use and finds that the claim/belief that medical marijuana will decrease later prescription opiate abuse is unfounded.

The case consultation is about whether and how mood stabilizers should be used long-term in type II bipolar illness.

As always, CME credits are available for this and all prior PL issues online.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Schizophrenia revisited

Understanding a classic disease

Diagnostic considerations

The original phrase was “dementia praecox,” by which Emil Kraepelin meant a range of psychotic symptoms that began in adolescence (“praecox”), and remained present chronically throughout life, with gradual worsening of function (“dementia”). Before Kraepelin, different psychotic states were identified (hebephrenia, catatonia, paranoia), which he pulled together in the single dementia praecox diagnosis. Kraepelin’s view was that the specific symptoms variations didn’t matter; they all started in adolescence, were chronic, and worsened in function; they were the same illness.

Kraepelin put forward these views in the 1890s. Within two decades, though widely accepted, they were transformed by the Swiss psychiatrist Eugen Bleuler, a prominent leader in academic psychiatry. Bleuler (the mentor of Carl Jung) was influenced by Freud, and applied Freudian ideas to psychosis. Bleuler felt that symptom differences in Kraepelin’s dementia praecox mattered, specifically that the flatness of affect of these patients was central to the illness. They had a splitting (“schizo”) of their affect from the thoughts in their head (“phrenia”), hence the new diagnostic term. These psychotic symptoms were auditory, and tended to be in the third person, with a running commentary on the patient’s behavior. Bleuler’s schizophrenia was much broader than Kraepelin’s dementia praecox. No longer did patients need to begin with the illness in adolescence; it could be diagnosed in a middle-

aged person for the first time. Nor need it be chronic; the symptoms could go away and come

back later. Nor was there a decline in function; some patients recovered completely and permanently.

For most of the 20th century, Bleuler’s concept held sway, until the 1970s, when researchers showed that Bleuler’s definition, then the status quo in American psychiatry, led to the diagnosis of schizophrenia in manic states that might only last a few days, preceded and followed by complete normality. Similarly psychotic symptoms that occurred only during depressive episodes were mislabeled schizophrenia. Since new treatments then were available, the neuroleptics, but they had serious long-term risks, like tardive dyskinesia, it was important to know who had long-term need for treatment for psychosis, and who did not. The classic US-UK

diagnostic project identified the overly broad sweep of Bleulerian schizophrenia and led to the return to a “neo-

Kraepelinian” definition in the West, codified in 1980 in DSM-III. Again, there was a requirement for chronic decline in function, which ruled out brief psychotic symptoms during affective episodes. This return to a Kraepelinian view did not lead to a change in diagnostic label, though. Bleuler’s “schizophrenia” phrase continues to be used, even though it is meant these days to reflect something closer to Kraepelin’s dementia praecox.

DSM-III and IV maintained some of the non-Kraepelinian aspects of diagnosis by listing the symptom variations as subtypes: paranoid,

catatonic, undifferentiated, simple, and residual. DSM-5 has dispensed with these subtypes, to the consternation of some experts, especially in Europe.

A particular concern that has been raised is that the diagnosis of catatonia is now absent from the DSM system, since it is no longer an aspect of schizophrenia. Further, many experts hold that catatonia is not, and never was, simply a kind of schizophrenia.

A final diagnostic consideration of importance is the concept of schizoaffective illness. In clinical practice in many settings in the US, this diagnosis is made more commonly than schizophrenia proper.

Schizoaffective illness

Soon after Kraepelin put forward his diagnostic concepts of dementia praecox (DP) and manic-depressive illness (MDI), he was opposed by those who felt the distinction was wrong. Some held that the two major diagnoses were too broad: many different diseases existed within each of the larger diagnoses (e.g., bipolar and unipolar illness instead of MDI; catatonia and paranoia instead of schizophrenia). Others held that the two major diagnoses were too narrow: only one unitary psychosis existed, subsuming both DP and MDI.

This latter unitary psychosis view was supported by family history and course of illness studies, but the strongest support was symptomatic: by the 1930s, clinicians identified patients who had symptoms of both schizophrenia and affective illness, hence the “schizoaffective” label. The

“...the inherent chronicity of schizophrenia confers treatment resistance to all treatments...”

term was codified in DSM-III in 1980, and has changed little since then.

Yet research on the schizoaffective picture suggests that one thing is clear: it is not a valid separate diagnosis. Hence if the label is used, it should be understood as a clinical picture, not a disease. Patients present with these symptoms, but this presentation is not its own separate disease (see PL September 2015). This conclusion would have important implications for treatment and for interpretations on prognosis.

Treatment

Schizophrenia has been the most studied psychiatric illness. For over a century, a great deal of attention has been given to research on the biology and treatment of this condition. Despite

this extensive research database, it is true unfortunately that most treatments for schizophrenia are symptomatic and modest in effect. They are important nonetheless, especially during but you exacerbations of psychosis, but they have not had extensive benefit in modifying the disease or altering the course of the illness, unlike the larger benefits seen with lithium and mood stabilizers in bipolar illness. The extent to which the dopamine blockers are helpful and schizophrenia, and not, requires careful discussion.

It is important to begin by noting that the inherent chronicity of schizophrenia confers treatment resistance to all treatments. It should not come as a surprise that the dopamine blockers are not very effective in the treatment of schizophrenia, since no treatments are very effective in this chronic condition. As with

Alzheimer's dementia, the failure of treatments is not a reflection of the weakness of those treatments, but rather of the chronicity of the disease. This reality is reflected in the standards used by researchers and the FDA in the determining that treatment benefit is seen with medications for schizophrenia. Treatment response in antipsychotic trials of schizophrenia and schizoaffective illness is defined by a 20% reduction in psychosis symptom scales, such as the Positive and Negative Symptom Scale (PANSS). This 20% reduction is a much lower threshold than the 50%

reduction required in mood rating scales for studies of medications in mood conditions. This lower standard is a reflection of the inherent chronicity and treatment refractoriness of schizophrenia. Hence, it should be kept in mind that when studies report treatment response in schizophrenia, they are referring to a mild improvement in symptoms.

With this qualification, there are many studies with dozens of dopamine blockers, conducted over decades, which demonstrate that these agents are more effective than placebo in treating acute psychotic symptoms in schizophrenia. These benefits are more robust for "positive" symptoms of delusions and hallucinations than for "negative" symptoms of flatness of affect or apathy or for cognitive impairment symptoms. Yet the improvement seen in delusions and hallucinations, especially during acute hospitalizations, has been dramatic and clear in the past few decades.

The most important question in relation to efficacy is whether dopamine blockers are effective for anything beyond acute reduction of positive psychotic exacerbations. In other words,

"... do they alter the course of the illness or confer any other longer-term benefit?..."

do they alter the course of the illness or confer any other longer-term benefit?

100 years of schizophrenia

A central resource to answer this question is a large meta-analysis conducted by James Hegarty and colleagues about two decades ago. This classic study was titled "100 years of schizophrenia," because when it was published it sought to examine a century of research on the outcome of this condition ever since its initial description by Kraepelin in the 1890s. In an effort that required digging up studies and old journals in multiple languages, 320 studies from 1895 to 1992, with 51,800 subjects, were included in the project, which was one of the first meta-analyses in psychiatry. The main question was whether schizophrenia improved or not. This question involves both the effect of natural history and of treatments. Before the 1960s, dopamine blockers were not available to be used in the treatment of schizophrenia. Hence, the meta-analysis was able to compare outcomes in the pre-treatment era versus the treatment era. For much of the 20th century, there was great debate about whether schizophrenia was incurable or not. Kraepelin's view was that schizophrenia was chronic and deteriorating, and thus did not improve with treatment. It was analogous to the dementia that his research group discovered in older persons, named after his colleague Alois Alzheimer. In contrast, other researchers reported in the mid-20th century that many patients with schizophrenia appeared to improve, especially after receiving either psychoanalytic psychotherapy or other kinds of social interventions. After the introduction of the dopamine blockers in the 1950s and 1960s, some

researchers also reported massive benefit with those agents. This meta-analysis was complex because it involved hundreds of studies in many countries using different criteria both for the definition of the diagnosis of schizophrenia and for the definition of improvement in outcome. For the purposes of the study, good outcomes were defined variably as examined in different ways in different studies. For instance some studies considered a good outcome to be discharged from hospitalization, while other studies in another setting defined good outcome as improved function or being able to live independently. These varying definitions of outcome should be kept in mind, since in no case was a good outcome defined as complete remission of all symptoms and recovery of completely normal function. Nonetheless, with the relatively low standards of good outcomes defined, the meta-analysis found that overall about 40% of patients with schizophrenia appeared to improve one followed for about five years. In other words, even with a low standard for the definition of improvement, the majority of patients with schizophrenia did not improve. The authors then examined whether improvement rates differed during the pretreatment and treatment era. Surprisingly, they found slightly lower rates of improvement during the treatment era from 1960 to 1990, with only 36% improvement in studies during that period. This outcome rate compared unfavorably with higher improvements in the 1920-1960 period of 48%.

Somewhat more surprisingly, when these rates were compared to outcomes from 1890 – 1920, the overall recovery rate of 35% observed was almost exactly the same as the rates seen in the treatment era. The researchers noted that diagnostic definitions changed during the three

"...How good is your treatment?... It's as good as your diagnosis...."

treatment periods they described. In the 1890 – 1920 era, the Kraepelinian definition of schizophrenia, which was narrow and required chronicity of psychosis and deterioration as part of the diagnosis, was used. In the 1920 – 1960 era, a Bluelerian definition of schizophrenia, which was broad and did not require chronicity, was used. In the 1960 – 1990 era, there was a return to the Kraepelinian definition. Therefore, the authors observed that the differing outcome rates seen correlated best with diagnostic definitions. If the narrow chronic Kraepelinian definition was used, only about one-third of patients improved. If the broad Bluelerian definition was used, likely including many patients with schizoaffective illness or even bipolar illness, about one-half of patients improved. The use or nonuse of dopamine blocker treatments did not appear to influence outcomes as defined in these studies. In other words, the dopamine blockers did not appreciably alter the course of schizophrenic illness, even though they provided clear benefit for acute symptom exacerbations. Besides this

lesson, the larger lesson of this classic meta-analysis of outcome and schizophrenia is that diagnostic definitions predict outcomes powerfully. This lesson is important in terms of the impact of DSM definitions on the outcome seen in clinical practice, as described in chapter 16. These diagnostic definitions appear to be even more important than treatment effects of specific drug classes.

This observation is consistent with the teaching of Dr. Edwin Cassem of Massachusetts General Hospital, codified in this text as the First Truth of psychopharmacology. How good is your treatment? Dr. Cassem asked residents on rounds

one day. He answered the question himself: It's as good as your diagnosis.

The CATIE trial

A second key source of evidence regarding the treatment efficacy of dopamine blockers in schizophrenia is the classic NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study.

In that study, 1432 patients with schizophrenia were double-blind randomized to 18 months of treatment with a range of different dopamine blockers. Treatment response was defined at a low bar as treatment discontinuation. Rather than using standard psychosis symptom rating scales, partly for practical reasons since the study was so large, the judgment was made that a pragmatic outcome could be defined as treatment discontinuation, assuming that patients would continue with their treatments if they had benefit, and would stop those treatments if they did not have benefit.

All patients were supervised in clinical settings, and thus continuation or discontinuation of treatment in this study was not dependent on the patient's opinion alone, and thus did not reflect treatment noncompliance. The primary outcome was time to discontinuation, with more benefits seen with olanzapine as opposed to other agents. 64% of subjects discontinued olanzapine, as opposed to 74% with risperidone, 75% with the traditional neuroleptic perphenazine, 79% with ziprasidone, and 82% with quetiapine. Overall, 74% of all subjects discontinued dopamine blocker treatment over 18 months or less.

As can be seen with these results, about three-quarters of patients with schizophrenia these days

"...about three-quarters of patients with schizophrenia these days do not respond to any dopamine blocker"

do not respond to any dopamine blocker given, even with the very low threshold definition of simple medication continuation over one year. These results are consistent with the meta-analysis of outcome above, even in the pretreatment era, where it was observed that with Kraepelinian definitions, only about one third of patients improved by natural history or with dopamine blocker treatment. In the CATIE study, with similar Kraepelinian definitions, only about one quarter of patients improved with dopamine blocker treatment, which is lower than natural history rates of improvement in the early 20th century.

The CUtLASS study

After CATIE, the next most influential recent RCT in schizophrenia likely is the Cost Utility of Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) from the UK. In CUtLASS, 227 patients with schizophrenia were randomized

to treatment with first and second generation dopamine blockers for one year. Similar outcomes were seen in the PAN SS and quality-of-life scales in both groups of treated subjects. Side effects also reported to be similar, and thus the researchers concluded that the older dopamine blockers are just as effective and safe as the newer ones. In a second phase of the study, 136 subjects were randomized to treatment with clozapine versus other second-generation dopamine blockers, and clozapine was found to be more effective in reducing symptoms but less effective in improving quality of life. The judgment that new dopamine blockers, which are more expensive, need not be used unless older agents fail can be questioned since the study did not assess long-term risks such as tardive dyskinesia.

TD has been shown to be much higher in prevalence with the first generation dopamine blockers than with the second-generation agents, and thus long-term treatment over five years or longer would seem to be more harmful in effect with older than newer agents. This study does not disprove that literature which demonstrates more harm, at least with TD, with the older than newer dopamine blockers. The result regarding clozapine is important since that agent has been proven to be the most effective dopamine blocker. It is however also associated with the highest rates of metabolic syndrome and cardiovascular disease. Along with market weight gain and risk of agranulocytosis, these medical risks and harms negatively influence quality-of-life with clozapine. Although it is an important agent in the most severe cases of schizophrenia and schizoaffective illness, this study highlights the fact that symptom benefit may not be associated with improved quality of life.

“...dopamine blocker treatment hastens or worsens the process of progressive cortical atrophy...”

schizophrenia had a chronic and deteriorating neurological effect on the brain, as Kraepelin had predicted. The researchers also found that treatment with dopamine blockers had an independent effect of causing more cortical atrophy. This effect was present with both first and second generation agents. Illness severity, controlling for treatment, also had independent effect with more severe symptoms being associated with more cortical atrophy over time.

A meta-analysis of 30 longitudinal MRI studies with a mean of over one year of follow-up compared cortical atrophy in 1046 patients with schizophrenia versus 780 controls. Progressive cortical atrophy was observed during follow-up, and was most associated with dopamine blocker treatment. Such atrophy was not strongly associated with either severity of illness or duration of illness.

In sum, although a larger literature demonstrates that neurodegeneration probably is part of the illness of schizophrenia, it appears that dopamine blocker treatment hastens or worsens the process of progressive cortical atrophy over years of long-term treatment of this illness. Such neurodegenerative worsening does not appear to be better necessarily with second-generation dopamine blockers compared to earlier agents. A conclusion that could be given to this discussion of treatment of schizophrenia with dopamine blockers is that this chronic and deteriorating condition is difficult to treat, and dopamine blockers appear to have most of their benefit for immediate symptom relief of positive psychotic symptoms. In long-term treatment, there is not good evidence that they alter or improve the overall course of illness, and there is evidence that they may worsen the underlying

Neurotoxicity of dopamine blockers

Besides long-term outcome, a final line of evidence regarding the efficacy of dopamine blockers for schizophrenia as a disease has to do with effects on the brain. This literature is growing and suggestive that not only is there no benefit for brain structures with dopamine blocker treatment, there appears to be some harm.

In a study of 211 patients with schizophrenia, who were followed after their first episode, with MRI scans over a mean of seven years (up to 14 years), researchers observed that longer follow-up was associated with smaller brain volumes and more cortical atrophy. In other words, over time,

neurological abnormalities that are present in this condition. In brief, they have important symptomatic benefits, but no disease-modifying effect in this illness.

The PL Bottom Line

- The essential feature of schizophrenia is flatness of affect, not delusions or hallucinations.
- Dopamine blockers improve delusions/hallucination symptoms, but do not modify the disease itself (course of illness).

- Schizophrenia is a chronic disease that is inherently treatment-resistant.
- About three-quarters of patients do not improve notably with standard dopamine blockers.
- Schizoaffective illness is a presentation that is more treatment responsive.
- Dopamine blockers, at least the first generation agents, worsen cortical atrophy over time.

PL Reflection

When I entered the profession, psychological intervention was, practically speaking, synonymous with long-term, individual, psychodynamically-oriented psychotherapy. The present could be understood if the past was known. Understanding the past was the key in the regulation of dysfunctional behavior. I felt intuitively that this view, though enlightening, was unduly restrictive. Being a war child and a Holocaust survivor, I had witnessed that there are other forces than those historically determined that shape human behavior. Reward and punishment, for instance, and fright and relief. I had seen the behavior of my friends change dramatically when the Jews were outlawed soon after the German invasion of Holland. Friendship turned to detachment; intimacy gave way to estrangement. Self-protection transformed perceptions as well as behavior on very short notice.

I got to know mind-set as another powerful force in shaping human behavior. In the concentration camp, hope, even hope against better judgment, had significant survival value; defeatism, on the other hand, proved to be a sure way to death.

And finally I had learned that human interaction is as revealing a way to self-knowledge as introspection is. The group to which one belongs mirrors significant provinces of one's inner life and can, thus, serve as a vehicle to reshape individual behavior according to social expectations. What seemed to be true for normal individuals in abnormal circumstance should also be valid for individuals behaving abnormally in relatively normal circumstances.

Then, soon after I finished my residency, the psychotherapeutic horizon suddenly opened up. Strategies other than interpretation and insight, such as behavior modification and cognitive therapy, were introduced....For me, this was a major revolution, one of the same magnates as the psychopharmacological one.

Hermann van Praag
"Make believes" in psychiatry, or The Perils of Progress,
1993

Current Study of the Month: *Marijuana use increases later opiate abuse*

M Olfson et al, Cannabis use and risk of prescription opioid use disorder in the United States. Am J Psychiatry 2018; 175:47-53

Claims for medical marijuana appear unfounded

In the debates around medical marijuana, one of the arguments made was that cannabis use for pain would reduce later use or abuse of opioids or other addictive substances. In the setting of the current opioid crisis, the claim, if true, would have important potential impact. In this study, this claim was disproven. Marijuana use doubles the likelihood of later prescription opioid abuse.

The researchers used the National Epidemiological Survey on Alcohol and Related Conditions to examine cannabis and opioid use (total sample 34,653 persons). Initial analysis of cannabis use data was based on results from the study in 2001-2002. At that time, 1267 persons in the sample used cannabis (compared to a control sample of over 33000 subjects). They then examined prescription opioid use in the study a few years later in 2004-2005.

This was an epidemiological study, not observation of clinical treatment patterns. In other words, the researchers in the National Epidemiological Survey actually went out into the community and interviewed the general population, using the same interview methods in all persons. They did not base their results on clinical records from hospitals or medical settings, which would be limited to those persons seeking treatment, and which often are not detailed or accurate because medical records are not collected for research purposes.

In the total sample of over 34,000 persons, it was found that cannabis use increased later abuse of prescription opiates by an odds ratio of 7.76.

When corrected for other clinical factors such as mood/anxiety disorders and age and demographic factors, the odds ratio fell to 2.18 (95% confidence intervals 1.14-4.14). This means that the risk was about two-fold higher and it was statistically meaningful (the confidence interval did not cross the null value of one, which is the same as statistical significance). A similar general effect size was seen when cannabis was used for moderate to severe pain as when it was used for other reasons. Due to a small sample with pain (n=6920), the risk of opioid abuse in those with pain had a confidence interval that crossed the null (95% confidence intervals 0.95-4.83) but the overall effect in the subgroup with pain (OR= 2.14) was almost identical to the total population (OR = 2.18).

The claimed benefits of medical marijuana for prevention of opioid use and abuse are not supported by these data.

Clinical implications

When patients request medical support for marijuana use for pain, they should be warned that they will have a two-fold increased risk of prescription opiate abuse in the following two years. They should be told that the cannabis use will not increase future opiate abuse risk.

The PL Bottom Line

- Medical marijuana does not decrease risk of later opiate abuse; it increases it.

Curbside Consult

Questions and cases from you

Question: I'm a new subscriber and read with interest your "drug of the month" piece on citalopram (November 2017). It states that citalopram is not effective for bipolar depression. Is this the case with all SRIs?

The background to this question is that I had a patient who was diagnosed by his initial psychiatrist number as having bipolar II. Then he later saw another psychiatrist who asked him whether the periods of low mood were more troublesome than the periods of hypomania. Because the depressive episodes were longer and subjectively less pleasant the patient said the former. His suggestion was that the patient try an antidepressant rather than a so-called mood stabilizer, which was the advice given by the first psychiatrist.

The patient preferred to take a wait and see approach to the current depressive episode and preferred psychotherapy rather than medication.

When he came to see me, the patient said that he was not anti-drugs but that he preferred to see them as helpful in a crisis rather than as part of a long-term preventative treatment plan. However if taking a mood-stabilizer long-term is the best available option currently available (combined with therapy, psycho education and improved self-care) then he was open to the idea.

What is the PL perspective on these issues? Further, does PL recommend any specific resources to assist with the emotional distress that accompanies the experience of bipolar illness.

PL : This is an excellent question. As discussed in PL February 2016, there have been many studies over three decades of monoamine agonists in bipolar depression. The most recent meta-analysis of those randomized clinical trials published about a year ago confirms prior meta-analyses that have been done repeatedly in the last decade or so. In general, studies of so-called antidepressants for acute bipolar depression find that those agents are either the same as placebo or only minimally better than placebo. Any benefits seen, being very small in size, do not have clinical meaning. In other words, the so-called antidepressants do not benefit depression and bipolar illness. Hence the preference for the term monoamine agonists, which would help with the linguistic mistake of thinking that these agents are useful for bipolar depression.

There are those who claim otherwise for type II bipolar illness, as opposed to type I. They claim that SRIs and other so-called antidepressants are effective in type II bipolar illness, even in monotherapy. There are a number of randomized trials to that effect, conducted by Amsterdam and colleagues, a group of excellent researchers. It is not the fault of these researchers, but the mistaken conclusion, in the PL opinion, of these studies is based on an invalid research design. Those studies use the "enriched" design, which preselects patients to be treatment responders acutely for depression. They are then studied for maintenance prevention of depression. This approach prejudgets the matter. Treatment response is selected to assess treatment response. It is a tautology. And it never fails: studies are always positive, which is proof that the design is invalid, because some drugs would have to be ineffective for some illnesses at some point.

This matter is complex and controversial, and discussed in more detail in PL March 2016, and in scientific articles by the PL editor.

In short, because of the invalidity of the “enriched” research design, PL does not believe the results of the type II bipolar depression studies which claim benefits with antidepressants.

Returning to the literature on antidepressants in bipolar depression, these studies are of the acute phase, meaning short-term. Other issues that also are relevant, besides acute inefficacy, are possible risks. These include the risk of acute mania, and, perhaps more importantly, the risk of long-term rapid-cycling, with more and more mood episodes over time. The available randomized trials generally support that the so-called antidepressants have these risks. They can cause acute mania and also more and more mood episodes over time in bipolar illness. In other words, in the long-term, they are mood destabilizers, which will counteract benefits of mood stabilizers.

One of the mistakes in the case you describe is that the second psychiatrist focused on severity of symptoms as the main focus on which to target treatment. This is very common, but it is medically and biologically unsound. There are many illnesses in which the most severe symptoms are not at all the relevant targets of treatment. For instance, a fever can be quite high with HIV infection, but it should not be the target of the main medication treatment. Symptoms can be quite uncomfortable, and should be managed as needed, but they are not the main target for improvement of the underlying disease. This so-called target symptom-oriented approach to psychopharmacology has been very common for the past few decades, and it results in purely symptomatic treatment. It does not improve the

underlying illness. Bipolar illness is the best example of the weakness of this approach, in that the main treatments for the underlying illness are the mood stabilizers, like lithium and lamotrigine, which have less, or in some cases no effect, for acute symptoms, as opposed to prophylaxis, where they are most effective. Thus, the decision to wait and see with the depressive episode was wise, since all mood episodes resolve by natural history in bipolar illness. As long as the episode is not completely disabling or leading to suicidal ideation or behavior, a wait-and-see approach can be taken. The use of psychotherapy to assist with such acute worsening can be helpful. Medications are not always needed for acute episodes.

Thus the PL approach is rather the opposite of what the patient describes in this case. The PL approach is *not* to use drugs mainly for crises, but rather to use them long-term for prevention of the crises in the first place. In other words, PL prefers using medications for the underlying disease, not for symptoms. This is the classic Hippocratic approach. In the case of bipolar illness, whether type I or type II, a mood stabilizer is needed to prevent future mood episodes, whether depressive, hypomanic, or manic. It has been proven that the four standard mood stabilizers, namely lithium, lamotrigine, valproate, and carbamazepine, have been proven effective to prevent mood episodes. The SRIs have been proven *not* to prevent mood episodes in bipolar illness. Hence the recommendation would be to use a mood stabilizer long-term, rather than to save medications for symptomatic use during crises. Taking this approach, medications will not be needed during crises, since those crises will not occur (or will occur less frequently and less severely).

Of course, a balance needs to be obtained between risks of medications and their benefits. As William Osler said, the art of medicine is the art of balancing probabilities. The science of medicine tells us that mood stabilizers should be used long-term for bipolar illness, whether type I or type II. The art of medicine is in the hands of the clinician as to which agents to use, and at what doses, to achieve the best balance of long-term benefit over harm. Stated otherwise, the clinician's job mainly is to decide which mood stabilizer to use, based on risks and benefits, and at which doses. The question is not whether to use a mood stabilizer, but how.

PL Reflection

Delusions are true; they're just not *that* true.

Elvin Semrad

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THE PSYCHIATRY LETTER

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Genetics and psychiatry

The Special Article in this issue examines the hot topic of genetics and psychiatry, focusing on work on the human genome. The article concludes that many genes of small effect are relevant for serious psychiatric diseases, and, importantly, that modern genomics disproves the basic diagnostic structure of the DSM system.

The Article of the Month examines childhood psychopathology and brain MRI abnormalities, finding that the former seems to cause the latter, rather than vice versa.

The Guest Commentary is presented by Ronald Pies MD, who provides an analysis of antipsychotic effects on the brain, arguing against the PL perspective from last month where concerns regarding neurotoxicity were raised.

The case of the month involves a first-episode manic psychosis, and questions around possible induction by marijuana, as well as need for long-term treatment.

As always, CME credits are available for this and all prior PL issues online.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - Thomas Huxley

Special Article: “The gene for”

What if there are too many, and they don’t do much?

Everybody's excited about genetics. Wait until we find the gene for X. We'll finally have our disease figured out once we know the genes. Symptoms are subjective; the genes will tell us the reality. These are the kinds of statements you sometimes hear, among clinicians and researchers and academics, in public and in private. But these hopes are misplaced; even the geneticists will tell you so.

This special article expands upon an overview written by a consortium on leading psychiatric geneticists. (Psychiatric Genomics: An update and an agenda. PF Sullivan et al, Am J Psychiatry 175: 15-27). They make their living on psychiatric genetics, and they are committed to it. But the review raises some cautions and questions of which we should be aware.

Remember that genetics is Mendelian or non-Mendelian, which is the same thing as saying it is qualitative or quantitative. In qualitative Mendelian genetics, you only need to count to four. There are two chromosomes for each parent, and, if passed to a child, the gene on a single chromosome either causes the disease (autosomal dominant) or it does not (autosomal recessive). In the recessive case, two genes are needed for disease, so if both parents provide one gene, the disease occurs, or if not, the recessive gene is passed along potentially to the next generation, again in a one in two likelihood of transmission. This classic Mendelian genetics works for uncommon, purely genetic diseases, like Down's syndrome (Trisomy 21).

Most medical illnesses, when they are genetic, are not Mendelian and qualitative. They are non-

Mendelian and quantitative. This means that many genes are needed for a disease to occur, not just one or two. You have to count much higher than four. Ten, twenty, hundreds, even thousands of different genes, acting together, may cause a disease. The disease may be purely genetic, as in schizophrenia or bipolar illness, but it is non-Mendelian: many many genes are needed for the disease to happen. Each single gene has little effect, and sometimes it can be absent completely and replaced by other genes which have enough effect to cause the disease.

Don't be surprised. As the authors note, there are about 13,000 genes expressed in the brain, and about 2000 genes at each synapse.

“... When psychiatric diseases are genetic, they are non-Mendelian and each gene has a small effect....”

This is the core problem of psychiatric genetics. Some psychiatric constructs just aren't genetic, or not very genetic, like personality traits or disorders. When psychiatric diseases are genetic, they are non-Mendelian and each gene has a small effect.

In recent years, as the human genome has been detailed, with Genome-Wide Association Studies (GWAS) scans, there was hope that we would find the genes for many diseases. The problem in psychiatry is that there are many genes for one disease, and each gene is small in effect, which makes them difficult to find. In this overview, the authors provided a figure.

What is shown there is what would be seen in a study with 2000 subjects, 1000 cases of a disease and 1000 controls. The assumption is that there would be 90% statistical power, which means that the study would correctly report that there was no

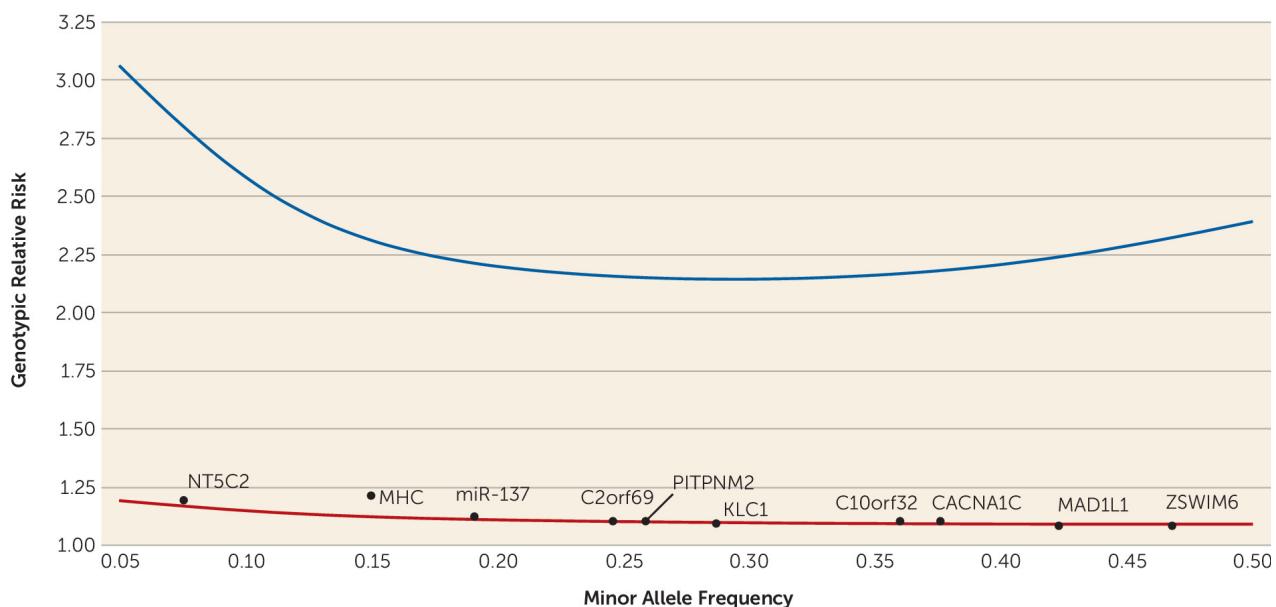


FIGURE 1. Theoretical Power of Genome-Wide Association Studies (GWAS) and Observed Genetic Effect Sizes

association of a gene with a disease 90% of the time, if indeed there was no association with disease. As seen there the relative risk would have to be at least 2-3 for such an association to be detected. This means that to be detected in this study, a single gene would have to double or triple the risk of having a disease. The line at the bottom of the figure reflects the actual relative risks for the genes that have been found to be associated with relative risks greater than one (meaning they are associated with schizophrenia). They all have relative risks of around 1.20-1.25, and all are lower than 1.25. This means that each gene that increases the risk of schizophrenia does so with about a 10-20% increased relative risk, and not more than 25%. 2000 subject studies would need 10 times higher effects, an increased risk of 100% (which means a doubling of risk), to be able to detect those associations. The actual small genetic associations shown in the figure have been found with studies as large as 37,000 cases of schizophrenia. These are the sizes needed to study the genetics of schizophrenia.

In the work of this consortium, there have been 155 genes associated with schizophrenia, 44 with

unipolar depression, and 19 with bipolar illness, followed by 12 for reported ADD, and three or less for all other conditions. Sample sizes range from about 20,000 for bipolar illness to about 60,000 for schizophrenia to about 130,000 for unipolar depression. This is a scratching of the surface. The authors estimate that there probably are about 1000 genes associated with schizophrenia. The identified genes for schizophrenia so far only explain about one-half of the genetic heritability of this disease. (Schizophrenia is about 80% heritable genetically, based on twin studies, meaning that it is almost completely genetic; these 155 genes explain 45% of that heritability.)

The non-Mendelian quantitative genetic nature of schizophrenia and affective illness means not only that this research is hard, cumbersome and expensive, it also might mean that all we will find out is that each gene is minor in its influence.

Genetics researchers are aware of these critiques, but they hope that with all these limitations, we still might find that a single gene could have an impact on a disease, and be a “druggable” target.

For instance, diabetes and cardiovascular disease are similarly non-Mendelian moderately genetic conditions. One of the genes associated with cardiovascular disease is a gene for LDL cholesterol, which is a major target for disease prevention. A similar process may pan out for one of the genes for schizophrenia or affective illness.

A larger concern is that no matter how good the genetic analyses, they will fail if they do not correspond to a real clinical phenotype; by “real” we mean something that is in nature, not made up by a DSM committee. The genomic consortium researchers admit that they started with the “fast phenotype characterization” of the DSM standard definitions, and a consequence of their analyses is that they disprove DSM-III through 5. These DSM definitions do not correspond to the genes. The genetic analyses overlap notably among conditions (like schizophrenia and bipolar, bipolar and unipolar, all three with ADD), and they also overlap with normal traits. These consortium researchers claim that their next step will be to further characterize the clinical features of their genetically-defined subjects. “By tackling nature as it is, and not as we might want it to be, we hope to provide considerable new knowledge about the fundamental basis of psychiatric disorders.” Let’s hope so, and then maybe we can get rid of DSM.

Clinical implications

How are genetics relevant to clinicians today? All these GWAS studies are irrelevant since each gene with a small effect is too uncommon and

“... no matter how good the genetic analyses, they will fail if they do not correspond to a real clinical phenotype.....”

insufficiently important to be useful for diagnostic tests. Further, what these genes do is not helpful for treatment decision making, given current medications. Some of these genes are quite common and generic genes, such as the major histocompatibility complex, which has to do with blood types.

Instead, clinicians are left to count; they should count relatives with defined psychiatric illnesses, focusing on schizophrenia, bipolar illness, and severe depression, which are the only reliable highly genetic diseases of psychiatry. Even so, they occur in about 10-20% of relatives, and thus one has to assess aunts, uncles, and cousins to be able to examine family genetics. The nuclear family is not sufficient. Further, clinicians should err on the side of overdiagnosis, not under diagnosis, of relatives, since stigma impedes the seeking of help, and thus diagnosis, by most of the general population.

The PL Bottom Line

- Modern genomics has refuted the basic DSM diagnostic groups.
- The genetics of schizophrenia and severe affective illness is non-Mendelian.
- Many genes of small effect are present. No single gene is of diagnostic importance. About a thousand genes likely are involved in schizophrenia.
- Current genomic research is hindered by small single gene effects, requiring huge samples for research.

PL Reflection

The patient needs an experience, not an explanation.

Frieda Fromm-Reichmann

Current Study of the Month

Childhood psychopathology alters the brain, not vice versa

RL Muetzel et al, Tracking brain development and dimensional psychiatric symptoms in children: A longitudinal population-based neuroimaging study. Am J Psychiatry 2018; 175:54-62

Brain MRI abnormalities are effects, not causes

Here is the typical story. A researcher shows a colorful picture of the brain, with a certain part being too small or too large, or having too little or too much blood flow. Then the researcher claims that these brain imaging changes support the validity of a certain diagnosis. In children, the common claim is that brain imaging changes support the validity of the diagnosis of ADD.

The problem, as all know, is that correlation cannot be assumed to be causation. The brain is always changing. How do we know we are dealing with an illness? There are differences in the brain PET scans of Republicans and Democrats. Are those diseases?

Further, which way does the arrow of causality go? Are the brain changes causing the illness? This is what is assumed usually. But there is another possibility: It could be that the illness is causing the brain changes.

This study is able to answer this question in relation to the construct of childhood ADD because it is prospective: it examines clinical diagnosis and brain imaging at different times moving forward in childhood. Its conclusion: brain changes are effects, not causes. They do not prove validity of ADD.

In this study 845 children received brain MRI testing at ages 8 and 10. They also had clinical assessments at ages 6, 8, and 10. The researchers divided clinical symptoms into two basic categories of “externalizing” (agitation, excitation,

impulsivity) and “internalizing” (sadness, anxiety, withdrawal) symptoms.

Higher externalizing symptoms at age 6 were associated with later smaller total brain volume, with reductions in both gray and white matter, and smaller subcortical brain volume. Over four years, the association of externalizing symptoms remained strongest for smaller subcortical brain volume.

Higher internalizing symptoms at age 6 had no associations with brain changes initially, but after four years, there was some association again with smaller subcortical brain volume.

Neuroimaging at age 8 did not predict changes in externalizing or internalizing symptoms at age 10.

So, the prospective design allows for some claims of causality. If one event happens before a change in another event, the first event is more likely to be a cause. If one event does not precede another event, then the first event is not likely to be a cause. Here, MRI brain findings did not correlate with any later changes in psychiatric symptoms. In other words, MRI findings did not “cause” anything. In contrast, psychopathological states were associated with later changes in brain MRI. Or, psychopathology seemed to cause brain MRI changes. Specifically, externalizing symptoms of impulsivity and excitation caused atrophy of subcortical brain structures.

What are we to conclude? Rather, this study tells us what not to conclude: Brain MRI

abnormalities occurring along with psychiatric symptoms does not mean that the former cause the latter; it could be the other way around.

Lastly, how can symptoms change the brain? We know that psychomotor excitation (e.g., mania, stress reactions, psychosis) is associated with overactivity of the hypothalamic-pituitary axis (HPA), with overproduction of steroid hormones, which are excitotoxic in the brain, causing cortical atrophy. This link is rather well established. It could be a mechanistic explanation for the clinical/biological finding of this study: clinical psychopathology leads to brain abnormality, not vice versa.

Clinical implications

These results could support the view that controlling psychopathological symptoms is beneficial for the brain, and that short-term symptom improvement could have long-term neurological benefits.

The PL Bottom Line

- MRI brain abnormalities may be the effect, not the cause, of psychopathological clinical symptoms in childhood.

PL Reflection

The phenomenon of uncompromising belief stands against science. The great majority of people subscribe to “belief” not as “perceiving the truth of something” but as “taking this as the basis for life.” The second belief is much firmer and more fixed than the first one...It can sometimes be upheld to a point where it seems completely absurd, and...then it only ends with the death of the believer....

But there must always be a fundamental complementarity between deliberation and decision. In the practical decisions of life it will scarcely ever be possible to go through all the arguments in favor of or against one possible decision, and one will therefore have to act on insufficient evidence. The decision finally takes place...by cutting off all further pondering. Even the most important decisions in life must always contain this inevitable element of irrationality. The decision itself is necessary since there must be something to rely upon, some principle to guide our actions....

[We need] a new kind of balance between thought and deed, between activity and meditation.

Werner Heisenberg
Physics and Philosophy

Guest Commentary

Do antipsychotics really thin the brain?

Ronald Pies MD

This commentary relates to the Special Article in last month's PL on dopamine blockers.

Those of us who trained in the late 70s and early 80s readily recall the infamous "Haldol shuffle"—the very distressing akathisia that many patients taking haloperidol developed, usually after a week or two of treatment. We had no doubt that, despite their (limited) benefits in acute psychosis, *neuroleptics* (meaning, "seize the neuron") were quite capable of injuring the nervous system. When the second generation of antipsychotics agents came along in the 1990s, there was considerable fanfare over these supposedly "atypical" drugs. Indeed, compared with the first-generation antipsychotics

[FGAs], the second-generation antipsychotics [SGAs] generally showed a reduced frequency of acute extrapyramidal symptoms, and probably a reduced risk of

tardive dyskinesia. The first of these SGAs, clozapine, also appeared to be more effective than the first-generation antipsychotics [FGAs] for severe or treatment-resistant schizophrenia, even showing enhanced efficacy for negative symptoms. Over the ensuing decade, however, it became clear that some of the SGAs (such as risperidone) could induce acute EPS in a dose-dependent manner, as well as cause some serious metabolic disturbances (e.g., with olanzapine). And, with the likely exception of clozapine, it has been difficult to demonstrate significantly improved response or outcomes in schizophrenia with use of the SGAs vs. FGAs.

"...this study found no significant association between changes in cortical thickness and clinical and cognitive outcome....."

Brain "Thinning" with Long-term Antipsychotic Use?

In the past 10-15 years, a more subtle issue of antipsychotic neurotoxicity has arisen. Reports suggest that the use of antipsychotics in patients with schizophrenia is associated with volume reduction or "thinning" in certain brain regions, including the prefrontal cortex. Interpretation of these studies is complicated by considerable evidence showing that schizophrenia itself is associated with numerous volumetric and structural brain abnormalities, which may be seen even in "drug-naïve" patients experiencing a first psychotic episode. Nevertheless, some data point to a "dose-duration" effect, with greater cortical thinning linked to higher antipsychotic dose and/or duration of exposure. (On the other hand, brain volume reductions may simply be associated with

more severe illness, which is then treated with higher doses of antipsychotics). Some studies report that FGAs reduce gray matter more than SGAs, while others do not; and some data suggest that SGAs may both increase or decrease cortical thickness. One randomized, controlled, 1-year study of haloperidol, risperidone and olanzapine found no significant differences in the effects of the agents on cortical gray matter. Importantly, this study found *no significant association between changes in cortical thickness and clinical and cognitive outcome*--a point we will return to shortly.

What Do MRI Studies Really Tell Us?

Interpreting data obtained from MRI and functional MRI (fMRI) studies is just that—an act of *interpretation*. This cautionary note sounded by Weinberger and Radulescu is well-worth remembering:

"MRI is not a direct measure of brain structure. MRI is a physical-chemical measure, based on radio-frequency signals emitted from energized hydrogen atoms influenced by the magnetic properties of the microenvironment of surrounding tissue...before jumping to the conclusion that MRI differences between a patient sample and a control sample represent microstructural abnormalities of pathogenic significance, one needs to be mindful of other plausible possibilities. For example, a simple change in brain perfusion associated with acute drug administration has been shown to masquerade as a change in MRI volume measurements... We recommend that researchers using structural MRI techniques remain highly

skeptical of the basis of changes that are found in comparisons of patient and control samples and refer to them as 'differences in MRI measurements,' not as 'cortical thinning' or 'loss.' Patient samples should be carefully characterized for potential confounders...[such as] smoking, alcohol and cannabis use, body weight, blood lipid levels, corticosteroid levels, exercise routines, and general health."

Furthermore, it is far from clear that this "thinning"—if that is what we are measuring—has any significant impact on the actual cognitive functioning of the patient, or, indeed, of the patient's clinical response to antipsychotic

"...while short-term treatment with antipsychotics was associated with prefrontal cortical thinning, treatment was also associated with better cognitive control and increased prefrontal functional activity....."

medication. In the study by Roiz-Santiáñez et al, there were no significant associations between changes in cortical thickness and clinical or cognitive outcome (e.g., on Continuous Performance Test Degraded-Stimulus or Rey Complex Figure Test). Furthermore, in a study of antipsychotic effects on brain structure and function in first-episode schizophrenia, Lesh et al found that while short-term treatment with antipsychotics was associated with prefrontal cortical thinning, treatment was also associated with *better cognitive control and increased prefrontal functional activity*. Similarly, Veijola et al found no evidence that loss of brain volume had adverse effects on global levels of symptomatology, global cognition, or level of function. Indeed, meta-analyses have generally found mild to moderate cognitive improvements associated with the use

of both atypical and typical² antipsychotic medication in schizophrenia. On the other hand, naturalistic data from Finland found an association between higher lifetime antipsychotic dose-years and poorer cognitive performance, at age

43 years. The Finnish study did not find differences in the cognitive effects of typical and atypical antipsychotics. The small sample size (60 participants with schizophrenia and 191 controls) and the naturalistic design limit interpretation of these data, and do not establish a causal connection between antipsychotic use and cognitive deficits.

Conclusion

Some critics of psychiatry have claimed that antipsychotics "do more harm than good" in the long-term treatment of schizophrenia, and the supposed "brain thinning" effect of these drugs is sometimes cited as evidence for this claim. Yet, as

we have seen, interpretation of MRI findings is complex and prone to numerous confounds, including such common factors as heavy alcohol use and vitamin deficiency. More to the point: putative cortical “thinning” is not necessarily an indicator of impaired cognition or level of function.

To be sure, antipsychotics are often over-prescribed in some settings—e.g., for “agitated” patients with dementia and for behaviorally disturbed adolescents—and are often continued indefinitely in patients who might benefit from gradual tapering and a trial period off the medication. Yet epidemiologic data have not validated the “more harm than good” narrative and the preponderance of evidence—admittedly, mostly short-term (<1 year), non-randomized studies—points to significant benefits of antipsychotics, including reduced rates of psychotic relapse and suicide among persons with schizophrenia.

There remain many unanswered questions concerning antipsychotic-associated alterations of gray matter. For example, it is not clear whether apparent antipsychotic-related gray matter reductions are partially or fully reversible with cessation of treatment, though one MRI study of inpatients with schizophrenia found evidence for reversibility with very short periods of withdrawal from antipsychotics.

Until we know more about the long-term effects of antipsychotics on brain and cognition, it behooves clinicians to use the lowest effective antipsychotic dose for the shortest clinically feasible length of time. This requires a fine-grained, risk/benefit calculation for any given patient. While most patients with severe, chronic schizophrenia may need life-long antipsychotic treatment, carefully-selected patients with a first

*“...epidemiologic data have not
validated the “more harm than good”
narrative.....”*

episode of psychosis often warrant gradual dose tapering and a closely-monitored discontinuation trial. The cerebral effects of long-term antipsychotic treatment is indeed a gray area—but the need to safeguard our patients’ gray matter is crystal clear.

Note: This piece is condensed and modified from an editorial to be published in the Journal of Clinical Psychopharmacology (in press).

PL Comment: Dr. Pies brings a wide knowledge of the scientific literature to bear on this important question. Two points can be added to his erudite commentary. First, improvement in cognition does not invalidate neurotoxicity.

Amphetamines are proven neurotoxic repeatedly in many animal brain studies. Yet they clearly improve attention and executive function. Thus, drugs can be harmful to neurons, and not show cognitive impairment; in fact, they can improve cognition. Second, the issue of harm to neurons with dopamine blockers is not based solely on human MRI studies of “thinning.” There are some animal studies which show direct toxicity of dopamine blockers to neurons. The evidence is not like a definitive randomized trial open and shut case. Like cigarette smoking it is based on observational long-term clinical data in humans combined with preclinical data in animals.

There’s plenty of smoke. Whether there’s a fire depends on whether you are worried enough to run based on the current evidence, or whether you want more. There may be some harm, or maybe not. Even if there is harm, as Dr. Pies notes, the question of how much benefit is obtained with treatment, especially in schizophrenia, deserves to be weighed against it.

Curbside Consult

Questions and cases from you

Case: A 19 year old male is hospitalized for a first psychotic episode 6 months ago. He had no prior psychiatric problems. He was diagnosed in the hospital with bipolar illness. He was treated there with olanzapine 10 mg twice daily and divalproex 500 mg twice daily. Before his episode, he had been using marijuana for about two years, with increasing usage before hospitalization. Is the diagnosis of bipolar illness correct, or does the patient have drug-induced psychosis? Is the treatment appropriate?

Background: He has no medical illnesses, no drug allergies, and drinks alcohol with a few beers used monthly. He denies any other drug use.

Family history is positive for depression in multiple relatives, but none diagnosed with bipolar illness or schizophrenia.

The setting of hospitalization involved not sleeping for about 4-5 days, with rapid speech and increasingly unusual behavior, such talking about traveling backward in time and taking pictures of things so that he could take them with him in time travel. He became agitated in the hospital and had to be put in restraints. He also heard voices, and thought he was smarter than everyone else. His family reported that he was highly energetic, and these symptoms were different from his baseline. In the emergency room, his conversation was tangential and did not make sense to the interviewer. He reported feeling anxious. He denied having an illness. As his symptoms improved in the hospital, he attributed them to stress. Toxic screen was positive for

“...the coincidence of using alcohol and marijuana does not mean that those agents are causing psychiatric symptoms.....”

cannabis but negative for other agents. Head CT was normal.

PL: This is a classic case of first-episode mania. The situation is typical: a young male, delusions, poor insight, substance use, suggestive but non-definitive family genetics. With a first-episode, should long-term treatment be instituted? What about drug-induced psychosis?

In high functioning individuals, this first episode is almost always a manic psychosis, not schizophrenia, since the latter is associated with impaired functioning longer-term. It is common for concomitant drug use to be relevant, because of the elevated use of drugs in general. It is estimated now that about one half of the high school population in the United States has used marijuana, and a substantial minority regularly uses or

abuses it. This number is increasing due to the decreased stigmatization of marijuana use occurring with increasing legalization in many states. Similarly, alcohol use is and always has been common in the US high school population.

As is well known in science, correlation is not causation. In other words, the coincidence of using alcohol and marijuana does not mean that those agents are causing psychiatric symptoms. It is true that alcohol can cause or worsen depression, and that marijuana can cause or worsen paranoia and depression. But they do not cause repeated mood episodes or chronic psychosis as in bipolar illness in schizophrenia. When one is dealing with the first episode of illness, the question becomes more relevant since recurrence of episodes has not yet occurred. In this situation, one must move from the symptoms, to the other three validators of a

diagnosis, namely course of illness, family genetics, and treatment effects. Where no treatment has occurred, one is left with the course of illness and family genetics. The course of illness provides limited information in a child or young adult, since future episodes have not yet occurred, and usually the course of bipolar illness is not fully apparent until the decade of the 20s or 30s. However, some course features can be relevant: the average age of onset for bipolar illness is 19. This patient meets that age of onset almost exactly. Other course features will need to be able to be evaluated a few years into the future.

Regarding family genetics, there is a report of multiple relatives with depression. However it is reported that bipolar illness and schizophrenia do not occur in the family. The concept of manic-depressive illness before

1980, before it was divided into bipolar illness and unipolar depression, was that this was a highly genetic biological disease consisting of recurrent mood episodes of any kind, depressive or manic. In other words, unipolar depression and bipolar illness were inherited together. In fact, four more decades of research since 1980 has shown that there is major overlap in the genetics of bipolar illness and unipolar depression, and that the two conditions do not distinguish well genetically. In other words, in a person with bipolar illness, there will be relatives with unipolar depression frequently. And sometimes in a person with unipolar depression, there will be relatives with bipolar illness. This overlap supports the older concept of manic-depressive illness, that unipolar depression and bipolar illness are subtypes of the same overall illness, as opposed to being different diseases. This family genetic history would be consistent with bipolar illness since multiple

"Regarding marijuana, it is unlikely that it is the sole or main cause of this patient's initial first manic psychosis....."

relatives with depression would be expected in that situation. It also could be the case that some relatives with depression in fact have bipolar illness, which is initially misdiagnosed as unipolar depression in 40% of cases. Nonetheless, the actual presence of bipolar illness in relatives would not be necessary to be consistent with the genetics of this condition, as long as depression was present.

Regarding marijuana, it is unlikely that it is the sole or main cause of this patient's initial first manic psychosis for two reasons. First, marijuana does not cause mania. It causes paranoid symptoms, but not decreased need for sleep, increased energy, and other manic symptoms as this patient possessed. Secondly, his marijuana use had been ongoing for 3 to 4 years before the first manic episode, and

thus it is not time course related directly to the episode. If one were to assert a drug-induced psychosis, it would have to occur with a drug being used just before the psychotic episode occurred, with the drug not being used previously when a psychotic episode had not occurred. Given that this patient has multiple years of marijuana use without psychosis or mania, a causal relationship would not be supported.

The next question that would come to mind if the diagnosis of bipolar illness was accepted is how the patient should be managed from this point forward. There is very good research that shows that after the first episode of mania, a second episode is highly likely, with the probability of 90% or more within five years. Most likely, the next episode will occur within about a year or two. Typically the following episode is a depressive episode, which is then followed by

another manic episode. Preventive treatment with mood stabilizers for prophylaxis of depressive and manic episodes in the future makes sense given the 90% or higher likelihood of such recurrence within the next few years. In a young healthy person, the use of lithium for long-term treatment would raise concerns since there is about a 1-5% risk of chronic renal insufficiency with about 20 years of treatment. In this case, such risk would occur in the third or fourth decade of

life, which is of concern. Thus, all other things being equal, it is likely preferable to avoid lithium as the main treatment for such young persons. However, if the patient has any suicidality, some lithium would be life-saving, literally, and there would be no risk of future kidney problems if suicide were to occur. This is an important point, since the risk of suicide with the diagnosis of bipolar illness is about 5-10%, which is hundreds fold higher than the general population.

Other alternatives are divalproex and carbamazepine, both of which are proven effective in general. Importantly, lamotrigine is completely ineffective for treatment of acute mania and has very limited preventive effects for mania as well. Thus in a person with a severe acute manic psychosis, lamotrigine would

"Preventive treatment with mood stabilizers makes sense given the 90% or higher likelihood of such recurrence within the next few years..."

probably be the least useful agent for long-term treatment.

The use of an antipsychotic agent acutely certainly makes sense, but whether or not it would be necessary long-term is a question that would need to be reassessed 6 to 12 months after the acute episode. It has been shown in many randomized trials that if an antipsychotic agent is stopped within 6 months of treatment of an acute manic episode, rapid

relapse occurs, usually within months, back into the same acute manic episode. It takes 6 months or longer for natural remission to occur, such that the patient is not likely to become manic again immediately if medication is stopped. So, about 6 months or longer from now, the antipsychotic could be stopped, and one could see if the patient remained well on a single mood stabilizer.

It is difficult understandably to commit to long-term treatment based on a single episode of illness, but this kind of first manic psychotic hospitalized episode has been studied well for decades, and its natural course is very well defined. When the odds are 90% or more in one direction, it is risky to bet on the minority outcome.

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THE PSYCHIATRY LETTER

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Legal aspects of practice

This issue turns to some practical aspects of clinical practice, particularly legal and regulatory features. In the special article this month and next month, these legal aspects of practice will be discussed in detail. Concerns to be addressed include not only malpractice, but also the influence of state regulatory boards, and day-to-day administrative and clinical features of practice that can increase or decrease legal risks.

The Study of the Month examines a large "network" meta-analysis that examines antidepressants for major depressive disorder (MDD). The authors claim that all agents are better than placebo and that some are more effective than others. A careful analysis of the absolute benefits seen shows that the study confirms prior meta-analyses finding that antidepressants have little clinically meaningful benefit for so-called MDD. The claim that some are "better" than others is addressed in the Statistical Corner where the idea of network meta-analysis is examined. It's found that network meta-analysis produces invalid results scientifically, and worsens the limitations of traditional meta-analysis. College basketball tournaments, like "March Madness," provide a good real-world analogy to why network meta-analysis is invalid scientifically. It may be published in prestigious journals, but the results may still be wrong. The Statistical Corner explains the concept of "network" meta-analysis. This month printed newsletter doesn't have a Curbside Consult due to space constraints but see the web newsletter for a bonus Curbside consult case.

Please continue to apply for CME credits online via the PL website.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Legal aspects of practice - Part I

Self-preservation is a necessary part of clinical work

Legal aspects in the practice of psychiatry, especially when prescribing medications, include informed consent, defensive medicine, important side effects, off-label prescribing, cost-containment and economic factors, and psychological aspects of the doctor-patient relationship. In this special article, some of these aspects will be examined, followed by a second part completing the discussion in next month's special article. This discussion will focus on practice that involves prescribing medications, but many aspects will apply as well to the legal risks and limitations of psychotherapy.

Informed consent

Informed consent is a central aspect of the practice of psychopharmacology: clinician and patient must assess the risk-benefit ratio of every clinical decision. This means that in each decision, not only should benefits be assessed but also harms. The concept of informed consent has been addressed in the setting of research, where it must be written down explicitly and approved by an ethics review committee. In the setting of clinical practice though, informed consent tends to be verbal, and there is no formalization of a written consent under most circumstances. This fact does not preclude the obtaining of written consent, as often happens before some kind of physical procedure. Yet it is not required in writing in the dispensation of medications. The verbal discussion of informed consent is expected though, and it is best if some form of

documentation of that verbal discussion exists in the patient's medical chart.

Specific problems that can arise in psychiatry involve the competency of patients to provide consent when they are severely symptomatic, such as with delusions or hallucinations, but also in manic states or other states of impaired insight. Sometimes patients are paranoid, and the psychological state of paranoia can interfere with the ability to rationally assess risk-benefit aspects of medication decision-making. Other times patients are extremely agitated, or highly anxious, and although they are not technically incompetent from legal perspective, their thinking is impaired in such a way that they may have difficulty fully engaging in a risk-benefit analysis. In such cases, the question sometimes arises whether clinicians should provide extensive discussion of potential side effects to an anxious

patient, given that their anxiety may increase when thinking about such side effects. It is relevant that such patients will always be anxious, whether they

receive such information or not, and it is important that the most important side effects always be discussed.

Side effects

When discussing side effects, there is no reason to go through every single one that might be found on the Internet or in the labeling of the medication by the FDA. It's the clinician's job to provide the patient with a metabolized summary

of the most important side effects. One way of approaching the discussion of side effects would be to divide them into a few major groups: medically important side effects, common nuisance side effects, and infrequent nuisance side effects. The first two groups should be discussed under most circumstances, and at the very least a discussion of the first group of medically important side effects should be documented in the chart. For example with lamotrigine, the chart should always document a discussion of serious rash or Stevens-Johnson syndrome as a potential medically serious side effect. A list of infrequent nuisance side effects need not be documented nor even discussed in most cases. It is important to note that a handout of side effects is not sufficient to protect against potential legal problems, if there is no documentation in the chart of a discussion of that handout.

Turning to serious side effects that are of legal importance, the example of

Stevens-Johnson syndrome with lamotrigine was just given. Other examples

include tardive dyskinesia with traditional dopamine blockers, agranulocytosis with clozapine, and long-term kidney impairment with lithium. These types of standard serious medical risks should be documented in the chart in most cases when these medications are begun. If the patient develops any of these problems in the future, that initial documentation will protect the clinician in most cases.

Regarding the use of medications in FDA non-approved indications, it's important to realize that the FDA explicitly allows for physicians to use medications outside of FDA indications. What is not allowed is for pharmaceutical companies to

"the FDA explicitly allows for physicians to use medications outside of FDA indications..."

market such use to physicians. However, physicians can discuss such use among themselves, study those uses, publish those uses, and hold conferences that are not promotional in nature about non-FDA indicated uses of medications. In other words, it is an accepted part of standard medical practice that clinicians are the individuals who have the right to decide how and for whom to use medications. FDA indications are meant primarily to regulate marketing by the pharmaceutical industry, not to regulate clinical practice. Where specific problems arise in medical practice that are brought to the attention of the FDA, the FDA will bring that information to clinicians in alterations of language regarding specific medications. For instance, a serious side effect will be included in a "black box warning," which would be added to the labeling of some medications. These recommendations are in the form of advice, not strict regulations, and certainly not legally bound judgments. Nonetheless,

in the setting of malpractice cases or other legal complaints, patients and their lawyers often use FDA labeling to criticize clinicians and to argue that poor treatment occurred. Many clinicians are sensitive to this aspect of practice, and are loath to use medications outside of FDA labeling. It is true that the use of medications within FDA labeling gives legal protection to clinicians; it also is true that good medical practice requires treatment with medications outside of FDA labeling, as discussed further below.

Economic factors

Economic factors also are important in influencing legal aspects of psychopharmacology.

These factors include limitations placed by insurance companies and pharmaceutical companies on availability of drugs, and their cost. The availability of generic compounds certainly helps in decision-making, but with new medications it is frequently the case that generic compounds are not available, and costs are high in the early phases of patent life. Insurance companies respond by putting high barriers to approval of medication in their first years on the market. Clinicians are left in a quandary in deciding whether and how to give such medications to patients. The short-term use of samples of medications is insufficient due to the need for long-term treatment if patients respond.

Given these economic restrictions, clinicians can be faced with an ethical problem in that they may feel that the best treatments are new but not allowed to be given to patients. They may provide older cheaper agents, which may cause harms or prove ineffective, with later possible legal consequences. It's wise to document the clinician's preferred treatment choices, irrespective of cost and availability, and then to document insurance or government restrictions on the clinician's options.

Administrative aspects

Besides the above general issues in relation to legal aspects of psychopharmacology, there are some specific administrative issues that deserve attention: these include providing sufficient time for patient appointments, chart documentation, and awareness of the risks involved with complaints to state medical boards as opposed to traditional malpractice lawsuits.

"Legal problems arise when clinician-patient relationships are strained, and a simple factor relevant to that problem is the amount of time given to the appointment."

Regarding administrative matters, a key issue involves brevity of appointments. The "med check" visit, often 10 to 15 minutes in duration, can lead to misunderstanding on the part of both patient and clinician. Insufficient time to explain the rationale for treatment, or to explore diagnosis, can lead to the feeling that decisions are being made too quickly or unscientifically. Brevity of clinical appointments also impairs the ability of clinician and patient to connect interpersonally. The problem of the psychological "transference" always is present in psychiatric care. This problem is exacerbated when appointments are brief and relationships are established in a setting where many misinterpretations can occur. Legal problems arise when clinician-patient relationships are strained, and a simple factor relevant to that problem is the amount of time given to the appointment.

Another key administrative feature that is well known is the matter of chart documentation. The classic teaching is that if it isn't documented, it didn't happen. As far as the state medical boards or lawyers are concerned, as soon as any complaint arises, they will ask for the chart. The clinician can write a letter at that time explaining what may or may not have happened, but such explanations generally are disregarded or are interpreted skeptically. What is written in the chart counts for much more, because it predates the complaint. It is for this reason that one cannot overstate the importance of adequate chart documentation for legal purposes. By stating that this documentation needs to be intended for legal purposes, what is meant here is

that clinicians need to learn that chart documentation is not for themselves, nor for other clinicians, but really should be aimed at future potential legal evaluation. In short, clinicians should write as if lawyers or state board staff would read the chart, not as if other clinicians would read the chart. Obviously, the original intention of medical charts was for communication between clinicians, and this remains the case to some extent. It is fair to say, though, that in these days, the legal use of medical charts is their most important use. Clinicians should adjust their documentation accordingly. The chart is not meant primarily to provide medical information to other clinicians, but rather to demonstrate that the treating clinician is providing adequate care.

This demonstration requires some expression of the rationale for decision-making regarding treatments, and consideration of alternative treatments and alternative aspects for diagnostic judgments. Any potentially serious side effects should be documented in some way, even if briefly.

Off-label treatment

As noted above, FDA labeling is a key issue. Many clinicians give medications mainly when they have FDA indications for specific diagnosis, and rarely if ever make diagnoses in any other way than the method accepted by the FDA. Drugs rarely are prescribed off-label. The problem with this approach is that it limits practice, at least in contemporary psychiatry, solely to features that are promulgated by the pharmaceutical industry. This outcome is the case because FDA labeling is intended primarily for the purposes of

pharmaceutical marketing. Put another way, FDA indications exist only because some pharmaceutical companies make the economic judgment that it would make sense to conduct certain studies on certain indications and then to market those treatments to clinicians. These comments are not intended to deny that such indications or treatments might be valid, but rather to suggest that if practice is limited primarily to those treatments and indications, then clinical practice would be limited to whatever the pharmaceutical industry felt was worthwhile.

Since those judgments are primarily economic rather than clinical, such clinical practice would

"FDA indications exist only because some pharmaceutical companies make the economic judgment that it would make sense to conduct certain studies on certain indications and then to market those treatments to clinicians."

ignore many aspects of care that have no economic value, such as the use of generic treatments, or the use of diagnoses for which no treatment has yet been

developed, or the application of creativity in clinical practice leading to innovation that may produce future FDA indications for treatments originally developed for other purposes. Clinicians can go too far in the direction of innovation, using medications in ways that are idiosyncratic, but this danger is no worse than slavishly following FDA indications.

Many clinicians take the super conservative FDA-indication approach to treatment on the grounds that they will be protected legally. Any legal complaints against them will be weak if they can show that they simply followed FDA guidelines. This is true generally, but this approach veers too far in the direction of defensive medicine in a pejorative sense, and puts too little emphasis on

the need to provide the best care possible to patients.

In sum, there needs to be a balance between self-preservation and the patient's best interest. Clinicians shouldn't ignore their own self-preservation, and they should take steps to protect themselves, including refusing to treat certain patients or terminating care. At the same time, they shouldn't go too far in the direction of excessive defensive medicine, and shouldn't practice solely based on FDA labeling and guidelines. Some level of clinical creativity and innovation is justifiable, within the constraints not only of FDA labeling but also of current

scientific knowledge, as well as with attention to staying sufficiently near the standard of care so as to protect oneself legally.

The PL Bottom Line

- Clinicians can't ignore their self-preservation, and need to attend to legal risks in practice.
- Among relevant factors, brief appointments increase legal risks.
- Clinicians shouldn't limit themselves to FDA labeling, which are intended to regulate pharmaceutical companies, not clinical practice.

PL Reflection

In his last book, Oliver Sacks discusses the fragmentation at the stage of science that follows pure description:

"...the fragments must somehow, sometime, be gathered together and presented once more as a coherent whole. This requires an understanding of determinants at every level, from the neurophysiological to the psychological to the sociological -- and of their continuous intricate interaction."

Then he adds this footnote:

"A somewhat similar sequence has occurred in 'medical' psychiatry. If one looks at the charts of patients institutionalized in asylums and state hospitals in the 1920's and 1930's, one finds extremely detailed clinical and phenomenological observations, often embedded in narratives of an almost novelistic richness and density (as in the classical descriptions of Kraepelin and others at the turn of the century. With the institution of rigid diagnostic criteria and manuals (the Diagnostic and Statistical Manuals, or DSMs) this richness and detail and phenomenological openness have disappeared, and one finds instead meager notes that give no real picture of the patient or his world but reduce him and his disease to a list of 'major' and 'minor' diagnostic criteria. Present-day psychiatric charts in hospitals are almost completely devoid of the depth and density of information one finds in the older charts and will be of little use in helping us to bring about the synthesis of neuroscience with psychiatric knowledge that we so need. The 'old' case histories and charts, however, will remain invaluable.

Oliver Sacks
The River of Consciousness

PL thanks Dr. Richard Berlin for offering this reflection

Current Study of the Month: *All antidepressants work!?*

A. Cipriani et al, Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; 391:1357–1366

An example of abuse of meta-analysis

It is common these days for the most prestigious medical journals, like the *Lancet*, to publish huge “network” meta-analyses, with resulting high levels of attention to the publication. This article is produced by the Oxford University psychiatry department’s very active meta-analysis research group. That group of researchers has published many meta-analyses, and the entire activity of a central core of those researchers is devoted to meta-analysis. This paper seeks to summarize the whole antidepressant literature in so-called major depressive disorder (MDD), and it concludes that all antidepressant work! They are all more effective than placebo.

It also claims some differences between agents.

“...network meta-analysis provides invalid results as it is used in this kind of psychiatric treatment research...”

A PL reader requested an analysis of this study, which is provided here. But before doing so, it is important to note that the key feature to analyzing this study is to understand the concept of meta-analysis, and even more, to understand the concept of “network” meta-analysis. A specific discussion of the meaning, strengths, and limits of meta-analysis - and network meta-analysis in particular - is provided in the accompanying *Statistical Corner* column.

On reading that column, readers will appreciate why PL feels that network meta-analysis provides invalid results as it is used in this kind of psychiatric treatment research. This viewpoint is not shared, obviously, by peer reviewers and editors at major journals such as the *Lancet*, which PL readers should take into account. This need

not mean that the *Lancet* is right, and PL wrong, or vice versa. Readers should adjudicate the issue as best as they can based on understanding the concepts involved. The *Statistical Corner* section this month tries to provide that explanation.

We’ll return to the statistical issues, but first let’s just report the basic findings of the meta-analysis:

The authors looked at 522 antidepressant versus placebo randomized clinical trials in MDD. In total, 21 drugs were examined, and the overall sample exceeded 100,000 patients. Overall, all

antidepressants were more effective than placebo, and in the “network” analysis (see below), the authors report the lowest direct efficacy (with an odds ratio, OR of 1.36) for reboxetine, and the highest efficacy (with an OR of 2.13) for the tricyclic antidepressant amitriptyline. On side effects, most agents had similar dropout rates versus placebo, with the exception of agomelatine and fluoxetine, which were the only two agents with lower dropout rates than placebo.

In comparisons between drugs, the authors claimed that some agents (agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine) were more effective than others (fluoxetine, fluvoxamine, reboxetine, and trazodone).

If these results were accepted at face value, we would conclude that clinicians should feel

confident that all antidepressants are effective in MDD in general, and they would lean towards the agents listed above that were “more” effective, and against those that were “less” effective.

But PL doesn’t accept these results at face value.

On the positive side, the authors included much unpublished data (52% of all the studies), and their results are not limited to or mostly influenced by, the published literature, which is known to be markedly biased in favor of antidepressant drug efficacy (this is because pharmaceutical companies usually have not published negative studies of antidepressants).

That’s the main positive in the study; turning to its many problems:

Nowhere in this dense and detailed paper did the authors report the absolute effect size of benefit with antidepressants on the depression rating scales used. They provide odds ratios, which are relative effect sizes over placebo. So a drug might be 50% better (an OR of 1.50), but this could be a difference between 2 points with drug and 3 points with placebo on a depression rating scale (a tiny and clinically meaningless effect), or it could be a difference between 20 points with drug and 30 points with drug on the scale (a huge and clinically meaningful effect). In other words, how much better did patients get?

One has to turn to the 289 page appendix to answer this question. On page 150, the authors report what we want: what was the actual difference between drugs and placebo, before and after treatment, on the depression rating scales? The result is reported as a standardized mean difference, which means that the actual scores are

“... 86% (18 /21) of antidepressants have clearly small effect sizes that are not clinically meaningful....”

divided by standard deviation. This allows studies with different scales to be compared directly. This effect size often is called “Cohen’s d” and it is a simple way to compare the absolute benefit seen. A general rule of thumb with Cohen’s d is that a score of 0 to 0.25 is small to no effect, 0.25–0.50 is a mild benefit, 0.5–1 is a moderate to large benefit, and above 1.0 is a huge benefit. Some hold that a Cohen’s d of 0.5 or larger is the threshold for clinically meaningful benefit.

In this network meta-analysis on page 150 of the appendix, the smallest benefit was 0.17 with reboxetine and the largest was 0.48 with amitriptyline. For some reason, the authors didn’t provide a summary number that combines all the antidepressants. This is unfortunate, because it would have provided a direct comparison to other prior meta-analyses, which generally found an overall rate of benefit of about 0.30 on Cohen’s d. This is a mild benefit, and it is below the 0.5 threshold for clinically meaningful benefit, as discussed on the PL website.

But this analysis didn’t provide an overall number. It is notable though that of the 21 antidepressants listed on page 150, 13 agents have effect sizes of less than 0.30. Five agents have effect sizes of 0.30–0.33. In other words, 86% (18 /21) of antidepressants have clearly small effect sizes that are not clinically meaningful. Interestingly, the three agents at the higher end of the effect sizes are among the most noradrenergic agents included in the study (mirtazapine and duloxetine had effect sizes of 0.37 and amitriptyline was 0.48). It’s also worth noting that this study included only two tricyclic antidepressants, clomipramine (effect size of 0.33) and amitriptyline. Perhaps a more clear conclusion

than anything else is the old well-proven fact that the tricyclic antidepressants are more effective than newer agents. (There were no MAOIs in this meta-analysis).

The main point to conclude from the above description is that almost all antidepressants had small, clinically meaningless benefits. And no agent, not one of them, exceed the threshold of a Cohen's d effect size of 0.50 or greater, which can be considered clinically meaningful benefit.

In short, one has to go to page 150 of the appendix to find the real result of all this effort: *This meta-analysis confirms the results of prior meta-analyses that find that antidepressants have small overall effects in "MDD," and do not provide major clinical benefit in general.*

This conclusion puts aside the more important issue of the scientific validity of the MDD concept itself, as discussed in prior PL issues.

Because of the concern that PL has regarding the validity of "network" meta-analysis, one can ask the question how the results look with traditional meta-analysis, as described below. The authors report those traditional meta-analytic results too, though they don't provide any pleasant figures, but rather a busy appendix table on page 142.

There the Cohen's d standardized mean difference effect sizes range from a low of 0.19 to a high of 0.62 with amitriptyline. Now we see that amitriptyline exceeds the clinically meaningful threshold of 0.50, with a traditional meta-analytic method, which PL considers more valid. No other drug does so, with the closest second place being fluvoxamine with a p-value of 0.44.

Looking at all the agents, 10 drugs have p-values that are less than 0.30, and thus very small and clinically meaningless. 4 agents have effect sizes from 0.30 to 0.34. Thus 74% (14/19) of antidepressants clearly have little or no clinically important benefit in this analysis (for some reason no data are provided in this table of traditional meta-analysis with two drugs). Four drugs have effects sizes of 0.37-0.44, and as noted, one agent exceeds the 0.50 threshold (amitriptyline).

The "network" analysis makes direct comparisons of agents, which is meaningless scientifically, for the reasons given in the Statistical Corner. But even if one wanted to believe those claims that some agents are "better" than others, one has to appreciate those claims in the context of the overall limited benefits seen with all agents. In other words, one would have to say that these antidepressants have a small amount of benefit, which usually is not clinically meaningful. And, within that small amount of clinically meaningless benefit, this drug is "better" than that one. Such claims aren't important clinically.

The only clear take-away from this analysis - besides confirming the prior analyses that antidepressants aren't very effective - is that amitriptyline is the most effective antidepressant tested, and apparently the only one with clinically meaningful benefit. That's it.

The PL Bottom Line

- This "network" meta-analysis is scientifically invalid in its comparisons between agents.

- Its main finding, though not reported in the main paper, is that most antidepressants have small benefits that are not clinically meaningful.
- The only agent with the largest benefit, which likely was clinically meaningful, was amitriptyline.
- The overall results, to the extent they are valid, may support using noradrenergic agents in general, and more specifically, support the idea that older antidepressants from the tricyclic era are more effective than newer agents.

Statistical Corner

What is “network” meta-analysis and why is it wrong?

Watch “March madness” college basketball

In the United States, college basketball is very popular. Teams play each other in the regular season, followed by a playoff tournament in the spring, colloquially referred to as “March Madness.” Teams with the best record have the highest ranking (1st seed, 2nd seed, etc) and teams with lower records have lower rankings (down to 16th seed). Every year there are upsets, and many fans try to predict who will win in each phase of the tournament with varying degrees of success. These guesses, often involving some betting with money, is called “brackets.” There never has been a perfect bracket in recent years, meaning choosing all the winners correctly. This is because teams with better records and higher seeding regularly lose to teams with worse records. Anyone can win any single game.

Often these teams have faced each other in the regular season, and one team that won in the regular season will lose to the same team in the

playoff. For instance, in the regular season, suppose Duke beat Kansas, it will be common to see that Kansas can beat Duke in the playoff. In short, the playoffs are unpredictable: better teams often lose to worse teams, and the same team may lose to another team it had beaten previously.

Now imagine this: Suppose Duke beats Kansas, and Kansas beats Michigan, would it be guaranteed that Duke would beat Michigan?

This is the assumption of “network” meta-analysis. The claim is that if Prozac is better than placebo by 5 points, and Paxil is better than placebo by 3 points, then Prozac is better than Paxil. This assumption seems logical, but it’s false, just as would be the claim that Duke should beat Michigan. Logic doesn’t translate to reality.

Let’s back up: the assumption is part of transitive logic dating back to the Greeks: If $a > b$, and $b > c$, then $a > c$. This is true for numbers, but it isn’t true outside of abstract logic and mathematics. It doesn’t apply to physical reality. College basketball is its disproof.

One reason it won’t work is that the Prozac studies might have more benefit than placebo for reasons having to do with the study: perhaps there was a lower placebo response because the investigators were more experienced, or there were fewer sites, or the raters were better trained (all factors which reduce placebo responses). These factors would have nothing to do with intrinsically better prozac response. Conversely, maybe the Paxil studies were done poorly, with inexperienced raters and sites which inflated placebo responses. Maybe the patients were more ill in the Paxil study, and thus more resistant to treatment. Maybe the patients were misdiagnosed more in the Paxil study, or drank more alcohol, or were more noncompliant in general. All these factors can differ between the

drug trials, called “heterogeneity,” and it’s the same concept as confounding bias, discussed previously in the April 2015 PL issue.

So “network” meta-analysis suffers from added assumptions that studies are all the same, which just isn’t true, and thus it magnifies the inherent weakness of meta-analysis in general, namely that it’s prone to confounding bias, and can be invalid.

Let’s turn to a general discussion of meta-analysis.

Meta-analysis defined

The rationale for meta-analysis is to provide some systematic way of putting together all the scientific literature on a specific topic. *Meta-analysis represents an observational study of studies.* In other words, one tries to combine the results of many different studies into one summary measure.

Apples and oranges

Meta-analysis weights studies by their samples sizes, but in addition, meta-analysis corrects for the variability of the data (some studies have smaller standard deviations, and thus their results are more precise and reliable). The problem still remains that studies differ from each other, the problem of “heterogeneity” (sometimes called the “apples and oranges” problem), which reintroduces confounding bias when the actual results are combined. The main attempts to deal with this problem in meta-analysis are the same as in observational studies. (Randomization is not an option because one cannot randomize studies, only patients within a study). One option is to exclude certain confounding factors through strict inclusion criteria. For instance, a meta-analysis

“Meta-analysis represents an observational study of studies.”

may only include women, and thus gender is not a confounder; or perhaps a meta-analysis would be limited to the elderly, thus excluding confounding by younger age. Often, meta-analyses are limited to randomized clinical trials (RCTs) only, as in the Cochrane Collaboration, with the idea being that patient samples will be less heterogeneous in the highly controlled setting of RCTs as opposed to observational studies.

Nonetheless, given that meta-analysis itself is an observational study, it is important to realize that the benefits of randomization are lost. Often readers may not realize this point, and thus it may seem that a meta-analysis of 10 RCTs is more meaningful than each RCT alone. However, each large well conducted RCT is basically free of confounding bias, while no meta-analysis is completely free of confounding bias. The most meaningful findings are when individual RCTs and the overall meta-analysis point in the same direction.

Meta-analysis as interpretation

Ultimately, meta-analysis isn’t the simple quantitative exercise that it may appear to be, and that some of its aficionados appear to believe is the case. It involves many interpretive judgments, much more than in the usual application of statistical concepts to a single clinical trial. Its real danger, then, is that it can put an end to discussion, based on biased interpretations cloaked with quantitative authority. Meta-analysis can clarify, and it can obfuscate. By choosing one’s inclusion and exclusion criteria carefully, one can still prove whatever point one wishes. Sometimes meta-analyses of the same topic, published by different researchers, directly

conflict with each other. Meta-analysis is a tool, not an answer. We should not let this method control us, doing meta-analyses willy-nilly on any and all topics (as unfortunately appears to be the habit of some researchers), but rather cautiously and selectively where the evidence seems amenable to this kind of methodology.

Origins

It's an interesting fact that meta-analysis is the product of psychiatry. It was developed specifically to refute a critique, made in the 1960s by the irrepressible psychologist Hans Eysenck, that psychotherapies (mainly psychoanalytic) were ineffective. Meta-analysis is a useful concept, if used appropriately, but it is now being abused, so PL will give Eysenck the last word, from a 1994 paper which is among his last writings.

Wrote Eysenck: "Rutherford once pointed out that when you needed statistics to make your results significant, you would be better off doing a

better experiment. Meta-analyses are often used to recover something from poorly designed studies, studies of insufficient statistical power, studies that give erratic results, and those resulting in apparent contradictions. Occasionally, meta-analysis does give worthwhile results, but all too often it is subject to methodological criticisms....Systematic reviews range all the way from highly subjective "traditional" methods to computer-like, completely objective counts of estimates of effect size over all published (and often unpublished) material regardless of quality. Neither extreme seems desirable. There cannot be one best method for fields of study so diverse as those for which meta-analysis has been used. If a medical treatment has an effect so recondite and obscure as to require meta-analysis to establish it, I would not be happy to have it used on me. It would seem better to improve the treatment, and the theory underlying the treatment."

PL Reflection

Exercising the right of occasional suppression and slight modification, it is truly absurd to see how plastic a limited number of observations become, in the hands of men with preconceived ideas.

Francis Galton
1863

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THE PSYCHIATRY LETTER

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What is "atypical" depression?

And a message on the future of PL

This month's special issue addresses the concept of "atypical" depression. The PL viewpoint is that the concept is not meaningful scientifically, but rather reflects a number of other depressive subtypes, like neurotic and mixed depression.

The Study of the Month examines a new study that claims no benefit with lithium in the drinking water for dementia. The PL critique finds the study to be wrong.

The historical corner listens to Freud's thoughts on war given during the First World War, with an ear for its long-term relevance.

The Curbside Consult is about an unusual case of rapid-cycling manic-depressive illness.

As always, CME credits are available for this and all prior PL issues online.

Please note a message on the future of PL in the special message that follows this introduction. I announce there that PL will stop production of monthly issues at the end of this calendar year. The PL website will remain available and new monthly posts on new studies will continue to be posted. Further e-books will be prepared from past PL issues, and made available for current and future readers.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

A special message on the future of PL

Monthly issues will end in 2018. The website will continue.

PL would like to announce to its readers that the December 2018 issue will be the final monthly issue of PL. After that date, PL will be available on its website as will be described below, and no new monthly full issues will be produced. PL will close to new subscriptions and to renewal or prior subscriptions beginning in June 2018. All prescriptions that have renewed in 2018 will remain in effect until the end of the calendar year. Remaining months will be pro-rated if requested or subscribers will have the option of receiving a complimentary free e-book as an alternative to the pro-rated refund.

This change is happening after 4 years of monthly production of PL for a number of reasons. The most important reason for the change is that the PL editor feels that he has provided the material that he wished to provide to clinicians. From this point forward, as regards the Special Article material that represents the core of the clinical content of PL, much that would be said would be repetitive and refer to prior PL issues. 4 years of monthly material has produced a clinical core of thinking which is now available to all current PL subscribers. Repetition of that material would seem to be an inefficient way to teach it.

Rather, the alternative approach that will be taken will be to organize the 4 years of PL content into e-books, so that they will be more easily accessible. The plan will be to organize e-books of special articles by content, and to provide new e-books of other connected topics, such as the drugs of the month, or classic articles, or current articles that address similar topics. As a thank you to prior subscribers, PL will make one e-book available complimentary. For new visitors to the PL website, e-books will be available for sale.

Further, past PL material will be made available freely on the website for future visitors, beginning January 2019. The purpose of making this material free to all readers is to maximize its influence on clinicians and the public. PL subscribers have been able to have access to this material until now, but in the future it makes sense to give access to everyone in indexed form. As noted, e-books will still be for sale as a more organized mechanism of spreading PL content.

Finally, from January 2019, two key aspects of PL will remain accessible to all readers, again complimentary. First, all readers will be able to ask questions and request input on Curbside Consults. The PL editor will respond to as many questions and consults as feasible on a monthly basis. Second, the PL editor will continue to comment on new research studies on a monthly or bimonthly basis. So those two aspects of the PL newsletter will live on, but they will do so as part of the PL website, rather than as a monthly newsletter issue.

Lastly, another resource that will be available as the monthly PL newsletter ends is a new textbook authored by the PL editor, to be published at the end of 2018 by Oxford University Press. Titled "Clinical Psychopharmacology: Principles and Practice," this new textbook includes a number of essays published in PL, organized in the context of a comprehensive textbook of psychopharmacology. It is another way that PL readers will be able to access material in past PL issues, as well as have access to other new content. The textbook represents a complete description of the approach to psychiatry that is taken in PL.

When PL was begun 4 years ago, the editor had some ideas he wanted to share with the clinical

community. It has been a wonderful experience to have the kind of positive feedback that has occurred in the past four years. One benefit of PL has been the ability to connect to clinicians all over the United States and all over the world. Such a connection would be very difficult to achieve in any other way. The goal of PL was to make that connection, and the editor is very thankful that he has been able to do it.

This connection need not end with the final monthly issue. It can and should continue with the PL website, which will not go away, which will become free to all, and which will continue to expand with new posts on new studies and with continued interaction with readers on clinical cases and questions. E-books will become

available for the first time and can be another important resource on the new website.

PL is changing because it has accomplished some of the goals it set out to achieve, and now it is shifting to other goals. We hope that current PL subscribers will continue to be avid followers of the PL website, will use its e-books, and will study the new textbook that grows in part out of the PL experience.

The editor would like to thank all of you, the current PL subscription community, and invite you to remain involved with the PL website in the years to come.

For now, there is still half a year of PL monthly issues to read and the PL editors hope you continue to enjoy those issues.

PL Reflection

Research opportunities in psychiatry have proliferated astronomically since I was a young man, when incentives were few and training non-existent. Of course, opportunities have always existed, because fruitful research depends far more on the seeing eye and the questing mind than on any other factor. It is an adventure in discovery. Each one of us has the opportunity of expanding the bounds of human knowledge. Whatever we find ourselves in, whether it be the apparent backwater of a country mental hospital or the research department of a teaching hospital, the opportunities are there to be seized.

But my experience has been that intellectual curiosity, a hunger for new knowledge for its own sake, is a relatively uncommon quality. Most of us, including many highly intelligent and useful citizens, have an inescapable tendency to accept things as they are. We are content with present knowledge. We often absorb it in vast quantities and make skillful use of it, but yet have no inclination to take the initiative in extending its bounds.

John Cade

Presidential Address, Australian and New Zealand Society of Psychiatrists, 1970

Special Article: “Atypical” depression and other depression subtypes

Reconceptualizing DSM concepts

Depression subtypes: DSM and non-DSM

The main depressive subtypes in the DSM system in the past have been “typical,” “atypical,” “psychotic,” and “melancholic.” DSM-5 has added “mixed” and “anxious” subtypes. The PL view is that these subtypes include some that are valid scientifically and some that are not. The PL perspective focuses on four subtypes: melancholic, mixed, pure, and neurotic. The DSM system uses different terms to avoid the phrase “neurotic.” It also has tended to avoid the concept of “mixed” depression, until DSM-5. By avoiding the neurotic and mixed concepts, DSM-III and DSM-IV used

the phrase “atypical” to capture some of the same characteristics that are typical for neurotic and mixed depressive states. In this CME article, PL will try to explain how the atypical depression concept is a conglomeration of other depressive subtypes, and not valid in itself.

The role of anxiety

The beginning of a critique begins with what we mean by typical. In the DSM tradition, typical depression involved decreased sleep and appetite, while atypical depression involved increased sleep and appetite. Further, atypical depression often was seen as involving more mood lability and anxiety. When one thinks about the PL subtypes, one sees that mood lability is a hallmark of mixed depression (depression with manic symptoms), and anxiety is present in mixed depression as well, to a severe degree and episodically as part of marked psychomotor agitation. Further, anxiety

is central to neurotic depression, though in a different way than in mixed states. In neurotic depression, there is no psychomotor agitation, but patients are constantly worried and nervous, to a mild to moderate degree. In other words, anxiety is present in both mixed depression and neurotic depression, but in the former it is severe and episodic, while in the latter it is mild to moderate and chronic.

The atypical depression concept conglomerates the concomitant anxiety seen in the mixed and neurotic subtypes, and it also combines those patients with those who have mood lability as part of mixed states.

“The atypical depression concept conglomerates the concomitant anxiety seen in the mixed and neurotic subtypes.”

On the other neurovegetative symptoms, the diagnostic literature does not show that they separate out as the DSM subtypes claim. In other words, decreased sleep and appetite don’t go together consistently, nor do increased sleep and appetite. Sometimes they do, but it is common to see opposite states, i.e., decreased sleep with increased appetite, or increased sleep with decreased appetite.

Other DSM subtypes

The other DSM subtypes have varied relevance. The “psychotic” depression subtype is not a separate disease but rather is diagnostically nonspecific. It can happen in most other subtypes: in other words, one can have mixed depression with psychosis, or not; or melancholia with psychosis, or not; or pure depression (neither mixed nor melancholic) with psychosis, or not. The only subtype which is not psychotic in

general is the neurotic depression subtype, mainly because that subtype is mild by definition, while psychosis is a severe state by definition. (One might have paranoid ideation in a mild depression, but not full delusions).

Treatment effects

Turning to treatment, it often is claimed that atypical depression may be valid because of studies which claim differential treatment response. It is held that monoamine oxidase inhibitors (MAOIs) are more effective than tricyclic antidepressants (TCAs) or serotonin reuptake inhibitors (SRIs) in atypical depression. But this claim is not diagnostically specific, since MAOIs are more effective than TCAs or SRIs in almost any kind of depression, including melancholia or pure or typical depressive definitions.

"If the concept of atypical depression is invalid, so is the concept of "typical" depression."

"Comorbidities"

Some claim that atypical depression is more common in borderline personality. But this is another example of DSM legislating comorbidity. Since mood lability is defined to be part of atypical depression as well as borderline personality, of course they would be seen as co-occurring. If the concept of mixed depression is accepted, then much of what is called borderline personality based on mood lability and unstable relationships would be reconceptualized as mixed depression. (This would contrast with clinical features that are more specific to borderline personality, like sexual trauma and self-cutting).

Typical or pure?

If the concept of atypical depression is invalid, so is the concept of "typical" depression, as DSM defines it. In the PL view, the neurovegetative symptoms of sleep and appetite don't define a depressive subtype, but rather psychomotor activity does (increased in mixed depression and decreased in melancholia). Further, anxiety defines a depressive subtype, combined with severity and course of illness, such that mild to moderate chronic anxiety defines neurotic depression. The analogy to "typical" depression is better termed "pure" to contrast with mixed, melancholic, or anxious. In other words, if depression occurs without anxiety and without psychomotor extremes, but otherwise all the core features are present (sad mood, low interest and energy, suicidality), then the term "pure" depression can capture the clinical picture. This term allows us to avoid the typical versus atypical distinction which is not well-validated scientifically.

The PL Bottom Line

- "Atypical" depression is a conglomeration of features of mixed depression and neurotic depression.
- Most DSM depression subtypes are not valid scientifically.
- The "typical" versus "atypical" distinction is not as clean and clear as the "pure" versus "mixed" versus "neurotic" depression distinctions.
- Case examples provided include mistreatment of antidepressant-induced mania and lamotrigine related Stevens Johnson syndrome.
- Clinicians need to protect themselves while attending to their patients' needs.

Current Study of the Month: *Lithium in the water revisited*

A Mulick et al, Research letter: Association between groundwater lithium and the diagnosis of bipolar disorder and dementia in the United States. JAMA Psychiatry 2018; May 23, published online

How false use of statistics can mislead

In the October 2017 issue of JAMA Psychiatry, Kessing and colleagues published a nationwide analysis in Denmark of the relationship between lithium in the water and dementia prevalence. As context, for the past 40 years, over a dozen other studies have looked at groundwater lithium and its association with suicide, homicide, crime, and other behavioral outcomes. The relationship with suicide prevention was the strongest, and had been demonstrated in multiple randomized clinical trials separately from these epidemiological studies.

The problem with epidemiological studies is that they include many potential confounding factors, such as other causes of the outcome in question (suicide, dementia) that cannot be controlled. Some are measurable, like age and gender and geographical residence, but many are not. That's why randomized trials are more valid scientifically, since by randomly assigning subjects to two groups, all potential confounding factors are equalized and cancel each other out, thereby allowing for an inference of causality between the predictor of interest and the outcome being studied.

In the case of the question of lithium and prevention of dementia, there are now multiple RCTs that show benefit in some way, although more studies are needed to be more definitive. This matter has been reviewed in a systematic review.

The idea that lithium can prevent dementia stems from two sources: the extensive animal preclinical

evidence that lithium is neuroprotective, and keeps neurons alive longer; and well-designed observational data from human studies which find a strong correlation between lithium use and decreased dementia rates in patients with mood illnesses.

The Danish study was the first epidemiological study that assessed lithium in the water and risk of dementia. It found that there was an association of higher lithium levels with lower dementia rates. Specifically, the "low" lithium group was defined as 2-5 micrograms/liter, and lower rates of dementia were seen in the "high" lithium group of 15 mcg/liter or higher (Odds ratio 0.83, 95% confidence intervals 0.81-0.85). Comparing these two extremes a benefit of 17% reduction in odds of dementia was seen, as explained above. However, the middle numbers of 5 mcg/L to 15 mcg/L of lithium levels did not differentiate consistently from the low levels. The lowest range of 2-5 mcg/L of lithium is equivalent to almost no lithium available in the diet.

The standard diet involves about 1 mg/d of elemental lithium, which does not all come from water, but much of it comes from food which is grown in soil which contains water. In other words, most of the lithium in human diets comes indirectly from water, not directly. Thus, the areas in Denmark that are almost absent of lithium would produce local food that is very low in lithium. The studies on dementia rates of course don't take into account that people could buy food from other areas of Denmark or the world that would have higher lithium levels.

With all those caveats, the association was seen. Now we can turn to this recent US study.

First, let's point out that the authors of this report had commented already that they were very skeptical about the association of lithium with dementia prevention. For some reason, this idea bothers some people.

The new report is a "Research Letter" not a full article, which means it did not go through rigorous peer review, unlike the Danish study. Also, the new report in the US is based on partial information from limited insurance sources, unlike the study in Denmark which is based on the national health system's complete records for the entire country. Lastly, since most lithium comes from food, not water, the US results could vary also based on the wide range of geographic sources for food in the US (e.g., fruits and vegetables from the West Coast and Florida; meats and eggs from the Midwest).

All that being said, the US report claimed proof of an absence of association with lithium and dementia (as well as bipolar diagnosis rates). The cut-off chosen to compare "high" and "low" lithium was 40 mcg/L, based on a "natural break" in the lithium concentrations in the US. So "high" lithium was considered above 40 mcg/L and "low" lithium was considered below. It isn't surprising then that the mean lithium concentration in the "high" group was 141 mcg/L and in the "low" group was 6 mcg/L.

Refer back to the Danish study, where "high" was > 15 mcg/L and "low" was 2-5 mcg/L. In the US study what is considered "high" is super-high in the Danish database, and what is considered "low" in the US would be medium or even high in the Danish database. In other words, the US database didn't even test the hypothesis that was found in the Danish study, i.e., that dementia rates are high

where lithium is almost completely absent, compared to areas where lithium levels are at their highest. The almost absent lithium levels were not identified and separated out in the US study.

It's also interesting that the US study did find an association between lithium use and lower dementia rates, but that this association went away almost entirely when corrected for a measure of medical care resources (defined as number of hospital beds, physicians, and psychiatrists per population, as well as median household income). All these analyses were done on a county basis (not cities, or directly by subject). One might ask the question whether this statistical correction is valid. If true, it would imply that dementia rates markedly fall if there are a lot of hospitals and doctors and if one is wealthy. This is an interesting claim and observation. Since dementia is untreatable, why would having more access to medical care decrease it? And regarding income, it is found that dementia rates are higher in the high-income countries than low-income countries. ([/www.statista.com/statistics/471354/population-with-dementia-worldwide-by-income-classification/](http://www.statista.com/statistics/471354/population-with-dementia-worldwide-by-income-classification/)) So how could correction for low income reduce dementia rates? Of course, in the context of a minimally reviewed research letter, the authors don't address any of these questions.

Adding on the other study advantages in Denmark (a more systematic clinical assessment in the whole nation, probably less variation in origin of standard foods, more rigorous peer review), the US study can hardly be accepted at face value, much less used to reject the Danish data.

Some colleagues jump to conclusions though, and act as with US study is somehow definitive. An article in Medscape, for instance, cited a

purported expert as saying that “to some degree, we can lay this matter to rest.”

Actually not, if those experts bothered to read the details of the study carefully, and compare it to the Danish study, not to mention the rest of the scientific literature.

PL would emphasize the basic scientific error of making definitive judgments based on one study, ignoring the context of the entire literature. It is relevant that multiple RCTs find some benefit with lithium for improvement of dementia, and that there is a huge animal/preclinical literature on lithium’s neuroprotective effects, and that there is the clinical literature in mood illness.

In short, it is hard to explain why this poorly performed US research letter has been accepted so immediately, in contrast to its much more valid Danish precursor. There is no logical or scientific explanation for such mistaken scientific judgments.

The PL Bottom Line

- This study is poorly performed and interpreted and it does not disprove an association between lithium in the water and lower dementia rates.
- The prior Danish study is more valid and found such an association.

PL Reflection

The older I grow, the more I distrust the familiar doctrine that age brings wisdom.

H. L. Mencken

Historical Corner

Freud on war

PL introduction: In 1915, a year after the outbreak of the First World War, Sigmund Freud wrote an essay, “Thoughts on War and Death.” His own sons had volunteered to join the Austro-Hungarian Empire, allied with Imperial Germany, against France and England. That war was, in retrospect, the end of a century of peace and the beginning of a nearly a century of the most horrible violence in human history. Freud and his contemporaries knew that something terrible had happened. The 19th-century vision of progress and reason and science and democracy had ended, as the civilized nations of Europe turned their new knowledge into the deadliest warfare, including chemical weapons. There was no peace and prosperity, only death and destruction. The shock of the Western world was in the air as Freud decided to write about his thoughts on the subject. Readers today can think back knowing that a second and even more terrible World War would follow, and they might reflect on the continued violence and instability of the world today, even after victory of democracies in those wars and the end of the Cold War. Freud suggests some basic psychological roots for these conflicts between people:

“...In reality, there is no such thing as 'eradicating' evil tendencies. Psychological - or, more strictly speaking, psycho-analytic - investigation shows instead that the deepest essence of human nature consists of instinctual impulses which are of an elementary nature, which are similar in all men and which aim at the satisfaction of certain primal needs. These impulses in themselves are neither good nor bad. We classify them and their expressions in that way, according to their relation to the needs and demands of the human

community. It must be granted that all the impulses which society condemns as evil - let us take as representative the selfish and the cruel ones - are of this primitive kind.....

It is not until all these *vicissitudes to which instinctual impulses are subject* have been surmounted that what we call a person's character is formed, and this, as we know, can only very inadequately be classified as 'good' or 'bad'. A human being is seldom altogether good or bad; he is usually 'good' in one relation and 'bad' in another, or 'good' in certain external circumstances and in others decidedly 'bad'. It is interesting to find that the pre-existence of strong 'bad' impulses in infancy is often the actual condition for an unmistakable inclination towards 'good' in the adult.....

Civilized society, which demands good conduct and does not trouble itself about the instinctual basis of this conduct, has thus won over to obedience a great many people who are not in this following their own natures. Encouraged by this success, society has allowed itself to be misled into tightening the moral standard to the greatest possible degree, and it has thus forced its members into a yet greater estrangement from their instinctual disposition. They are consequently subject to an unceasing suppression of instinct, and the resulting tension betrays itself in the most remarkable phenomena of reaction and compensation.....

We may already derive one consolation from this discussion: our mortification and our painful disillusionment on account of the uncivilized behaviour of our fellow-citizens of the world during this war were unjustified. They were based on an illusion to which we had given way. In reality our fellow-citizens have not sunk so low as

we feared, because they had never risen so high as we believed.....

...it would seem that nations still obey their passions far more readily than their interests. Their interests serve them, at most, as *rationalizations* for their passions; they put forward their interests in order to be able to give reasons for satisfying their passions. It is, to be sure, a mystery why the collective units should in fact despise, hate and detest one another - every nation against every other - and even in times of peace. I cannot tell why that is so. It is just as though when it becomes a question of a number of people, not to say millions, all individual moral acquisitions were obliterated, and only the most primitive, the oldest, the crudest mental attitudes were left. It may be that only later stages in development will be able to make some change in this regrettable state of affairs. But a little more truthfulness and honesty on all sides - in the relations of men to one another and between them and their rulers - should also smooth the way for this transformation".

PL Reflection

The mere knowledge of a fact is pale; but when you come to *realize* your fact, it takes on color. It is all the difference between hearing of a man being stabbed to the heart, and seeing it done.

Mark Twain

Curbside Consult

Questions and cases from you

Question:

I saw a 56-year-old lady today who appeared depressed but narrated a very unusual pattern of symptoms. For the last two years, she has been sleeping for 48-72 hours and then remaining awake for 48-72 hours.

In the time that she is asleep, she does not wake up at all; not even for meals or medications. It is very difficult to wake her up. When she awakens, on the first day she feels heavy in her limbs but that does not last long. She talks a lot (according to her sister) and even talks to herself at times. She may even exhibit some activity such as vacuuming or doing dishes but she does them in an "improper way" moving from one task to another without completing anything.

There is no sexual disinhibition, no elation of mood, no racing thoughts, no overspending or risky behavior. Her sister has only heard her laugh once in the past 2 years. Most of the time, she feels that she is a burden on her family and feels bad for not being able to recover.

There have been three similar episodes in her life. The first was after the birth of her 3rd child. The second and third were not really post-natal. But the family states that this is the worst one.

I have considered bipolar disorder with rapid cycling but am not sure whether there are hypomanic episodes or not.

She has come to me on a combination of valproate, mirtazapine and desvenlafaxine. She has been on the valproate for 7 years.

I just wanted to ask your opinion, as I have not seen a case so far with this regular alternating pattern of sleeping and waking in 3-day cycles stretching over a 2-year period.

PL : This is a unique case, as you note. We can return to the concept of the four validators of diagnosis: symptoms, course, genetics, and treatment. Let's go through them one by one:

Symptoms

She has brief periods of marked reduction in activity and increased sleep. The concept of clinical depression in traditional psychopathology was a *slowing down* of one's thinking, feeling, and movement. These are brief depressive periods.

You might say that she is completely asleep during these 2-3 days. Is that depression? One could reply that it sounds like catatonia: a complete immobilization, in this case associated with sleep as well. Depression merges into catatonia in its extreme states. Thus, one could see these as catatonic depressive periods, alternating with hypomanic states, as described below.

She also has brief periods of notable increase in energy with no sleep at all, increased activity, talking, and distractibility (beginning activities but not ending them). Manic symptoms were defined in traditional psychopathology as a *speeding up* of one's thinking, feeling, and movement. These are brief manic periods.

Course

You ask whether these are "hypomanic" episodes. You are looking for a DSM definition, perhaps, which is four days or longer of multiple manic symptoms, as she has. Her symptoms last 2-3 days. There is no scientific evidence at all to support the DSM cut-off of 4 days or longer. In fact, there are a number of studies which support the 2-3 day

cutoff as more scientifically valid (based on correlating with the other there diagnostic validators of genetics, course, and treatment effects). Thus, her symptoms are consistent with a scientifically defined concept of hypomania. DSM definitions, as noted in PL, are not valid scientifically in many cases. Hypomania is a definite example.

So these are hypomanic episodes. You may then be concerned to call the 2-3 days periods of complete sleep as “depressive” periods. This concern could come on multiple grounds. First, a course criterion that they are not 2 weeks or longer, as required in DSM. Again, this cut-off is arbitrary. Why not one week or ten days? The concern in DSM was about people who only have one or two periods in their entire lifetime of depression. If someone has depressive for 2-3 days once in 80 years, we do not want to diagnose a “mental illness.” But in this case, you have 2-3 days of depression over and over again for 2 years, meaning hundreds of such depressive episodes. They can’t be ignored, and they aren’t normal. Angst has used the term brief recurrent depression to refer to people who have many episodes of depression that last less than 2 weeks in duration. The DSM cut-off is arbitrary; it provides no proof that no episodes can occur which are briefer. In fact, Angst’s work shows that one can validate episodes that least 1 week or so, or even less.

Thus, the PL view would be that we must put DSM aside again, and view these as brief recurrent cyclic depressive and hypomanic states (one can avoid the word “episode” so as not to face DSM duration claims). They are indeed rapid-cycling since hundreds of mood states per year far exceed the minimum official DSM criterion of four or more mood episodes.

Further on course of illness, you note that she has had three prior periods of similar manic and depressive states, with the first being postpartum after her first child. This would bring the age of onset into the typical range for bipolar illness of around the decade of the twenties, assuming that was when her first child was born.

Genetics No information is provided, but if someone in the extended family (aunts, uncles, cousins, nieces, nephews, grandparents) had severe depression or suicide attempts or suicides, such family history would support the view that this illness is a mood illness. Of course, mania or bipolar illness would be more confirmatory even.

Treatment

She has had no benefit for 7 years with valproate. She takes two antidepressants. No full-blown mania is reported to confirm possible bipolar illness on this diagnostic validator. On the other hand, if one were to claim that she had unipolar illness, failure to respond to two antidepressants would argue against that diagnosis.

It is not clear how long she has been on either of the two antidepressants. If it is the case, as is often true, that she has been on one or another antidepressants for most or all of the past seven years, then those agents would act as mood destabilizers, potentially counteracting the benefits of the mood stabilizer, valproate. In that case, one cannot claim that valproate failed, but rather that she never had a full, fair trial of it, which could occur only if she received valproate *without* any concomitant antidepressant. If that’s the case, the primary PL recommendation would be just to taper off the two antidepressants, and see how she does with just valproate alone.

If she has had months or a year or longer on just valproate, without antidepressants, then the problem could be also that rapid-cycling bipolar

illness just does not respond to a single mood stabilizer, as discussed below.

PL recommendations

In either of the above two scenarios regarding antidepressant treatment with valproate, the problem here is that the diagnosis of rapid-cycling bipolar illness has important implications. Even if the word “bipolar” is rejected on DSM grounds, PL would make the diagnosis as rapid-cycling “manic-depressive illness” (MDI), as described on the PL website. Using the MDI terminology in analogy to the research literature on bipolar illness, the most important treatment implications are twofold: First, when rapid-cycling bipolar illness is present, patients do not respond to a single mood stabilizer of any kind (whether lithium or valproate or another anticonvulsant). Second, the only intervention shown to improve rapid-cycling bipolar illness is antidepressant discontinuation. In other words, antidepressants have been shown to cause rapid-cycling, and

rapid-cycling will not improve no matter whatever else is done if antidepressants are not stopped.

Thus, the main PL recommendations are to stop the two antidepressants, and then to continue valproate by itself for 2-4 months to see if the rapid-cycling would slow down off the antidepressants. If there isn’t sufficient improvement, then a second mood stabilizer should be added to valproate, with lithium being the most tolerable and effective. If there still isn’t enough improvement, then a dopamine blocker (like risperidone or lurasidone or asenapine, but preferably not agents that worsen medical morbidity like olanzapine or quetiapine) could be added to one or two mood stabilizers. In all these interventions, 2-4 months are needed to observe gradual slowing of cycling, and antidepressants should remain off the treatment regimen in all occasions. If severe or acute suicidality occurs, ECT could be instituted as an emergency.

PL Reflection

Half of what you'll learn in medical school will be shown to be wrong within five years of your graduation; the trouble is that nobody can tell you which half—so the most important thing to learn is how to learn on your own.

David Sackett

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THE PSYCHIATRY LETTER

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A summer double issue:

Cape Cod Seminar 2018

This month, PL is provided as a longer double issue for the summer. The recently completed Cape Cod summer seminar led to varied and active discussions and debates, which are included in this issue.

The Study of the Month examines the proportion and motivation behind the current misuse of prescribed amphetamines.

The historical corner reviews a classic article about psychiatric education by the 20th-century psychiatrist John Whitehorn.

The Curbside Consult is about a case of gastrointestinal side effects and lithium.

As always, CME credits are available for this and all prior PL issues online.

As noted last month, PL will stop production of monthly issues at the end of this calendar year. The PL website will remain available and new monthly posts on new studies will continue to be posted. Further e-books will be prepared from past PL issues, and made available for current and future readers.

I've received many heart-warming notes from subscribers, and I want to assure you that PL will continue to have a web presence, and that via e-books and continued Curbside Consults and Study of the Month analyses, readers can continue to utilize the resources of PL for their clinical work.

Thank you again for your loyalty to PL.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Cape Cod Seminar 2018:

Discussion and concepts

In the summer Cape Cod seminar series that was just held at the end of June and beginning of July, the PL editor had over a week-long discussion with many clinicians who participated in a course on psychopharmacology, diagnosis, and existential psychotherapies. This article provides a glimpse of some of the discussion and debates that occurred there. Comments from the clinician-participants are followed by discussion provided by the PL editor. Some topics are brief, others are longer.

Audience:

How does a non-psychiatrist clinician engage psychiatrist colleagues when the non-psychiatrist clinician feels that there are some problems with the medications prescribed?

PL:

The question here is presented in the setting where the non-psychiatrist clinician feels that the psychiatrist is prescribing medications in some ineffective or unhelpful way. This perspective may or may not be correct, of course. But there are cases where it could be correct. In such settings, non-psychiatrist clinicians often find that it may be difficult to communicate with their psychiatrist colleagues. One should avoid putting the patient in the middle, as a kind of messenger between clinicians. The best scenario is to talk directly with the psychiatrist. If this is not feasible, then it makes sense to recommend that the patient should get a second or third opinion with other psychiatrists, to whom the non-psychiatrist clinician could present the medication concerns at hand.

"Since antidepressants are ineffective at best and harmful at worst in bipolar illness, they should all be stopped."

Audience:

A 57-year-old female patient with bipolar illness type I is on multiple antidepressants, Adderall, benzodiazepines, and brexpiprazole. She used to respond to lithium, but has been off for ten years due to worsening creatinine. She is near requirement for dialysis. She could not tolerate valproate due to muscle pains. Lamotrigine was ineffective. She has been very depressed for a number of years and is nonfunctional. What do you recommend?

PL:

Since antidepressants are ineffective at best and harmful at worst in bipolar illness, they should all be stopped. This may require some time and effort to taper off SRIs gradually. She may resist coming off Adderall, in which case it can be left for last, but its dose should be reduced at least. Benzodiazepines should be reduced in dose and decreased to just one agent. Brexpiprazole can be continued or later replaced with a different dopamine blocker if needed. She has not received carbamazepine, which would be the main recommendation, in addition to coming off the above agents. Carbamazepine should be given always in its generic slow-release ER formulation, which is tolerated much better than immediate release generic carbamazepine. It will reduce doses of other agents, especially used for kidney disease, so other medications should be adjusted accordingly. If it is not effective or not tolerated, lamotrigine could be retried and it may be effective without antidepressants, in contrast to inefficacy in the past with antidepressants, since the latter are mood-destabilizing agents which

counteract the benefits of mood stabilizers. Further, dopamine blockers could be changed in combination with carbamazepine or lamotrigine; for instance, brexpiprazole could be changed to aripiprazole or lurasidone or asenapine.

Audience:

I work in a prison system and each time a patient is dosed, he has to stand in the medication line, which is time-consuming and sometimes dangerous. Can psychotropic drugs be given less frequently?

PL:

The mechanism of action of a number of the main psychotropic drug classes involves second messengers and signal transduction inside neurons, not neurotransmitters or receptors. In other words, the effects of these agents are intraneuronal, not synaptic. This general statement applies to monoamine agonists

(antidepressants), dopamine blockers, and second messenger modifiers (mood stabilizers). It does not apply to benzodiazepines, which have direct and immediate ion channel effects. That's a reason why benzodiazepines have immediate clinical effects. The other psychotropic drug classes have delayed effects, though, because second messenger and internal protein effects in the neuron take weeks to months to happen. Since this mechanism involves weeks to months inside the brain, it has no relationship to hourly blood level changes. Thus, the belief that drugs need to be dosed multiple times daily to keep a stable blood level is irrelevant to the real weeks to months effects in the brain. On these grounds, once daily dosing should be fine for most drugs. The exception is benzodiazepines where effects are immediate and may need to be dosed

repeatedly with short half-lives, as with alprazolam.

Audience:

The mechanism of action of lithium is unknown. How can we explain it to patients?

PL:

In fact, the mechanism of action of lithium is known. It involves second messengers and intraneuronal signal transduction proteins. It doesn't involve the synaptic neurotransmitters or receptors. For instance, lithium is a PKC inhibitor, a GSK-3 inhibitor, a stimulator of some G-proteins and an inhibitor of other G-proteins. It also inhibits the phosphatidyl-inositol phosphate (PIP) cascade and BCL-2, an apoptotic protein. These multiple signal transduction mechanisms probably underlie the range of mood effects of lithium, with both benefit for depression

and for mania and for prevention of mood episodes. Further, these effects lead to changes in genetic transcription, which lead to alterations in the actual structure of the neuron and its connections. These effects are neuroprotective, and lead to growth and enhanced viability of those neurons. These longer-term effects are thought to underlie the disease-modifying effects of lithium in mood episode prevention, improved course of illness, prevention of suicide, and possibly dementia prevention.

Besides the above discussions, the course involved the presentation of a number of concepts, described below.

Symptom suppression versus disease modification

A key distinction in psychopharmacology is between two basic effects of drugs: symptom improvement versus disease modification. Drugs either are symptomatic or disease-modifying. In fact, the vast majority of psychotropic drugs are symptomatic, without any profound effect on underlying psychiatric diseases. Only a few agents likely are disease-modifying, most prominently lithium, and also probably valproate, carbamazepine, and lamotrigine. What do we mean by disease-modifying? That means that the drugs affect the known pathophysiology of a disease, such as circadian rhythm mechanisms in bipolar illness. Or drugs change the long-term course of the illness, as in preventing any future symptoms or episodes. The research literature was reviewed for antidepressants in major depressive disorder (MDD), and it was concluded that the evidence is not strong to claim that those agents prevent future depressive episodes. In the STAR*D study, SRIs and other antidepressants were found to have a cumulative 97% relapse rate in persons who responded acutely to those agents. In contrast, about 2/3 of patients responded acutely in cumulative effect. So the antidepressants appeared to have much greater short-term than long-term effect. Their effects are symptomatic, not disease-modifying. The same conclusion applies to dopamine blockers in schizophrenia, where they improve short-term psychotic exacerbation symptoms, but they do not improve the long-term course of the chronic psychotic illness.

Before the 1960s and 1970s, prior psychotropic medications were known to be symptomatic. The thought was that the new classes of antidepressants and antipsychotics were different, and in some way more effective. In fact, they have

been proven more effective symptomatically, but they have not proven to be disease-modifying. In that sense, the change with the new psychotropic drugs of the latter 20th century was quantitative not qualitative.

Symptomatic drugs are like acetaminophen for fever or headache. These are not drugs that should be taken continuously for years, but rather intermittently and short-term. The analogy is not insulin for diabetes or statins for cholesterol or antihypertensives. All those interventions are long-term and disease-modifying. In contrast, steroids are short-term symptomatic drugs, which can be life-saving and very helpful, but are not more effective long-term and in fact tend to cause more harm than good if taken longer term. The PL suggestion is that the evidence of benefit for

[new drugs] have been proven more effective symptomatically, but they have not proven to be disease-modifying.”

SRIs and most antidepressants is along the lines of steroids, not insulin or antihypertensive agents.

The same concern would apply for dopamine blockers, with the added complicating factor that there are to date no better options for long-term suppression of symptoms in schizophrenia.

In the course, we observed video interviews of or about key existential psychiatry leaders, specifically Leston Havens, Viktor Frankl, and Rollo May.

Leston Havens video

Leston Havens was a famed psychiatrist and psychoanalyst in the Harvard/Boston area for the second half the 20th century. He trained generations of residents and was viewed as a consummate interviewer and psychotherapist. He taught and worked in the existential psychiatry tradition, in addition to his psychoanalytic training.

The video of Leston Havens involved an interview with a hospitalized patient, and later a discussion between Havens and psychiatric residents who had observed the interview. The video can be found on the excellent website (www.lestonhavensmd.com) devoted to providing free links to multiple videos of Havens' interviews and lectures. PL highly recommends this website to readers. The specific interview observed can be found at <https://www.lestonhavensmd.com/video/session-1/>.

In this interview, Havens talks to a woman who is hospitalized and treated with antipsychotic medications. Her diagnosis is unclear. The interview happened in the mid 1980s, when many patients with abnormal thoughts were diagnosed easily with schizophrenia.

Havens doubts this diagnosis, partly based on his ability to establish a rapport with the patient. In the course of the interview, Havens frequently makes comments and conjectures, to see how the patient responds. He rarely asks questions. It's often unclear where he is going in the interview, partly because he is going nowhere. That's part of the existential approach. There is no goal, whether establishing a diagnosis or testing a hypothesis or theory. The purpose of the interview is to experience what the patient is experiencing, and to establish a rapport, nothing else. Everything else will flow later. The aim of the first interview is to have a second interview.

In his discussion, Havens expands on the theme of psychotherapy as anesthesia. In surgery, a great deal of time is spent in anesthesia and preparation of the area for surgical incision. Much effort is expended in cleaning and detoxifying the surgical area. There is no rush. The surgical incision itself often is a rather simple procedure and quite brief.

"Havens expands on the theme of psychotherapy as anesthesia."

But hours can be spent in preparation. Similarly, much of psychotherapy involves a slow process of psychological anesthesia, of preparing the patient very gradually for the discussion of painful themes. Months even years can pass in the preparation phase. The psychotherapist is gaining the trust of the patient; he is creating a safe place for the therapy to occur. There is no rush, ideally. The process has to go at the pace that the patient's psyche allows. Often, after years, a very simple insight or interpretation can take place, which can be life-changing. But if it had been attempted earlier, before the psychological anesthesia was complete, the patient would have experienced too much pain, and either would have rejected or denied the insight.

Hence you cannot expect much from one interview, as Havens showed here. But you can show the beginning of the process of getting the patient to feel safe, and being able to begin a connection with the patient.

Viktor Frankl video

Viktor Frankl was a Viennese psychiatrist who was a prisoner in the Nazi concentration camps, and survived to write the highest-selling book in psychology, *Man's Search for Meaning*.

In the brief video clip shown at the conference, found at https://www.ted.com/talks/viktor_frankl_youth_in_search_of_meaning, Frankl is speaking in English with a classic Austrian accent to a large apparently American audience in the late 1960s. In entertaining language and demeanor, he focuses on the concept of meaning, which is central to all his work and to his approach to existential psychiatry.

In this video he talks about the basic idea that if you take people as they are, you make them worse. You have to see them as they could be, and

then you help them be better. He uses the analogy of flying an airplane, which he recently had begun to do. His flight instructors told him that he had to aim the plane a little above the horizon for it to go straight. Similarly, in life, he argued, we have to aim a little higher and farther. If we aim straight, we go down. His advice is similar to that of Emerson, who said that if you would hit the mark, you have to aim a little above.

This perspective also was described by the Boston psychiatrist Alfred Marguelis, as the concept of the empathic imagination (which was the title of his book). He made the point that many clinicians think that empathy means trying to connect with the patient's feelings and experiences as they are in the present. Instead, Marguelis thought, we need to imagine how the patient could be, in a better future. We should move the patient forward into that future, not just focus on the present. In a way, we are empathizing with a patient that doesn't yet exist, but which can come into being with the clinician's assistance, but only if the clinician imagines how that patient could be in the future.

One sees how all these existential thinkers - Havens, Marguelis, and Frankl - are future-oriented. Empathy is not about the present and the past alone; it's also about the future; it's perhaps primarily about the future. The present and the past exist only so that we can build a better future. If we don't turn to the future, the present and past become nothing but yokes, preventing anything better.

In short, Frankl and the other thinkers here are optimistic clinicians. They see a better future, even under the worst circumstances, and they seek to create a meaning in the life of the patient based on that better future.

"May emphasizes the concept that many psychotherapies involve a 'gimmick.'"

Rollo May video

Rollo May was the leading existential psychologist in the United States in the latter half of the 20th century. He perhaps can be credited with having the most influence in bringing existential thought to the United States in the mental health professions.

In this brief video clip, found at <https://www.youtube.com/watch?v=Cay743y-Sak>, May is being interviewed by another psychologist in the early 1980s, near the end of his life, as he reflects on the profession of psychotherapy, and how the existential approach fits into this work.

May emphasizes the concept that many psychotherapies involve a "gimmick." The gimmick could be concept x, y, or z - fill in the blank, it doesn't matter. Whatever the gimmick,

the psychotherapy will not have profound impact. The gimmick could be the Oedipus Complex, it could be cognitive behavioral theory, it could be spirituality, meditation, mindfulness, awe, play therapy, EMDR - it doesn't matter. It all fails.

Psychotherapy is all about the relationship between the therapist and the client, May explains, and about exploring their shared human condition, including its saddest and hardest aspects, like illness and death. There's no way around these human dilemmas; they can't be wished away. And there's no theory that makes them better. They can be faced though, honestly and forthrightly, with a sympathetic therapist who also struggles with the same human problems.

May's existential psychotherapy is less future oriented and perhaps less optimistic than Frankl. It's more empathic with present struggles and

pain, and focused on the natural anxieties of living.

A commentator on YouTube noted on this video: "Oh snap. CBT got served." Given how popular and omnipresent CBT is these days, it may be useful to think about ways it can fall short. This isn't to say that CBT isn't useful within its scope, but May reminds us that CBT and other such therapies have a limited scope. They don't lead generally to life-altering profound changes. They don't address the universal human dilemmas of existential suffering and loss.

A First-Rate Madness

The PL editor ended the conference with a discussion of the basic concepts in the book with the above title. The idea is

that there are positive aspects to some psychiatric illnesses, specifically manic-depressive illness. As Frankl and May and Havens often repeated, clinicians tend to focus on the negative and ignore the positive. They focus on psychopathology, and don't emphasize a person's strengths. They view experiences as symptoms, which are to be treated away, rather than accomplishments, as Frankl put it.

In the case of manic-depressive illness, a disease is present, and it has symptoms. But those

"...symptoms and illnesses are not merely harmful, but in some ways beneficial."

symptoms aren't purely negative. They have positive benefits in some persons and for some settings. Depression is associated with increased realism about the environment and enhanced empathy toward others. Mania is associated with more creativity and resilience to traumatic stress. Many great historical leaders - political, business, and military - can be shown to have had manic and depressive symptoms, and often severely so with full-blown clinical manic and/or depressive episodes.

These observations can be understood within the existential psychiatry tradition, reminding us that

symptoms and illnesses are not merely harmful but in some ways beneficial. Sick patients may even be better off than mentally healthy

persons in many ways. We see a new road to end stigma, not just on moral grounds (it's bad) but on scientific grounds (psychiatric illness is better, in some ways, than mental health). This observation is not simplistic, entailing a belief that there are no harms from psychiatric illnesses, like manic-depression. It simply is negating the opposite view - that there are no benefits from such illnesses. Both harms and benefits exist from psychiatric illness, as with mental health. Again, as Harry Stack Sullivan put it, we are all much more human than otherwise.

PL Reflection

The load of tomorrow, added to that of yesterday, carried today makes the strongest falter. Shut off the future as tightly as the past. No dreams, no visions, no delicious fantasies, no castles in the air....The future is today - there is no tomorrow! The day of a man's salvation is now - the life of the present, today, lived earnestly, intently, without a forward-looking thought, is the only insurance for the future. Let the limit of your horizon be a twenty-four hour circle...Waste of energy, mental distress, nervous worries dog the steps of a man who is anxious about the future. Shut close, then, the grease fore and aft bulkheads, and prepare to cultivate the habit of a life of day-tight compartments....

William Osler, *A Way of Life*, 1913

Current Study of the Month: *Prescription amphetamine misuse and abuse*

W. M. Compton et al, Prevalence and Correlates of Prescription Stimulant Use, Misuse, Use Disorders, and Motivations for Misuse Among Adults in the United States. American Journal of Psychiatry, published online 16 April 2018

Abuse is present and concerning

The use of amphetamines by prescription for purported ADD has been increasing in the United States in the last few decades, not only in children but in adults. It often is claimed that such agents are not abused when prescribed for ADD. The evidence for such claims is limited to small observational studies. It is well known that such agents have been abused whenever available, since their introduction in the world in the 1930s.

In this report, a huge national survey of over 100,000 persons in the US provides the largest treatment database to date on amphetamines in the US.

First, it's important to note that fully 6.6% of the US population is prescribed stimulant medications, mostly amphetamines. That's 16 million American adults.

The supposed adult ADD prevalence rate in the US based on standard epidemiological studies is about 3%. This indicates prescription rate is two-fold the reported prevalence of adult ADD. This fact alone should raise the question of whether these agents are being misused for other purposes. The most common rationale given for using them is to improve attention; hence enhancement of cognitive function, especially among students and those in intellectually active occupations, would be expected.

In this study, of the 6.6% prescribed amphetamines, 1.9% were found to misuse those

agents. That's 29% of those prescribed amphetamines.

Put another way, almost one-third of persons who are prescribed amphetamines misuse them.

How and why? This study found that most of those who misuse amphetamines do so by taking more than they are prescribed, typically by obtaining more of those drugs from family or friends (57% did so). The main rationale given for such misuse was to be more alert or to concentrate better (56%) - in other words, cognitive enhancement.

In short, contrary to common claims, the prescription of amphetamines for conditions such as ADD is associated with misuse and abuse. Such misuse happens in about one-third of adults who are prescribed such agents, commonly for extra cognitive enhancement. Further, amphetamine stimulants are prescribed far more than claims of purported adult ADD would justify.

The PL Bottom Line

- Amphetamine stimulants are misused or abused in about one-third of adults to whom they are prescribed.
- Amphetamine stimulants are prescribed twice as frequently in adults than would be justified by claims of adult ADD prevalence.

Historical Corner - I

Education for uncertainty, 1963

John C. Whitehorn MD

*John C. Whitehorn, "Education for uncertainty,"
Perspectives in Biology and Medicine, 1963;
7:118-123*

PL introduction: John Whitehorn was chairman of the department of psychiatry at Johns Hopkins University in the 1950s and 1960s, succeeding the great Adolf Meyer. Whitehorn was a psychoanalyst, and would later end his career at Harvard and McLean Hospital. He had huge shoes to fill when he succeeded Meyer, but Whitehorn continued Meyer's tradition of a pragmatic attitude towards the profession. In this essay, Whitehorn discusses how to educate psychiatrists and mental health professionals. It's interesting to see how this paper, published half a century ago, repeats many of the complaints and comments one hears this day about the limitations and problems of psychiatric training, such as too much attention to scientific research and too little to clinical acumen. Historical study is useful to remind us which of our current problems are new, and which are perennial.

Here is the bulk of Whitehorn's essay:

"Scientific knowledge and power over disease have grown rapidly in the last half-century. Such knowledge grows with ever-accelerating speed. With this growth there has been heavy emphasis upon science courses in the education of physicians. Science courses have often been taught as a heavy cargo of factual information rather than as a human enterprise; so, along with this "scientific" emphasis in medical education have come some hindrances to the development of clinical judgment and compassionate wisdom in

our physicians....But all of us who have been teachers of physicians have suffered disappointment at the slowness with which many medical students and young physicians attain a practical appreciation and a useful working knowledge of the human factor in illness and health. Impatiently at times we would like to teach such wisdom, fast, but we do not quite know how....

"Science is better symbolized by the question mark, signaling a doubt."

The educational programs generally experienced by the physicians of the past few generations have tended (without our intending it) to inculcate an expectation of certainty of knowledge and a phobic aversion for and intolerance of uncertainty, and the worst offenders have been teachers of science. This has been an error-a stultifying error. To inculcate the expectation of certainty of knowledge

is a serious betrayal of the essence of the scientific movement, which has been the great bold adventure of mankind in recent centuries.

Expressed in terms of punctuation marks, it is not right to symbolize science by the period, which closes a statement with an appearance of utter finality. Science is better symbolized by the question mark, signaling a doubt and a further look. It is the questing, not the finality, which best represents science as a powerful instrument of progress in our profession, and in general.

But how few of our medical students were fortunate enough to be introduced to science as a quest! How many have been forced by dogmatic teachers to accept science as a set of facts!....

Personally and temperamentally, I am opposed to uncertainty, yet challenged by it. Like many others who have spent years in laboratory investigation, I like the definiteness of chemical and physiological methods. Those who limit their responsibilities to

such areas may properly do so, but whoever as a physician takes the responsibility for the care and treatment of patients assumes thereby the responsibility for clinical judgment and for the guidance of living human beings; and the proper discharge of this responsibility requires knowledge of human nature and some skill in the leadership of real living persons. The conscientious physician cannot properly excuse himself from such concerns simply because he has a dislike for the uncertainties involved.

Human reactions are an inherent part of the disease-producing or health producing transactions between the human being and his environment. As we seek to understand more usefully the interactions between the human being and his environment, we must remember that this includes how human beings get along with each other—a prolific source of distress and disability. Probably one-third of the persons who seek medical treatment owe their distress or disability to functional disturbances which might have been avoided by better emotional habits and attitudes in their relationships to other persons; and another third have their illnesses seriously complicated by such emotional and attitudinal factors.

Yet the illusory expectation of certainty in knowledge, fostered by poor educational methods in science courses, has inclined medical students and doctors to fight shy of the human aspects of medicine because, by such false criteria, it seems "unscientific"—meaning unsatisfactorily deterministic and certain. For the thoroughly dogmatized mind this difficulty can, of course, be leaped by the bland assumption of determinism in human action. The same leap brings the dogmatized mind to the corollary position that

[there is an] illusory expectation of certainty in knowledge, fostered by poor educational methods in science courses."

the knowledge of human nature is at present so inadequately "scientific," so-called, that anyone with scientific aspirations should turn away from the human being and devote attention to the more gratifying and comforting areas of more certain knowledge, which is presently available in abundant supply.

The dogmatic assumption of determinism in human behavior, fostered in large part by the sophomoric expectation of certainty in knowledge, has a further pernicious effect in the actual practice of medicine. It inclines the doctor to deal with the patient as if he were a machine, and it blunts his perceptiveness in many experiences which might otherwise teach him better. This tends to set up a caste system, for the conscientious physician does not, of course, act as

if he himself were a mere machine. He puts great effort and study into the process of attaining to wise decision and action, but the patient is not viewed as a comparably responsible person and a partner in the pursuit of health. The patient often feels this caste distinction—feels deeply disparaged and disregarded. This situation is not to be corrected by any educational device which would simply make the physician more keenly sensitive to the patient's suffering. The doctor in the situation is already too kind—too condescendingly kind. The unbalanced expression of kind impulses, when not guided by good sense and human understanding, can be demoralizing.

In what direction should we look for improvement in this situation?.... We may, I think, hope for some improvement also from the humanistic emphasis in the medical education program. There is no magic in those studies called humanistic, but there is potentiality therein for the student's better appreciation of the human

struggle – an appreciation that men cannot struggle without faith and hope, an appreciation of the morale-building power of the shared danger and the shared struggle, an appreciation of the extraordinary human importance of leadership and its many subtle patterns.

Perhaps the greatest benefit of a liberal education is to escape the tyranny of first impressions and of naïve preconceptions – to learn to suspend judgment and action, not indefinitely and vaguely, but long enough and sturdily enough for the orderly review of evidence and the weighing of probabilities and values.

The liberally educated person becomes aware that in any new experience the human being is disposed to fuse his preconceptions with

his first sense-impressions in the form of precipitate conclusions which then seem axiomatic and tend to exclude alternative modes of comprehension. It is humanly difficult to weigh alternatives unless one can cultivate some tolerance of uncertainty.... Frightened and overanxious awareness of uncertainty is of little use, for it hinders the operation of good judgment. The technically trained physician, as distinguished from the educated physician, will, of course, become aware in his own field of the diagnostic risks of snap judgments and the risks of inadequate differential review, but if obsessed by the inner compulsive demand for certainty, he may lack the equanimity to face the uncertainties sensibly; he may try compulsively by the unwise and neurotic multiplication of tests and superfluous instrumentation to achieve the illusion of certainty; and such behavior may in actuality be only a manifestation of another type of superstition, but still a superstition--the superstitious faith in the lab report.

"It is humanly difficult to weigh alternatives unless one can cultivate some tolerance of uncertainty."

Such a physician, technically overburdened but inadequately educated in the human sense, is often inwardly constrained to maintain, in the face of his patients, a pose of certainty, a phony attitude of omniscience, which is likely to evoke in individual patients an uneasy suspicion and distrust.

There is also a tendency for physicians, when organized in professional associations, to present dogmatic, know-it-all attitudes and thereby to generate and to increase public distrust. For example, we have seen the organized medical

profession in the last generation engaged in a conservative, rear-guard opposition to group practice.....

A more reasonable awareness of uncertainty, a less dogmatic clinging to presumed certainties, a greater ability to face uncertainty with equanimity, a more generous and wiser sharing of leadership all these interrelated manifestations of a good education-might have done much to humanize medical leadership in the field of health care. There is much, therefore, to be gained by a more liberalizing type of education for physicians--not the mere requirement of an A.B. degree as a hurdle to clear before getting into medicine, but a continuing humanistic appreciation pervading all phases of medical education....

PL Reflection

Drugs are...the most uncertain element in our art.

William Osler

Psychopathology

Childhood versus Adulthood

Lessons from twin studies

In a classic book, *Genes, Environment, and Psychopathology*, the esteemed psychiatric genetics researchers Kenneth Kendler and Carol Prescott bring together a large body of their research to try to provide some insights into psychopathology. Among the many fascinating observations in this loaded book, they describe some findings (pp 188-191), which PL would like to bring to the attention of readers, regarding the evolution of psychopathology from childhood into adulthood.

This work is based mainly on twin studies. In these studies, identical (monozygotic) twins share all their genes, while fraternal (dizygotic) twins share half their genes. By comparing frequency of psychopathology in monozygotic versus dizygotic twins, researchers can use mathematical models to estimate the amount of both genetic and environmental contributions to causation of psychopathology. Further, those models can divide genes and environment into shared or specific subtypes. Shared environment means those experiences that siblings would share, such as common family environment as well as general cultural influences. Specific environment means those experiences which differ between siblings, such as peer experiences and random or spontaneous life events (e.g., accidents).

The specific section which PL will examine here involves antisocial personality. The aspect of this research that is unique is that Kendler and colleagues asked their twin subject to describe their antisocial behavior in different periods of

"...the genetic contribution to antisocial behavior increased with age. It was lowest in childhood, and highest in adulthood."

their lives: childhood (before age 15), mid to late adolescence (age 15-17), and adulthood (age 18). A limitation to this research is that it was based purely on self-report, and it is retrospective, based on the recall of twin subjects, as opposed to prospective observation.

Allowing for those limitations, some fascinating results were obtained. In childhood, it was found that the genetic contribution to antisocial behavior was 25%. In adolescence, it rose to 35%, and in adulthood it rose more to 45%. In other words, the genetic contribution to antisocial behavior *increased* with age. It was lowest in childhood, and highest in adulthood.

This observation conflicts with many assumptions in psychiatry. Clinicians tend to assume that if psychiatric symptoms or illnesses are observed in childhood, then those conditions might be more genetic, or more biological in some way. It is thought that if an illness, like bipolar disease,

is more severe, it will start earlier in life; if it is less severe, its onset will be delayed into adulthood. These data suggest the reverse, at least for antisocial behavior: this kind of psychopathology seems to be more environmentally influenced in children and adolescents. If it occurs in adults, it seems more driven by genetics. In other words, the genetic antisocial condition pushes through more clearly in adulthood. In childhood, it is less obvious, in the context of more environmental noise.

This twin research also can identify which genetic and environmental components are persistent and which are new. One of the observations was that both genetic and environmental effects change

over time. In other words, given a certain percentage of genetic or environmental effects, it's not always the same genes or environment that influence the results. Different genes cause antisocial behavior, to some extent, in children than in adolescents. Different environmental influences produce antisocial behavior in children versus later in adolescence. In short, even within the genetic or environmental realms, things are changing as the child develops.

Amazingly, the genetic component in adulthood for antisocial behavior is similar in overall percentage as adolescence (35-45%), but there is almost no persistence of the specific genetic contribution. In other words, completely new genes become active in adulthood to produce antisocial behavior, different than the genes which caused such behavior in adolescence.

Among environmental causes, specific environment (accidents and non-shared experiences) overall are more influential than shared environment (family and culture). This observation is found repeatedly in twin studies, conflicting with many of the assumptions of the mental health professions. Clinicians often assume that family matters a great deal for psychopathology: Blaming the mother was a parlor game for decades. Culture is assumed to be very influential. Twin studies suggest otherwise: Peer groups and unique life events seem to matter the most. In this research on antisocial behavior, it became clear that the influence of shared environment (family and culture), to the extent it was present, declined over time. It was more influential in childhood than adulthood. In contrast, genetic influences increased over time, becoming more powerful in adulthood.

"In child psychiatry, the influence of the environment can be seen as more relevant than genetics."

Clinical implications

What can clinicians conclude from this research? Among the conclusions one might draw, some of the following may be reasonable: In child psychiatry, the influence of the environment can be seen as more relevant than genetics. Most of the problems seen in children are not due to genetic diseases of the body, but rather environmental problems. Family is important, but so are peer groups and random life events. In contrast, in adult psychiatry, the influence of the environment is much weaker, while genetic causes gain in strength. The impact of one's family of origin is weaker and weaker with time, as genetics direct the course of psychopathology. Environmental effects are purely specific, short-lived unique triggers of limited consequence.

If one draws an inference, albeit simplistic, that environmental influences should be addressed by environmental means (such as psychotherapies and/or case management and/or public health interventions), while genetic influences should be addressed by biological means (such as medications), then these observations might be another source of evidence to minimize psychotropic medication prescription in children relative to adults. PL is aware that this analogy is not straightforward, and many objections can be raised against it, but neither is it meaningless, and some consideration should be given to at least considering some of its implications.

The PL Bottom Line

- Childhood psychopathology is more influenced by environmental than genetic sources.
- Adult psychopathology is more influenced by genetic than environmental sources.

Historical Corner - II

Psychopharmacology circa 1845

Jean Etienne Dominique Esquirol

PL Introduction: Esquirol was the great successor of Philippe Pinel, the French founder of modern psychiatry. In his classic text, *Mental Maladies*, Esquirol provides an exhaustive description of clinical psychopathology, much of which is consistent with our best knowledge today. In this excerpt (pp 404-412), we read about his approach to treatment. Readers will find the classic approach of purging and blood-letting, but with an awareness of how limited in benefit such approaches were. Pinel and his successors did much to diminish this kind of aggressive treatment in psychiatry, but they still had no other options, and used these approaches too. In reading this excerpt, PL asks clinicians to think about how many of our current medications might, in the long view of history, be seen as similarly limited in benefit.

Excerpt from *Mental Maladies*:

The administration of medicines, properly so regarded, calls for the most careful reflection....The same medicines should not be ordered indiscriminately to all maniacs and during all periods of the malady...We may employ one or two emetics...If indications of plethora are present, we employ and repeat blood-letting. We apply leeches behind the ears, or upon the temples; cupping glasses to the back of the neck; and frequently a small number of leeches to the anus....We must be cautious regarding sanguine evacuations. By enfeebling maniacs, we run the risk of throwing them into dementia. "Bleeding," says Pinel, "is an unusual evacuation, and one which constitutes an epoch in the hospital of the insane (Salpetriere). How numerous are the maniacs we have never lost blood, and been cured;

how many have been bled, and still remain incurable!"

We employ tepid baths, and continue them for... hours...We insist upon the use of cold, diluent and slightly laxative drinks. Lastly, we unload the large intestine by enemata, at first emollient, then purgative.....

[Esquirol goes on to describe much more extreme measures, such as near-drowning, and very rapid rotation in a chair, among other treatments]

Such are the remedial agent which have been signalized as suited to combat mania. We cannot deny that the success attributed to heroic remedies are fare less numerous than the cures obtained by a suitable direction given to the maniacs themselves, and those who serve them, by a proper regimen, and wise expectation; and that it is better to trust to time and the efforts of nature, than to the employment of remedies, often hazardous, rarely useful, and sometimes dangerous.

"...it is better to trust to time and the efforts of nature, than to the employment of remedies..."

Finally, in enumerating the principal medicines proposed, to overcome one of the most formidable of maladies, it will not be supposed that I advise the employment of them all, even successively, in each case of mania. I am to suppose that the well educated physician will here expect only the general indications... Each must make the application of them in individual case, which his wisdom, experiences and discernment may suggest.

Curbside Consult

Questions and cases from you

Question: A 58-year-old male has increasing gastrointestinal symptoms, of severe abdominal pain and bloating, with unclear diagnosis (possibly irritable bowel syndrome). These symptoms have occurred over the past 3 years. He has taken lithium for 25 years, currently on monotherapy of 900 mg/d. His mood had worsened 5 years ago when lithium was decreased to 600 mg/d, but then improved when it was increased again to the current dose. (Current lithium level is 0.9). In the past 3 years, as his gastrointestinal symptoms worsened, his mood also has become worse. He now has periods of low interest and energy and apathy lasting about 1-2 weeks, followed by about one week of feeling normal, followed by another 1-2 weeks of depression. He had a severe manic episode in his 20s leading to hospitalization, and multiple hypomanic episodes over the years, but none in the past 5 years. Otherwise he is medically normal and stable and there are no new major psychosocial stressors. He is compliant with his medications and appointments, and there is no substance abuse or other comorbidities. What would PL recommend regarding treatment?

PL: The patient now has a rapid-cycling course, since he has 1-2 depressive episodes per month. Rapid-cycling is defined as 4 or more episodes yearly, and he has over 20 episodes yearly. It doesn't matter that he doesn't cycle up into manic or hypomanic episodes; he is cycling from normality to depression. Lithium has been proven ineffective for rapid-cycling by itself, as are all agents, including anticonvulsants like valproate or carbamazepine. The BALANCE study shows though that valproate plus lithium is more effective than either alone, and thus combined mood stabilizer treatment likely is the best

approach for rapid-cycling illness. Given the patient's gastrointestinal problems, valproate may not be the best initial choice. Alternatives are carbamazepine, which combines well with lithium, or lamotrigine, and/or dopamine blockers. Among the latter, PL does not recommend those with antidepressant effects, like ziprasidone or brexpiprazole, since antidepressants have been shown to worsen rapid-cycling. Better alternatives would be agents like risperidone or asenapine or possibly aripiprazole. (PL recommends against olanzapine and quetiapine in general given their cardiovascular and diabetic harms, since there are so many other dopamine blockers which don't have those harms.)

In short lithium could be continued and carbamazepine added. Or lithium could be continued and then lamotrigine added, followed by dopamine blockers. Or lithium could be continued and dopamine blockers added directly.

A final thought would be to consider whether lithium could be contributing at all to the gastrointestinal symptoms. The time course doesn't correlate, but over time the body can develop different reactions. It could be that an underlying GI problem has developed, and is now interacting with lithium such that it is worse. One way to test this possibility is to reduce lithium dose gradually to see if GI symptoms improve. If done, it would be important to replace lithium with at least one of the anticonvulsants above, plus adding a dopamine blocker with it, otherwise it's likely that rapid-cycling symptoms would worsen.

Question: Media attention recently has focused on quetiapine (Seroquel) and risk of dementia. What are the risks?

PL: As far as available research, there isn't a clear relationship between quetiapine, or most other dopamine blockers, and dementia. Available reports are observational, and causal judgments can't be made without difficulty. Nonetheless, the FDA has expressed concern about such possible risks. One cannot state that those risks exist or do not exist.

What can be said is that quetiapine is antihistaminic to a marked degree. Strong antihistamine effects in older persons are associated with notable risk of delirium and altered mental status. Such effects can be a problem in hospitals and in other institutional settings, with increased risk of falls, which can be fatal.

So from the PL perspective, the risk of delirium is much more clear cut than the risk of dementia. In either case, PL would agree that it is important to minimize the use of agents like quetiapine in older persons, though less so for dopamine blockade, and more so for other biochemical effects, especially antihistamine and anticholinergic effects, which certainly produce delirium, although any possible increased risk of dementia is unknown and unproven.

PL Reflection

And those who were seen dancing were thought to be insane by those who could not hear the music.

Nietzsche

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THE PSYCHIATRY LETTER

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Savior treatments (ECT, Ketamine, VNS, etc):

Are they really better?

The prior summer double-issue of PL is followed here by a fall double-issue. The main topic in the special article is savior treatments, like ECT, vagus nerve stimulation (VNS), and most recently ketamine. These treatments, often devices as opposed to drugs, have been seen by clinicians as possible saviors for patients who fail to respond to standard medications, especially in severe refractory depression. The special article examines the claims for these treatments and finds them to have less benefit than often is claimed.

The Article of the Month reviews the maintenance efficacy of ECT and the claim that it is inherently better than pharmacotherapy. The History of Psychiatry section analyzes Freud's famous 1909 visit to Clark University in Massachusetts, the only time Freud ever gave an invited university lecture outside of Austria, and the only time he ever received an honorary degree from any university. The Psychopathology section discusses the theory and practice of four main approaches of psychiatry as explained by Leston Havens. The curbside consult questions address the validity of some DSM diagnostic cut-off rules and stigma issues around ECT.

We would like to remind readers that PL is nearing its final issues, which will end with the December 2018 issue. The PL website will remain open for questions and curbside consults, and will include commentary on new journal articles. E-books also will be made available there. In the meantime, PL readers also can buy a new psychopharmacology textbook authored by me, to be published by Oxford University Press in January 2019, now available for pre-order, as described in the sidebar.

Thank you for your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Savior Treatments in Psychiatry

ECT, TMS, VNS, Ketamine – Are they really better?

There have been a number of treatments in psychiatry that have been seen by clinicians and/or patients and the public as saviors, in one way or the other. These treatments have been seen as special, as better in some profound way than other treatments. Often these savior treatments have been devices, meaning non-drug interventions. Sometimes they have been drugs, but then they were usually not just pills, but rather intravenous injections or intranasal inhalants. Such interventions, superficially more profound than simply taking a pill, have been seen as more powerful than those pills. In this special article, PL will review a number of those savior treatments, beginning with historical antecedents (insulin coma, malaria therapy), and then the oldest in current use, electroconvulsive treatment (ECT), followed by transcranial magnetic stimulation (TMS), vagus nerves stimulation (VNS), and ending with the most recent claim to savior fame, ketamine and its derivatives.

Origins of ECT

ECT was introduced in psychiatry by Ugo Cerletti and Lucio Bini in Italy in 1938. They used electricity to produce convulsions, instead of drugs (camphor, metrazol), as had been introduced in Hungary by Ladislas von Meduna in 1934. Within two years of Cerletti and Bini's article on the topic, the first ECT demonstration was given at a 1940 APA meeting in the US. Competing with frontal lobotomy, also introduced in the 1930s, ECT became a central new

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treatment in psychiatry in the 1940s and 1950s. After the introduction of new antipsychotic and antidepressant drugs in the 1950s, frontal lobotomy use fell off, but ECT continued to be a prominent treatment.

Before ECT, there were two other new major treatments in psychiatry in the 1920s: insulin coma, and malaria therapy. It's worth discussing these treatments briefly, to provide historical context for the evolution of ECT, and for later recent claimants to the savior throne, such as VNS and ketamine.

Precursors to ECT: Insulin coma and malaria therapy

Contemporary readers may react with a certain recoil to names such as insulin coma and malaria therapy. But those interventions were not perceived in their age to be as harmful or illogically aggressive as they may seem today. It's worth appreciating this aspect of the matter as we later examine current claims to powerful treatment effects with new devices or interventions.

Insulin coma

Insulin coma was introduced in 1927 by the Austrian psychiatrist Manfred Sakel. High doses of insulin, which had been newly discovered as a remarkable cure for diabetes, were given over weeks or months to induce states of severe hypoglycemia, nearing or inducing coma states. Glucose would be given after a brief coma to bring the patient back to consciousness. The danger was that coma could lead to death if

hypoglycemia was too severe or rapid. The benefit was that patients often improved. These patients often had schizophrenia, or some kind of severe chronic psychotic state.

Did insulin coma work? If so, why did it work? Highly qualified and well-trained psychiatrists and researchers observed that insulin coma seemed to help psychotic symptoms. But it is hard to know whether this was the case in reality, as no control groups were used to correct for natural history of symptom improvement. If there was real benefit with insulin coma, one possible mechanism was the induction of seizures in some patients, which might help in the same way that ECT did later.

Insulin coma was used in the US prominently in the 1930s through the 1950s. It was used occasionally in Europe even into the 1980s in some hospitals.

Malaria therapy

In 1917, malaria therapy was introduced by the chairman of the department of psychiatry in the University of Vienna, Dr. Julius von Wagner-Jauregg. Blood from malaria patients was injected into other patients with chronic psychosis, often diagnosed with schizophrenia, sometimes with general paralysis of the insane (GPI, later found to be neurosyphilis). It was observed that psychotic patients would develop malarial fevers, and then their psychosis would improve. This treatment was revolutionary because he showed for the first time that a psychotic state could resolve completely with a biological intervention. This fact proved that at least some psychiatric conditions were biological diseases, that could be cured with physical interventions, as opposed to purely psychologically caused. As a result of this impact, von Wagner-Jauregg was the first

“...[Malaria therapy] proved that at least some psychiatric conditions were biological diseases, that could be cured with physical interventions, as opposed to purely psychologically caused...”

psychiatrist to receive the Nobel Prize in 1927. (The only other psychiatric treatment to receive a Nobel Prize was frontal lobotomy, given to its inventor Egas Moniz, in 1949).

Did malaria therapy work? If so, why? There is reasonable evidence that malaria therapy in fact worked for many psychotic patients, although again the absence of a control group means that we cannot know how much patients might have improved. There is more reason to think that malaria therapy worked than other treatments in that era partly because the effects were more rapid than in other cases.

If it worked, its mechanism likely involved the fact that many cases of psychosis in the early 20th century involved GPI. Neurosyphilis was indistinguishable in many of its phases from mania, depression, or schizophrenia. The spirochete is sensitive to heat. When malarial fever occurred, the heat would kill spirochetes in the brain, and the syphilitic disease would stop. This process of killing

the bacteria that cause syphilis was handled much more effectively with the introduction of penicillin into practice in the 1940s. By the 1950s, GPI was wiped out, the largest cure in psychiatric practice. Penicillin can be seen as the most effective psychiatric treatment ever.

But before penicillin, malaria therapy had shown the way. It proved too harmful by itself to be a long-term cure, though, since, as one critic remarked, it cured one disease by causing another.

Back to ECT

Despite the introduction of antidepressants and antipsychotics, ECT remained in common use for refractory depression especially since the 1960s

onward. In some countries, its use is limited by law, but in most countries, most clinicians support its use. An alternative was developed 1985, transcranial magnetic stimulation (TMS), which provides magnetic activation of neurons across the skull. TMS was used in neurology for various conditions and introduced for the treatment of depression in the 1990s.

The use of ECT and TMS is relatively common for acute exacerbations of psychopathology. ECT in particular is proven effective for acute mood states, especially depression but also mania. The efficacy of ECT is most proven for severe depression, especially of melancholic and psychotic subtypes. Such benefit is present in both bipolar and unipolar depressive illness. ECT is also used most commonly in hospital settings, and for older persons who may not be able to tolerate polypharmacy with psychotropic medications. In the United States, because of insurance restrictions, ECT is used in hospitals very frequently, as it is reimbursed without much trouble. Many clinicians believe that ECT is more effective than medications in general, including short- and long-term treatment. However this is not the case. ECT may be more effective than antidepressant medications for severe acute depression, in terms of overall efficacy or in terms of more rapid response. The enhanced rapidity of ECT response may be useful especially to reduce acute suicidality and to speed discharge from the hospital. However, the concept that ECT is more effective than most or all psychotropic medications in general is not true. Outside of the acute phase, in long-term maintenance treatment, one frequently sees that ECT is used on a monthly or more frequent basis for months or years of treatment, after patients fail antidepressant medications in particular. In the

“...ECT is not better than lithium and perhaps tricyclic antidepressants for long-term maintenance treatment...”

longest randomized one-year maintenance trial of ECT versus medications for treatment of refractory unipolar depression, though, ECT was not more effective than medications in maintenance treatment. In other words, ECT did not prevent mood episodes more effectively than medications, even in patients who had been selected to fail antidepressant agents. It is worth noting that in that study, the medications given for the maintenance phase were lithium plus nortriptyline, while most of the medications failed before entry into the study were serotonin reuptake inhibitors (SRIs). Thus, the similar efficacy of lithium plus nortriptyline to ECT may reflect the special maintenance effectiveness of those agents, lithium in particular, as opposed to serotonin reuptake inhibitors. Thus, it may be more accurate to say that ECT is not better than lithium and perhaps tricyclic antidepressants for long-term maintenance treatment of unipolar depression, but it is possible that ECT is more effective than SRIs.

It also is worth noting that the observed efficacy of ECT may not be entirely due to its biological effects. Randomized trials of ECT which compared to sham ECT, where anesthesia is given but no seizure is obtained, find notable benefit with sham ECT. In these studies, ECT often is better than sham ECT, which supports its efficacy, but it is important to note that sham ECT also has benefit, and thus some of the benefits seen in ECT may be due to placebo-like effects of receiving this intervention.

The mechanism of ECT

The mechanism of action of ECT involves the induction of seizure, which is thought to reduce

depressive symptomatology. It has been observed in the past that patients who have epilepsy can experience forced normalization, which is the observation that depressive states are more common when seizures are under control, and less common when seizures are more active. The idea then followed that depression could be treated by causing seizures. The exact mechanism by which seizure induction leads to depression improvement is unknown. There has been some work suggesting some changes in neuronal markers, such as BDNF, after ECT. But whether these changes are specific or nonspecific to ECT is unknown. Cognitive side effects are known to be associated with ECT, and they seem to be worse with long-term treatment and in those who do not experience antidepressant benefit with ECT. In those for whom ECT is effective for their depressive symptoms, cognition tends to improve.

TMS

TMS or transcranial magnetic stimulation is not as effective as ECT. It has been proven in treatment of Parkinson's disease and other neurological syndromes, and is shown to be effective for the acute depressive episode. However, unlike ECT, it has not been shown to be effective in treating refractory depression, and thus is not shown to be more effective than standard antidepressant psychotropic medications. TMS has much fewer side effects in ECT, but it also is less effective. Again, like ECT, it has not been shown to be effective or even studies outside the acute phase of treatment of depression long-term maintenance treatment is not been shown to be effective, and should not be assumed to be effective long-term.

"[VNS] was allowed onto the market without any randomized clinical trials (RCTs), unlike drugs..."

Vagus Nerve Stimulation (VNS)

VNS was developed, like TMS, for neurological diseases and then expanded to depression. Since VNS is a device, FDA regulations regarding it are different than for drugs. In general, FDA thresholds for approval of devices are lower than for drugs; in other words, it is easier to get a device onto the US market than drugs. In fact, in the case of VNS for treatment-resistant depression, the device was allowed onto the market without any randomized clinical trials (RCTs), unlike drugs. VNS entered the US market in 2006 based on observational studies showing benefit in persons with past nonresponse to antidepressants, a definition which, as shown below in the ketamine section, is not a valid manner of demonstrating treatment resistance.

Without randomized data, confounding bias makes it impossible to accept observational data as proof of efficacy. Last year, in 2017, many newsletters simplistically accepted the observational results of a 5-year database that the FDA had organized. In that database, there was a higher 5-year remission rate in the VNS plus treatment as usual group versus treatment as usual (without VNS; 43% vs 26% respectively). Those results are not true necessarily, though, and can reflect other outcome factors. For instance, those treated with VNS might have received more visits and more attention than those who did not. They might have been less ill by natural history. The placebo effect of VNS was not controlled at all; those who received it might have expected to improve more than those who never received it. In short, there are many confounding factors that could cause differences between the groups.

In sum, VNS still is not proven effective in a randomized trial versus a sham control. It involves surgery and a large neck scar, thus it is not benign. Given the lack of randomized proof of efficacy, and real risks, as well as expense, many clinicians and payers have not supported VNS, and PL shares their view.

Ketamine

An alternative to both ECT and TMS could be ketamine, given intravenously, or esketamine, given intranasally, which again would be effective for the acute depressive episode. Again, as with ECT, there is no proof of benefit outside of the acute phase. Therefore, maintenance efficacy with long-term treatment cannot be assumed, it has not been proven. There may be a benefit to ketamine for more rapid response in acute depressive symptoms and for more rapid reduction of suicidality, but again this short-term immediate benefit does not

translate into a long-term prevention of future symptoms. Unipolar depressive illness is a long-term recurrent disease, in which many mood episodes happened in a lifetime. All of these medications-ECT, TMS, and ketamine- are at best short-term treatments, for acute mood symptoms, and do not have any proven benefits for the long-term illness. This does not mean they are useless, but it also means that they are not profound solutions to the overall disease. Their use is much like steroids in autoimmune diseases, where benefits are present and even crucial for acute exacerbations, where steroids may be lifesaving. Long-term treatment, though, does not treat the underlying cause of the autoimmune disease.

“... [Most of the ketamine literature] is based on a definition of treatment resistance that is solely dependent on past recall of prior antidepressant treatment trials. This past recall is not accurate...”

Steroids also have more side effects when given long-term, without any proven benefit. The same would be the case with ECT and ketamine and TMS for recurrent unipolar depressive illness. These medications may have acute short-term benefits that may even be lifesaving, but they do not treat the overall disease, and may have no long-term benefits. They do have many side effects though which would increase long-term.

Invalidity of defining treatment resistance

Another factor that is important with the ketamine literature is that most of it is similar to the VNS literature, in that it is either purely observational, and not randomized, or it is based on a definition of treatment resistance that is solely dependent on past recall of prior antidepressant treatment trials. This past recall is not accurate, it seems. The evidence for the invalidity of this past recall can be found in studies of other treatments that have received FDA indications for treatment-

resistant depression, such as dopamine blockers like aripiprazole or quetiapine. Those agents had to conduct studies based on an FDA requirement of failing a prospective trial of a standard SRI agent. In those studies, patients were initially selected as having failed at least two or more prior antidepressant trials. Then they were treated with an SRI prospectively for 8 weeks, and had to fail that trial before entering the pivotal phase III randomized trial for FDA indication. Surprisingly, about 60% of patients with a history of multiple failed antidepressant trials actually responded to a simple open-label trial with a different SRI. This 60% response rate is similar to what is reported in non-refractory depression studies. In other words,

reported failure to respond to past antidepressant trials was not confirmed in a prospective trial as a valid way of defining treatment resistance.

In studies of ketamine, the vast majority are based on this invalid method of relying on past failed antidepressant trials. Then a ketamine trial is effective and it is claimed that ketamine is more effective than those other antidepressants. The only way to make this claim validly would be to follow the FDA paradigm of failing a prospective trial of an SRI. Ketamine itself has not been tested in this manner, but recently its enantiomer esketamine has been tested in this manner in the process of its development for FDA indication by its manufacturer.

As context, in the antidepressant literature, with over 500 RCTs, it has been found that the overall benefit seen with antidepressants is about 2-3 points greater than placebo on standard depression rating scales (such as the Hamilton Depression Rating Scale, HDRS, or the Montgomery Asberg Depression Rating Scale, MADRS). In the randomized studies which define treatment resistance retrospectively based on reported failure of past antidepressant trials, it was reported that ketamine produced a benefit over placebo of 5-10 points, which is larger than the 2-3 point difference seen with standard antidepressants. However, in a recent esketamine trial for FDA registration with a failure of prospective antidepressant treatment required, it was found that esketamine was better than placebo by about 3 points on the MADRS. This effect size of benefit is similar to what has been found with standard SRIs. Thus, this result would suggest that this derivative of ketamine may be

effective for depression, but not more effective than standard SRI antidepressants.

"PL does not recommend ECT or TMS or ketamine for long-term treatment of any depressive illness..."

Thus PL does not recommend ECT or TMS or ketamine for long-term treatment of any depressive illness, but PL would be open to their use for short-term acute mood episodes for which medication treatment is either unresponsive,

unavailable, or intolerable.

Based on the best available research literature, PL is not convinced that ketamine or its derivatives are more effective for depression, though, than other standard monoamine agonists.

The PL Bottom Line

- There are no savior treatments that work long-term in psychiatry.
- ECT is the most effective treatment among those reviewed, but it is effective acutely, not long-term.
- TMS is not more effective than standard antidepressants.
- VNS has not been proven effective with the same rigor as antidepressant drugs (i.e., with randomized data).
- Ketamine and its derivatives have not been proven more effective than standard antidepressants. Any benefit again is acute, not long-term.

Current Study of the Month: *Maintenance efficacy of ECT*

Electroconvulsive therapy in the continuation and maintenance treatment of depression: Systematic review and meta-analyses A. Elias et al, Australia and New Zealand Journal of Psychiatry. 2018;Vol. 52(5) 415–424

Limited proof of benefit, and clearly not better than lithium

This systematic review is a good summary of decades of RCT research on efficacy of ECT for the long-term, in maintenance prevention of depressive episodes. This outcome gets at the claim that ECT is better than other treatments in some inherent way. There is a difference between acute symptomatic improvement, as opposed to long-term disease modification. ECT provides acute symptomatic improvement, as described in the Special Article. But the question of whether it is better than other drugs inherently implies disease modification, something more than mere current symptom improvement. For that claim, one has to show long-term benefit, which means maintenance prevention trials.

As described above in relation to VNS, any claim to benefit for any treatment needs to be made with a RCT so that confounding bias can be controlled. The first observation to make in this review is that there only are five RCTs of ECT for maintenance efficacy. Seven observational studies have been published but they were not randomized. The five RCTs studied overall 436 patients with three studies having only 6-month outcomes. One study had a follow up of one year, and another study two years. In general, the maintenance phase of unipolar depressive illness is defined as beginning at one year. Thus, there only are two studies that are one to two years in duration for long-term ECT efficacy. Given the common use of ECT long-term in many patients, it is important to realize this fact, that only two studies, with 89 patients overall, actually examine

such long-term use. In other words, all this long-term treatment in practice is based on data on 89 patients.

Because there are so few studies, this meta-analysis mainly focused on the 6-month outcomes, so as to include all five studies. PL readers should keep in mind that these 6-month outcomes do not reflect the maintenance phase, but rather the continuation phase after acute improvement. In other words, initially patients were treated with ECT. If they responded, they were randomized to continue with ECT, or to switch back to medication use alone.

PL readers should realize that this is the classic “enriched” design, which PL has shown to be invalid (see PL website). In that design, only acute treatment responders are included in the study to assess further treatment response. This is a selection bias that massively supports apparent “response” for the drug which is selected to be included. So it is not surprising that ECT would be effective versus comparisons if only ECT responders are included in the study. This enriched selection bias is a problem especially around the acute episode. If ECT helps depression for 2 months, and then you stop it, and the patient relapses 2 weeks later, this is not maintenance prevention of new episodes, but rather the same acute episode continuing to happen. In fact, it is the case that the average unipolar depressive episode lasts 6-12 months untreated, and this is why the maintenance phase

is not viewed as beginning until after this 6-12 month period. Any relapse before that time is the same acute phase continuing, not a new episode.

Of these five studies, only one compared ECT alone versus pharmacotherapy alone (which was lithium plus nortriptyline). That study was the one that found absolutely no benefit with ECT. Both treatment options were the same. Even though that study preselected for ECT responders, it appears that lithium plus nortriptyline is so effective that these medications were just as good as ECT, even in a sample that was preselected to reflect ECT responders.

The longest study, which was a two-year trial, compared ECT plus nortriptyline versus nortriptyline alone, and found notable benefit with ECT.

Given these two studies, it appears that nortriptyline may not be the effective comparator agent to ECT, but rather lithium might have shown marked efficacy in the largest trial, to such an extent that ECT benefit in maintenance treatment was not seen.

The PL view is that this high drug response likely was driven by lithium, which, unlike nortriptyline, has extensive evidence of benefit for prevention of depressive episodes in unipolar depression (as well as bipolar illness).

Clinical implications

How should PL readers interpret this study's results in terms of how it applies to their clinical practice? The simplistic interpretation would be that the meta-analysis supports maintenance efficacy with ECT. But this conclusion, which is

made by the authors, ignores the fact that the 6-month outcome is not the maintenance phase, and that this conclusion requires not including the largest negative trial. Further, comparing the details of the various trials, it appears that ECT may be more effective than standard antidepressants for maintenance treatment of unipolar depression, but it is not more effective than lithium. Hence, these data could be interpreted as supporting using lithium for maintenance treatment of unipolar depression after acute treatment with ECT. Interestingly, in the 1970s-80s, before the SRIs were developed and came into common use in the 1990s, some clinicians practiced this way: ECT for acute depression, and lithium for prevention. The ECT maintenance RCT literature would seem to support this practice.

The PL Bottom Line

- Maintenance efficacy of ECT for prevention of new depressive episodes is based on a few studies, mostly of 6 months duration.
- Longer studies suggest ECT benefit over standard antidepressants, but not over lithium.
- Clinical practice that is supported with these data would be acute treatment of depression with ECT, followed by long-term prevention of depression with lithium.

History of Psychiatry

The discovery of modern antidepressants

PL Note: The story of the discovery of the first modern antidepressant, imipramine, involves a prominent existential-psychoanalytic psychiatrist, Roland Kuhn, who found that a new class of drugs did what the best psychotherapy could not. The psychiatric historian Edward Shorter describes this process well. What is not described here is that Kuhn also found that imipramine was most effective for his patients with melancholic (or "endogenous" depression, but not for those with non-melancholic (or "exogenous") depression. Kuhn and others used the phrase endogenous and exogenous as synonyms for melancholic and non-melancholic depression, though this is not the case. For our purposes, it's important to note that from the start, monoamine agonists were not effective for all kinds of depression, but only some kinds, specifically for TCAs, they were less effective in non-melancholic depression.

From: Edward Shorter, A History of Psychiatry, New York, John Wiley and Sons, 1997, pp 258-261

In 1950, the J. R. Geigy pharmaceutical firm in Basel asked staff physicians in the Munsterlingen asylum in Switzerland to see if an antihistamine that Geigy had developed might serve as a sleeping pill....One of these staffers was Roland Kuhn, then 38, a tall, distinguished, and cultivated psychiatrist who combined an exceptional grasp of the humanities with a background in biochemistry.....He was...an adept of psychoanalysis...and was a good friend of Ludwig Binswanger [a friend and follower of Freud, and a central founder of existential psychotherapy]...

Then Kuhn had one of those road-to-Damascus-type experiences. He had been treating with

psychoanalysis a young woman whose complaints seemed to be of a "neurotic-hysterical" nature. He made great progress with psychodynamic therapy, "bringing out unconscious material that corresponded exactly to Freud's theories. Everything went beautifully and she was cured. A few days later she came to my office again, garishly made-up and perfumed, with costume jewelry hanging all over her, dressed in loud colors...and demonstrating irritable and euphoric mood changes, pressured speech and flight of ideas." Kuhn then realized he had made a mistake. The correct diagnosis was mania. He had falsely ascribed a spontaneous recovery to his psychoanalytic "cure." As so often happened in those days, Kuhn had also missed her earlier depression given her a misdiagnosis of "hysteria." For Kuhn, manic-depressive illness was an organic condition having little to do with Freud's ideas.

Yet as Kuhn fell away from psychoanalysis, he asked himself, what can we do to help patients like this? Admitting her to the mental hospital for

ECT seemed a bit much. "How often I said to myself, 'We should improve the opium cure!' But how?"

Then in 1952, the discovery of chlorpromazine became known. Kuhn and his colleagues put depression and mania at the back of their minds for the moment. The Munsterlingen staff received free samples of chlorpromazine from Rhone-Poulenc for trials on their schizophrenic patients....Kuhn asked Geigy.. if the hospital might try another drug in antihistamine series, one with a chemical side chain exactly identical to chlorpromazine's.... The staff tried it on patients with schizophrenia. It makes many of them worse, converting quiet chronic patients into agitated whirlwinds of energy. Kuhn consulted with Geigy scientists on

what the drug could possibly be doing to procure such bizarre effects, and sometime in 1955 the decision was made to give it to some depressed patients. The response was "absolutely incredible, so exciting"....Kuhn and the Geigy people had obviously discovered a drug that could relieve depression.

In the first 40 depressed patients who received it, some of the recoveries were dramatic....The patients themselves spoke of a "miracle cure"...

In the spring of 1958 Geigy named the compound imipramine (Tofranil). Imipramine was the first of the "tricyclic" antidepressant...rival tricyclics flooded the market, the Merck Company, for example, bring out amitriptyline (Elavil) in 1961. By 1980 American physicians were writing 10 million prescriptions a year for antidepressants alone, the great majority of them tricyclics.....

PL Reflection

I like the dreams of the future better than the history of the past.

Thomas Jefferson
Letter to John Adams

Psychopathology

The four schools of psychiatry

PL Note: The psychiatrist Leston Havens explains here the four main approaches to psychiatry, which he described repeatedly in his work. They are the interpersonal, psychoanalytic, existential, and objective/descriptive schools. Here he summarizes their theory and practice.

From Leston Havens, Participant Observation: The psychotherapy schools in action, 1983, Northville NJ: Jason Aronson, pp 151-154

[There are]...four principles sharply separable from those underlying the best-known ways of doing psychiatric and psychologic work....

First, interpersonal work is directed at the 'other people' in the room, what I have called the social unconscious permeating human transactions. Until the medium of communications is cleansed of its distorting images, it is assumed that no reliable exchanges can take place.

Psychoanalysis, in contrast, incubates the distorting images. These in their fully developed form, the transference neurosis, constitute the lesion to be treated. The partly detached, neutral presence of the analyst invites the transference neurosis which, it is assumed, can then be dealt with interpretively.

Existential workers, in further contrast, neither offer themselves as screens, like analysts, nor attempt to move the distortions away to be examined elsewhere. By being where the patients are, they assume they offer no target for transference. Inside the patient, as it were, they look out at the patient's world.

In medical psychology, finally, and some psychoanalysis, doctor and patient form a cooperative alliance to examine and deal with the distortions. This point of view takes for granted that doctor and patient can be objective, that there is some part of the mental life of both doctor and patient untouched by the distorting introjects.

Second, interpersonal work assumes that the other people in the room make the patient anxious and can only be removed by indirect means. These means I have called playing the transferences. The principal device is talking about the introjects....

Psychoanalysis, in contrast, requires that the patient bear considerable anxiety. To reduce it prematurely would be to abort transference development. With transference development come the patient's characteristic ego processes, which are to be analyzed too.

In existential work anxiety is shared with the therapist.

Existential therapists, being with their patients, help bear the anxiety, as well as other feelings....

In medical psychology (what I have called elsewhere objective-descriptive psychiatry), anxiety is reduced by medication and reassurance. In behavior therapy, it may be reduced by gradual exposures to what is frightening....

Third, according to interpersonal theory, the presence of the other people in the room and the anxious responses to them have been learned. Introjects have rubbed off, as it were, from reality; the patient's projections are assumed to reflect the patient's experiences. People, in short, drive each other mad.

Psychoanalysis, in contrast, assumes the prince of instincts in conflict with each other or with psychic structures. The results of these conflicts are projected. These projects are fantasies that may reflect more of wishes and their counterforce than they do of the patient's actual experience. As a result, psychoanalysts are in danger of seeing everything as fantasy just as interpersonalists fall victim to blaming everything on reality.

Existentialists, in turn, are less likely to judge either the patient or the world. The two are to be helped bear one another. Therefore existentialists are in danger of accepting what needs to be changed.

The medical psychologists, in turn, when they are biologists, locate the lesions in the body and attempt to correct that. When they are educators, hypnotists, or behaviorists, they work on the mind. They fall victim to authoritarian manipulation and coercion.

Fourth, as long as the patient lives with the old anxiety-provoking projections, his or her behavior must remain the same. As soon as the medium between the patient and other is cleared and the past reconstructed, the behavior can change. Interpersonalists assume that in the absence of continued reinforcement old patterns will change.

Psychoanalysts, in contrast, regard social misperceptions as a product of internal conflict. Until the conflicts are resolved and the resulting fantasies dissipated, behavior cannot change. Psychoanalysts assume that surfacing and interpreting the fantasies, conflicting forces, and accompanying behavior will change them all.

Existential psychiatrists do not want to change the patients. Expressing unconditional positive regard and being with one another, therapists and patients may or may not change.

Finally, medical psychologists diagnose and treat. The behaviorists among them do not speak of perception and behavior, but of stimulus and response. They assume that changing the stimulus received need not change the response; the response itself must be altered.

Thus the great schools direct themselves at different targets: what occurs between people, what occurs within individuals, or the body and its behavior. Without seeing clearly how it can be built, one imagines a psychiatry ready to do battle on all or any of these fronts.

PL Reflection

Don't look for yourself outside yourself

Ralph Waldo Emerson

Curbside Consults

Questions and cases from you

Question: The background to my question is the following: I take particular interest in synthetic/designer drugs. With the advent of the internet, it has been very easy for people to import drugs, synthetic cannabinoids, synthetic cathinones, "research chemicals" such as "2C" and an astounding variety of other chemicals. Traditional testing usually does not reveal much: urine testing is usually limited to our traditional "NIDA-5" (cocaine, amphetamines, marijuana, opiates/opioids, PCP etc.) or a few additional chemicals.

My main question follows: We are now seeing people who consume a large quantity of these synthetic substances and remain psychotic or symptomatic for a long period of time. The DSM cut off of 1 month is clearly not enough as their symptoms don't remit for several months. What is the implication of this course for their diagnosis? Is this condition still just a substance-induced psychotic or mood disorder or something more? Could some substances cause some sort of permanent change in the brain that causes a fixed mental disorder?

PL: The DSM cut-off of 1 month has no scientific basis. It is, like most DSM criteria, a social construction based on the profession's social preferences at a given moment. 20 years ago the cut-off was 6 months. A prominent substance abuse expert once described searching for the scientific source for the 6-month cut-off. He went from scientific paper to scientific paper, each referencing another paper, until he finally ended up with a primary source reference in a textbook. He then went to the textbook and found that the 6-month cut-off was stated without any further

citation. In other words, there were many sources which ultimately lead to nothing.

This is the case with many such rules of thumb in psychiatry, which may have some pragmatic value, but are not based on some solid ground of scientific fact.

The 6-month cut-off was later changed in DSM to 1 month, mainly because of clinical opinion and concern that 6 months was “too long.” Too long based on what? There was no scientific ground for the original 6-month criterion, nor was there any for the one-month criterion. It was just felt clinically by many practitioners that 6 months was too long. That meant that you had to wait 6 months until someone stopped drinking or using drugs before you officially diagnosed them with “MDD” or “GAD” and then prescribed monoamine agonists. In fact, clinicians can prescribe medications whenever they want, without making a specific diagnosis. The making of a diagnosis need not lead to prescribing a medication, nor does it justify the latter. In medicine, we often make diagnoses without prescribing treatments. We often prescribe without making diagnoses. It should be the same in psychiatry.

But because of the DSM ideology and the attempt by the American psychiatric leadership to tie DSM to treatment, this medical approach has been replaced by an overly obsessive focus on using DSM criteria to justify treatment.

This ideological mistake plays out clearly with the question of substance abuse. There’s no scientific evidence that one month is a factual cut-off for any diagnosis related to substance abuse. Some substances cause clinical symptoms over minutes; others over hours; others over days; others over weeks; others over months; some might last years. One month is not a general scientifically

meaningful cut-off for anything. It’s just another pragmatic DSM claim, meant to put all of psychiatric practice into a single straight-jacket.

Here are some examples that disprove the one-month generic cut-off:

There is plenty of research, including in neuropathology, which shows that chronic alcoholism is associated with permanent changes in the brain. Cerebellar vermis degeneration is now well-known. Lesions in other parts of the brain are associated with Wernicke-Korsakoff psychosis, which involves chronic delusions lasting years. Further, chronic auditory hallucinations lasting years were associated with some forms of severe alcoholism.

So these conditions involve substance abuse with permanent changes lasting years.

Shall we use the phrase “substance-induced psychotic disorder” for Wernicke-Korsakoff syndrome and chronic alcoholic hallucinosis? We can do so if we want to be bureaucratic. Or we can just use the scientifically-based clinical diagnoses given above.

Another example is steroid-induced mania. Intravenous steroids can cause manic episodes, even in persons without spontaneous manic episodes (i.e., without bipolar illness). Once induced, such manic episodes can last weeks to months. There is no one-month cut-off.

So, in short, we know already that substance abuse, with well-known classic substances such as alcohol and steroids, can produce mood and psychotic states that easily last longer than one month. Further, it was the case in the past that 6 months was viewed as a cut-off before ascribing psychotic and mood symptoms to substance abuse alone. There is no reason one should be wed to the

one-month cut-off as having any scientific meaning.

It may be that these new designer substances may have longer lasting influences on the brain and thus cause longer clinical symptoms. This effect would not be surprising or unusual, as it is also the case with older traditional substances, such as alcohol and steroids.

Question: How do you convince reluctant patients to accept ECT?

PL: Many patients have a negative opinion about ECT in the United States, and in other countries, partly based on misinformation, and partly based on stigma. Misinformation can involve just the general principle of receiving a treatment that involves causing a seizure. The question could be whether it is reasonable to cause a seizure in the brain as part of a treatment for a psychiatric state. It would seem to be an extreme and excessive approach. There is some rationale to this concern. One has to admit that the concept of using seizures to treat depression or psychosis is speculative, based on an older epilepsy literature. Its biological mechanisms are not well known or worked out in detail. While accepting those limitations, it's also important to explain to patients that there is good clinical literature that supports the short-term acute efficacy of ECT, with multiple randomized trials showing benefit over sham ECT.

Perhaps the most important point to discuss regarding information about ECT is the risk of cognitive harm. Too often this potential harm is discussed in an all-or-nothing manner. Critics will say that ECT harms memory, period. Defenders will say that ECT does not affect memory, period. Neither are correct. ECT can worsen memory, by causing cognitive side effects, in some people. Usually, this cognitive harm seems to occur as a

short-term side effect, without long-term impact. In some people, though, there appears to be long-term cognitive harm. This should not be very surprising, as patients given ECT have long-term cognitive impairment anyway as part of their mood or psychotic illnesses. We know very well that manic-depressive illness, for instance, is associated with cognitive impairment, not only during mood episodes, but even permanently in periods of remission. The risk of dementia is increased 2-4 fold in such persons. Thus, they are predisposed to cognitive impairment, and anything which can worsen cognition, such as ECT, can lead to further cognitive impairment in such conditions.

It could be that the persons who experience the most cognitive impairment with ECT are those who do not improve with treatment. Their mood condition continues, and it worsens cognition, along with the direct effects of ECT.

In contrast, most persons who improve for their psychiatric condition with ECT do not experience cognitive impairment, at least in the long run.

Thus, the issue of potential cognitive impairment should be discussed in the context of the risk of cognitive harm from the mood illness itself, as well as whether or not someone improves with ECT.

In relation to stigma, rather than simple misinformation, the problem can be deeper. Some patients in the US have been influenced greatly by anti-psychiatry movies, such as Ken Kesey's "One flew over the cuckoo's nest." As with much that comes out about psychiatry in the media, that movie was ideologically one-sided, and it had a very harmful impact on the population. One can try to counteract such false beliefs with a patient if the patient has a good relationship with the clinician. But in the absence of such a

relationship, the cultural opinions of a patient will be difficult to change. In some countries, such as Italy, there has been long cultural debate about ECT with many critics of ECT and psychiatry having influence on public opinion. In such settings, a single clinician can do little to counteract generations of opinion formed by critics of ECT and psychiatry.

Question: I have the impression that SRI's often seem to work better for anxiety than depression, but that may be a reflection of depressive syndromes not necessarily being MDD. I'm not sure this is statistically answerable, but do you know how the effect size for SRI treatment response for unipolar MDD compares with the effect size for SRI treatment for anxiety disorders such as GAD or panic disorder?

PL: PL fully agrees clinically that SRIs are better for anxiety than depressive symptoms. The effect

size for "MDD" for difference between SRI and placebo is about 0.30 on Cohen's d (which is small and below the typical clinically meaningful effect threshold of 0.5). The effect size for "GAD" is a good question that has not been discussed in PL previously. In a review of a recent meta-analysis (B Bandelow et al, Int Clin Psychopharmacol, 2015, 30:183-192), PL found that the difference between most SRIs and placebo was about 0.5.

So the effect size of SRIs for MDD is 0.3, which is small; and the effect size of SRIs for "GAD" is 0.5, which is moderate. This research literature thus supports clinical impression: SRIs are more effective for anxiety than for depressive symptoms. This is another reason why the term "antidepressant" is not accurate. If anything, these agents should be called anxiolytics. In fact, they are monoamine agonists, and they have some clinical benefit for anxiety and depressive symptoms, more so for the former than the latter.

PL Reflection

God is asleep, not dead.

Rilke

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THE PSYCHIATRY LETTER

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Digital Psychiatry

PL continues with another double-issue with this newsletter. The main topic in the special article is digital psychiatry, the new and growing field of using computers and smartphone applications to measure or manage psychiatric conditions.

The Classic Article of the Month examines genetic heritability studies to see which psychiatric diagnoses can be seen as diseases. PL draws a conclusion that is different than the genetic researchers who conducted the review. This double-issue has two History of Psychiatry articles, the first a look back at the experience and predictions (circa 1982) of Roy Grinker, a prominent American psychiatrist of the mid 20th century. The second examines a little-known figure in psychoanalysis, Viktor Tausk, a young man who was in Freud's close circle for an early decade of Freud's growing work. Tausk originated some key concepts, like projection, but he likely had manic-depressive illness and committed suicide. The curbside consult question addresses the problem of autoimmune reactions with lamotrigine, and common misconceptions about the range of those risks.

We again remind readers that PL is nearing its final issue, with this one being the penultimate. The final PL issue will be the December 2018 issue that will follow. The PL website will remain open for questions and curbside consults, and will include commentary on new journal articles. E-books also will be made available there. PL readers also can buy a new psychopharmacology textbook authored by me, to be published by Oxford University Press in January 2019.

Thank you for your continued support.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Digital Psychiatry

Is there an app for that?

[Disclosure: The PL editor is involved in research at Novartis Institutes for Biomedical Research on a digital CBT application for schizophrenia]

In June 2007, Steve Jobs introduced the iPhone. Since then, smartphone applications have multiplied extensively, and the use of smartphones has become ubiquitous. The vast majority of persons now own those mobile devices. It was a matter of time before smartphone applications began to be used for medical purposes. Some even have advocated the use of mobile phone applications for treatment of medical illnesses. This is the field of “digital therapeutics.”

The majority of digital therapy applications on smartphones are “wellness apps,” the digital equivalent of over-the-counter (OTC) medications. They are not proven to be effective for specific disease, and have no specific FDA approvals. Instead, they are shown only to be safe, and, like alternative or herbal OTC treatments, they only can claim to improve health, not treat disease.

A second class of digital therapeutics are mobile applications that are intended to treat disease, and thus need FDA approval. This second class is very limited so far, but likely will grow in the future. The first class of wellness applications is larger, and already may be of relevance to clinical practice.

Besides the use of mobile or computer applications for treatment, there also is use of such digital technology for diagnosis or for outcome measures.

'digital phenotyping' promises to be a clinical tool to classify and even diagnose..."

In this review, PL will summarize the status of current digital technology in psychiatry, and possible future prospects.

Digital diagnosis

The role of artificial intelligence in identifying and interacting with people through digital technology is beginning to be explored. One of the potential avenues of use of software technologies that relate symptoms to each other is the field of “digital phenotyping.” This approach promises to be a clinical tool to classify and even diagnose patients.

Many new digital technologies look at objective measures of clinical phenotypes that may correlate with less measurable subjective symptoms. For instance, voice analysis (tone, timbre, and variability) is

being examined for depression and Parkinson’s disease. Sleep stages can be measured with some smartphone applications. EEG activity is being assessed with fewer leads linked to smartphones. Motor activity and physical location can be measured by smartphones with GPS capability, and can relate to depression or diseases of motor function.

Some universities and companies have started to promote projects to collect clinical psychiatric information from patients on a routine basis.

More commonly, electronic medical health records have become routine in medicine, although psychiatry lags behind other medical

specialties, with about 61% of psychiatrist now using electronic health records. The trend of the future is that almost all health records will be digitalized, with many benefits but also with privacy concerns as described below.

Digital outcomes

A major area of interest involves measuring outcomes using digital methods. A simple approach involves tracking symptoms, such as a mood tracker, or a daily symptom tracker. There are many varieties of these kinds of digital applications. The National Institutes of Health (NIH) recently has funded a major study to obtain health data, in its Precision Medicine initiative, including assessment of mood symptoms.

Many digital approaches are being explored for assessing cognitive symptoms, whether in psychiatric conditions or in diseases of cognition such as dementias. One example is a smartphone application to assess cognition in schizophrenia.

Digital therapeutics

Treatment using digital technology involves mainly the use of unregulated and unproven applications, which are equivalent to OTC treatments (“wellness applications”), and the beginnings of a new field of FDA-regulated digital treatments.

Wellness applications

There now exist over 10,000 mental health wellness applications. Some are used now commonly. For instance, Headspace is a common app used for mindfulness methods. There are

many meditation apps, some of which have a social media component, connecting users with others around the world who are meditating at the same time. Other apps take a cognitive behavioral approach or a positive psychology approach to overcome negative thoughts.

As with OTC medications and alternative and herbal treatments, since these applications are not FDA-regulated, they need not prove that they are effective before they are available on the market. This fact leaves open the question whether they really are effective. A recent study of Headspace versus a sham control arm found no benefit with the mindfulness digital application for cognitive outcomes.

Digital treatment

So far, only one digital treatment has received FDA clearance as a treatment for any psychiatric condition, in this case substance abuse. This digital application used cognitive-behavioral methods for treatment of substance abuse. This smartphone study is consistent with prior studies of computer-based or video-based CBT as being effective and equivalent to live in-person CBT in acute depressive states. Most proposed digital therapies appear to use CBT techniques.

Other interventions, which are not regulated by registration bodies, are beginning to be developed. For instance, in Australia, a phone application was developed to reduce suicidality.

Risks

Risks involved in digital psychiatry include privacy concerns, and harm caused by digital applications such as worsening of mental health.

Privacy

Hacking is a major concern in the modern digital world, as has occurred repeatedly with identity theft and financial information. If the practice of psychiatry becomes more digitalized, either in diagnosis or treatment, the concern about hacking of confidential psychiatric information will become a real risk. Many mental health applications do not have even basic privacy protections.

Worsening of mental health

There is growing evidence that the routine use of smartphone applications involving social media, especially in teenagers, leads to more anxiety and depression and even suicidality. The overall effect of digital technology appears to be harmful to the mental health of children and adolescents in particular, partly due to harmful consequences such as cyberbullying and sexting and abetting drug abuse.

Some applications are used with the specific purpose of causing psychiatric harm, such as assisting suicide.

“...the routine use of smartphone applications involving social media, especially in teenagers, leads to more anxiety and depression and even suicidality....”

Implications for clinicians

Most clinicians use smartphones in their daily lives, as do most patients. It is a matter of time before this usage enters into clinical care, for better or for worse. It already does enter into clinical care for worse, as shown by the harmful

psychiatric effects of social media on children and adolescents, as well as some adults.

This review highlights the potential for possible benefits as well in the future, if digital technology proves helpful for diagnosis, assessment of outcomes, and even treatment in psychiatry. In a world with over 10,000 applications, the future will require application of scientific methods, as in the rest of medicine, to show which digital approaches are valid, and helpful, and safe - and which are not.

Some clinicians, often older, are technophobic, distressing all digital technology. Some, often younger, are technophilic, thinking all digital technology is exciting and effective. Both groups likely are wrong.

Digital technology is harmful, and can be helpful, and it will be a major aspect of practice and research in the coming years to determine which is which.

The PL Bottom Line

- There are over 10000, mostly unproven, wellness applications in mental health.
- Digital methods will be used to study outcomes, like cognition, and phenotypes, like moods.
- Most digital treatments involve CBT or mindfulness methods.
- Digital social media is harmful overall for children and adolescents, causing depression and anxiety.

History of Psychiatry - I

A vision of the future circa 1982:

The prominent psychiatrist Roy Grinker diagnoses psychiatry

PL Note: In this book excerpt, we read the thoughts of a major leader in mid 20th-century American psychiatry. For decades, Roy Grinker was chairman of psychiatry at Michael Reese Hospital in Chicago. He was editor of the Archives of General Psychiatry for most of the 1960s. He was distinguished in many respects: trained as a neurologist as well as a psychiatrist, in the 1920s, and bilingual in German (his mother tongue) and English, he received personal psychoanalysis with Freud in the 1930s. In World War II, he published the first military textbook on what is now termed PTSD. He was one of the first to identify the borderline syndrome, and published key early studies in the epidemiology of schizophrenia. He led important studies of normal adolescence and adulthood, and he was a founding leader in the field of psychosomatic medicine (now called consultation liaison psychiatry). Along with all this, he led an alternative series of institutes for psychoanalytic training, separate from the primary institute structure headed by Anna Freud, and, along with George Engel, he created the concept of the biopsychosocial model. In this book, which was a series of interviews of prominent psychiatrists by the eminent English psychiatrist Michael Shepherd, Grinker sketches a portrait of psychiatry which it is useful for us to think about almost 40 years later. Some parts, like his criticism of non-MD mental health professionals, are dated; other parts, like his critique of psychoanalysis while appreciating it at the same time, and his warning about divorcing clinical work from research, remain relevant.

From "Roy R. Grinker Sr.", In Psychiatrists on Psychiatry, Michael Shepherd, editor, Cambridge University Press, Cambridge, 1982, pp. 29-40

"Most thinking...consists of dichotomies..."

Americans constitute a fashion-ridden, unstable society, even in the field of their scientific interests. Thus, the publications on the borderline syndrome, the narcissistic neuroses and psychoses as well as the spectrum concepts have spread rapidly, without concern for significant and empirical research. It is interesting that discursive writing rather than observational data dominates most of our psychiatric periodicals. Hardly a publication contains one third of plausible information.....

How do we educate the young psychiatrist? Research models exist, of course, but there are very few of them. Too frequently investigators are reductionists or humanists maintaining a consistency that can be termed bias. Most thinking, in fact, consists of dichotomies. To offset this grievous fault, we need an overall inclusive theoretical base, consisting of a unified theory....Without such a theoretical approach, properly used, we are destined to remain theoretical partisans....

The golden era of psychiatry, from the end of World War II to the early 1970s, is no longer with us. The interest in support of the field taken over by the government from the private sector of philanthropists has passed as government grants have dried up....

...Psychiatry is surrounded by enemies: encounter groups, lay therapists, clinical psychologists and nurse specialists. Everyone wants to get into the

therapeutic act, but few want to do research or teach imaginatively. Power is the word in community psychiatry!

The future of psychiatry obviously depends on the development of research in the field, which sadly needs intensive investigation. However, increased knowledge in the field of psychiatry can only be achieved through increased sophistication in research designs and in theoretical concepts. There is no longer room for superficial correlations which have satisfied us until now....The complications of human personalities, their high degree of variability and the tremendous difficulties in hold parameters constant understandably induce considerable frustration....

...we are in no way clear to the nature of the causes of the results which satisfy the therapist. A common factor to which we may attribute constructive results may be contact with an understanding, empathic human being for variable periods of time, with opportunities for ventilation of feelings and understanding, if not explanation, by the therapist.

It is in the field of treatment that my own resistances have a high titre, since there are so many possibilities of evaluating results that expect our capability for measurement. Thus, unless one is willing to work for decades within a single area, it may be wiser not to begin....

At the time of its heyday in the United States, psychoanalysis was considered to be the answer to all the problems of mankind. As a humanistic theory concerned with meanings, it failed to achieve the level required of a science, even

though its supporters frequently spoke of 'our science'....

The next important breakthrough came through the discovery of psychotherapeutic drugs....I look forward to great accomplishments in this field of neuropharmacology.

The concept of prevention in the framework of medical psychiatry has moved on to what might be called social psychiatry, which is action-oriented. It conceives of the possibility act if we can shift community functions to develop societies in which frustration, conflict and aggression are lessened, we may prevent mental illness. This pious hope has been confused with

community psychiatry, which is really a delivery system concerned with the organization of facilities. Social psychiatry is a different field: it is one which has not yet developed a paradigm, it has not developed research designs and it has not yet conceived of techniques for evaluation....

Finally I think there is a great deal yet to be done in the study of biogenetic and sound research in child development, although this is still in its early phases. We need to know a great deal about the development of normality in adolescence and adults, and in various conditions, the adaptations derived from ego functions, particularly in their coping devices.

In delineating the boundaries of modern psychiatry, it is well to remember that the psychiatrist functions solely in the realm of behavioral dysfunction. He is not an expert in dealing with poverty, overpopulation, urban renewal, automation, or war. However, he should

be capable of dealing expertly with the behavioral difficulties that might arise in people who suffer from deprivation, crowding, slums, unemployment, or massive stress. Though he may be tempted to overstep the boundaries so his expertise, the psychiatrist lacks the power to implement social action outside the mental health field.

This does not mean that we are sure that what we teach is immutable. What we think we know and teach is for the most part a body of knowledge that gives us only the illusion of certainty. We need to create and innovate, to check continually and evaluate. Thus, it is a sad mistake to separate clinical from research programs: neither can exist alone.

[When asked by the editor to elaborate on his critique of psychoanalysis, Grinker replied:]

There is no question that some aspects of psychoanalytical theory are extremely fruitful and would be valuable if they were subjected to operational research. I can think of no more important theoretical formulation applicable to clinical psychiatry than the theory of ego functions, which can be made operational....Indeed, psychoanalytical theory, when not totally ingested, is helpful in clinical understanding and it is important in understanding the therapist's self and some aspects of a specific patient. But theory devoid of empirical research and understanding has led to superordinate control by an authoritative establishment far removed from science.

PL Reflection

Today, we have achieved an understanding of the brain that is equal to the mind. And an understanding of brain worthy of mind. When I was in medical school, the brain was a blob....

Patients are hard to get at because their brains are individual organs. The central fact of psychology is that each one of us stares forth from an individually shaped and genetically determined nervous system into a world seen from this time and place in a way that will never happen again. No wonder we are hard to get at.

We psychiatrists are guardians of this individuality. The fear of our profession stems from this fact: we are guilty by association for threatening society with this mystery and confusion of human individuality. Still we need to stand from somewhere....

DSM-IV has been a gain as a destigmatizing asset but was purchased at a price: We thrust to one side the difficulty of getting at the patient. DSM accepted the assumption of medicine - that the patient is an objective reliable reporter. But this reporter problem is the main problem of psychiatry...

*Leston Havens
APA Distinguished Psychiatrist Lecture, 1995
What is psychiatry all about?*

Classic Study of the Month: Which psychiatric diagnoses are diseases?

Psychiatric ‘diseases’ versus behavioral disorders and degree of genetic influence.

O. Bienvenue et al, *Psychological Medicine*, 2011, Volume 41, pp 33-40

Twin genetic studies give us a clue: Schizophrenia, bipolar illness, autism – not much else

It is commonly asserted that psychiatric diagnoses do not represent diseases. Or at least we do not know if they represent diseases. The disease concept itself frequently is questioned in its relevance to psychiatry. DSM diagnoses are viewed, by critics and opponents alike, as social constructions, which do not correlate to biological diseases of the external world.

Frequently it is claimed we do not know if psychiatric illnesses represent diseases because we do not know the etiologies of those diagnoses. To the extent that etiologies are inferred, the most common category is genetics. Some psychiatric diagnoses are seen as genetic. But even there, it commonly is claimed that they are only partly genetic, because they are not Mendelian or autosomal in their inheritance. Instead a frequently heard summary is that psychiatric diagnoses are about half genetic and about half environmental. This eclectic summary syncs well with the biopsychosocial model concept: in this rendering, the half genetic/half environmental mental illnesses can be approached in a half biological and half psychosocial approach.

In this classic article, the authors, who are led by Kenneth Kendler, the prominent psychiatric geneticist, address the question of whether and to what extent psychiatric diagnoses are genetic, and whether any of them are genetic completely or sufficiently to state they are are “diseases” with a more or less purely genetic etiology. Readers will notice that the authors put genetics in quotes in the title, indicating their own skepticism, before and after their review, of the claim that any psychiatric diagnoses can be seen as representing diseases.

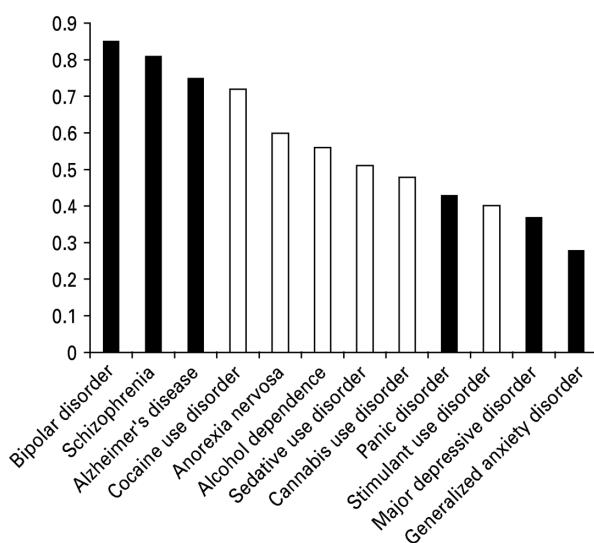


Fig. 1. Heritability summary estimates for psychiatric diseases/disease-like conditions (■) and behavioral disorders (□).

As can be seen in the summary figure, the authors found that recent genetic twin heritability studies strongly supported an almost purely genetic basis for three major diagnoses: Alzheimer’s dementia, bipolar illness, and schizophrenia. These conditions all were above 80% in heritability, which, for non-Mendelian diseases, means that they are mainly genetic. The remaining 10-20% is not necessarily even environmental, but could be statistical noise in quantitative genetic estimates.

In contrast, a number of “behavioral” conditions, which can be seen as syndromes which relate to behaviors or experiences, as opposed to genetic diseases, had lower heritabilities, mostly in the 40-60% range. This is mostly the case with a range of substance abuse and anorexia. These conditions are about half genetic and half environmental, which is consistent with the classic equal mix of biopsychosocial components.

In the figure, the authors color in black three other conditions which they consider “disease-like”, but which have lower heritabilities, mostly in the 30% range. These conditions are primarily environmental, not genetic, which would not be consistent with the idea that they are diseases. The conditions noted are “major depressive disorder”, generalized anxiety disorder, and panic disorder. The authors conclude: "Our results do not strongly support the prediction that psychiatric ‘diseases’ are more heritable than behavioral disorders." In other words, since disease-like conditions are present with both high and low genetic heritability, then genetics is not a good way to identify psychiatric diseases.

Readers of PL will note that the PL conclusion would be the opposite. The authors do not appear to appreciate the origins of MDD and GAD in the DSM-III process. GAD was invented out of thin air to get rid of the diagnosis of neurotic depression. MDD was created out of a mix of different depressive conditions, which

were all lumped together, and have remained connected despite research that opposes this DSM opinion. Conditions like melancholia and neurotic depression are combined as if they are the same, whereas they have different causes and features. Some research, for instance, suggests that melancholic depression is genetic, while neurotic depression is not. If the two conditions are mixed together in the “MDD” concept, then genetic studies would be inconclusive.

The authors are aware of this critique but dismiss it based on some data not supporting it. Yet they don't seem to doubt the validity of DSM definitions, like MDD and GAD, themselves based on weak and inconclusive studies. PL would conclude that this review does support “the prediction that psychiatric ‘diseases’ are more heritable than behavioral disorders,” but it inadvertently also provides more evidence that MDD and GAD not only are not diseases, but are not legitimate valid diagnostic phenotypes.

The PL Bottom Line

- Schizophrenia and bipolar illness are the most genetic psychiatric diseases, and they are almost completely genetic.
- Substance abuse is half-genetic and half-environmental.
- DSM constructs like MDD and GAD are not genetic, and may not be valid “real” phenotypes that correspond to genes.

History of Psychiatry - II

The tragedy of Viktor Tausk:

Origins of some key psychoanalytic ideas in depression and psychosis

PL Note: The great historian of psychoanalysis, Paul Roazen, wrote this brilliant book a half century ago now. In it, he revealed a long-lost story about an early psychoanalyst, Viktor Tausk. This story throws light on Freud in a special and personal way. It also reveals the origins of some key psychoanalytic concepts, like projection, grief in depression, and ego-support. Tausk entered Freud's circle in 1908 as a young medical student in Vienna. In a decade of engagement, he achieved much, but then disappeared. PL readers will see how Roazen's description of Tausk's symptoms and personality clearly matches a diagnosis of manic-depressive illness, which, apparently, was not made during his lifetime, or afterward.

From Paul Roazen, Brother Animal: The story of Freud and Tausk. Alfred A. Knopf, New York, 1969

Freud's preference was for the strong, not the weak. The truthfulness of the patient was reciprocated by the analyst's honest. His method of treatment assumed patients had considerable mental self-discipline and capacity for integrating their newly one insights....Psychoanalysis meant pulling problems apart, on the assumption patients were self-sufficient enough to now best how to put things together. As Freud once wrote, "psychoanalysis meets the optimum of favorable conditions where its practice is not needed - i.e., among the healthy."

Freud demanded that people grow up; he wanted the best out of people, and expected more of mankind. His therapy was based on the notion

that people can change, and overcome themselves. Freud said No - to dishonesty, ignorance, stupidity, symptoms, self-deceptions, suffering, but also to weakness, dependencies, support, tolerance, acceptingness....

While Freud strove to make people better than they were by giving them the tools for self-understanding, Tausk was more inclined to help people accept themselves. In one case of homosexuality...Tausk saw that the patient had so few heterosexual traces that he had to be helped to accept his deviation and to free himself from guilt feelings....For his time Freud was tolerant, and he wanted to understand the roots of perversion, but he found it easier to condemn such a person than to help. About one male homosexual case, Freud commented that "if worst comes to worst, one ships such people...across the ocean with some money, let us say to South America, and lets them there seek and find their destiny..."

Side by side with all Freud's moralism, he could at times be extraordinarily pragmatic. Masturbatory fantasies in intercourse were all right as long as they helped heterosexual potency. Female homosexuality bothered Freud little; in one case of a depressed middle-aged woman, Freud considered her transformation into an active Lesbian, without guilt, a successful outcome of her psychoanalysis....Freud always distinguished between health and worth - "There are 'healthy' people who are not worth anything, and on the other hand 'unhealthy' neurotic people who are very worthy individuals indeed."

Tausk represented a broadening of therapeutic interests of psychoanalysis. Like Adler and Jung, and each of the dissenters within classical psychoanalysis in future decades (e.g., Otto Rank and Sandor Ferenczi), Tausk wanted to extend the areas of psychotherapeutic treatment....[He realized that] removing self-deceptions presupposes that the patient's ego is capable of integrating the new insight presented to it. Otherwise, psychoanalysis may simply strip away a patient's defenses, leaving him sicker than he ever was.

Tausk and his friend [Paul] Federn were more compassionate about illness, and instead of labeling psychotics as narcissistic - being too self-involved - Tausk saw them as suffering from a deficiency in ego strength. The psychotic's problem was weakness rather than excess. Tausk felt that if a therapist could lend some strength to the psychotic's ego, his ability distinguish between the self and outside world would return....The notion of ego boundaries was Tausk's original formulation, and it was designed to emphasize that ego defects lay behind schizophrenia....After Tausk's death, Federn was responsible for developing these ideas within Freud's circle.

The study of ego psychology began under Tausk and Federn with the treatment of psychotic disorders. Subsequently, other analysts, like Anna Freud, became interested in the treatment of children, and made notable contributions in systematizing ego psychology. Erik Erikson, originally a student of Anna Freud's, has made famous the concept of "ego identity"....The concept of "identity" itself was first introduced into the psychoanalytic literature by Tausk....

"Tausk developed the concept of projection in a clinical psychiatric context..."

[Tausk also first presented ideas related to depression and psychosis, now common, involving grief and projection]

Tausk presented a paper on melancholia before the Vienna Society on December 30, 1914. During the discussion on Tausk's paper Freud first publicly expressed his views on manic-depressive problems...Shortly thereafter, in February 1915, Freud wrote a first draft of a classic paper called "Mourning and melancholia." Yet he did not publish it for two years.....

The paper that earned Tausk the greatest psychiatric fame discussed the symptom of the "influencing machine" in schizophrenia. Tausk read the paper before the Vienna society on January 6, 1918...a year later it appeared in print. In this paper Tausk developed the concept of projection in a clinical psychiatric context. Freud had postulated that psychosis involved a regression of the libido back to primary narcissism....Tausk showed how schizophrenic symptoms can represent the earliest stages of the ego's contact with reality. Feelings of inner strangeness best projected onto the external world. Changes in one's own personality are experiences as coming from the outside world.....

[We now turn to earlier parts of Roazen's book, where he touchingly describes the tragedy of Tausk's life, and Freud's role in it.]

Viktor Tausk was one of Freud's most talented early supporters, yet history can be capricious. For although he was a towering figure among pre-World War I psychoanalysts, he has since been completely forgotten....Tausk entered the world of psychoanalysis in 1908, and was dead by 1919....

In the past Tausk had clearly been disturbed. He had periods of depression in which he was full of despair. His depression could be agitated; for instance, at one time he used to go from movie to movie, afternoons and evenings....Knowing him as a living man, full of activity and love of life, no one would have guessed a melancholic past....

[Roazen describes how Freud had declined to analyze Tausk, and instead sent him to another analyst, Helene Deutsch. Tausk saw this as a personal rejection, and was concerned about the distance which Freud kept from him. Gradually, Tausk began to resent Freud, though, unlike Jung, he couldn't bring himself to break with Freud.]

Only slowly had Tausk's rebellion taken shape....Freud had sensed Tausk's latent rivalry for years. In the very first paper that Tausk presented to the Vienna Society, he referred to Plato and Aristotle, mistakenly making the latter into the former's master. Freud picked it up immediately: "Plato is not a successor of Aristotle; he was the older man, and a student of Socrates....."

Freud saw in Tausk only a danger to himself, so he was therefore unable to consider that Task was disturbed and in need of help....

Tausk was a man always in love. As Lou Andreas-Salomé wrote of him, he was a "berserker with a tender heart." With his whole succession of women, most of whom incidentally were Jewish, each time he would get passionately involved for a fairly sustained period and yet each time he drew back in fear....

The precipitating cause of Tausk's suicide was certainly his inability to go through with his marriage to Hilde Loewi. We do not know much about the three-month period between the end of his analysis [with Helene Deutsch] and his suicide. In that time, he met this woman, once again fell in love, and made preparations to marry....

[On his last day of life, the day before he was to marry, Tausk wrote a letter to Freud apologizing for not being able to make the Wednesday evening weekly psychoanalytic meeting at Freud's home. He spent the afternoon with his 17-year-old son Marius, who "was preoccupied with his own young troubles." Roazen writes: "Tausk left his son with one bit of advice - that he not let his life be guided by too rigid principles." Late that night, he wrote a will and two letters, one for Freud and the other for Hilde.

Roazen tells the story.]

By the early morning hours of Thursday (July 3, 1919) Tausk had determined to kill himself...he tied a curtain cord around his neck, put his army pistol to his right temple, and pulled the trigger. Here was a man utterly determined to put an end to his life. Besides blowing off party his head, as he fell he strangled himself....

Within a couple of days Marius went see Freud. [Anna Freud gave him his father's correspondence to Freud and the suicide note, which follows:]

Vienna, July 3, 1919

Dear Professor,

Please render kind assistance to my beloved fiancee....I thank you for all the good which you

have done me. It was much and has given meaning to the last ten years of my life. Your work is genuine and great, I shall take leave of this life knowing that I was one of those who witnessed the triumph of one of the greatest ideas of mankind.

I have no melancholy, my suicide is the healthiest, most decent deed of my unsuccessful life. I have no accusations against anyone, my heart is without resentment, I am only dying somewhat earlier than I would have died naturally....I hope you will have a long life, in health, strong and capable of working. I greet you warmly, Yours, Tausk. Please, also look after my sons from time to time.

{Roazen continues:]

Tausk withheld his motivation from Freud, leaving it enigmatic, but in the will he wrote early that last morning of his life Tausk made clear at least his conscious motives. "I am taking leave of my life, which I have systematically disintegrated since my childhood and which has now completely lost its sense since I can no longer enjoy it. My talent is too little to support me. The recognition that I cannot gladly enter into a new marriage, that I can only keep myself and my beloved ones in conflicts and torments, is the true conscious motive of my suicide. Good bye, mother, brothers, sisters and friends. Live better than I did, dear sons. Forget me all soon. I have deceive you all by living role to which I was not equal."...

He left instructions in his will for all his papers to be burned unread....

[Freud wrote an obituary for Tausk. He praised the younger man's intellect, but noted an excess of passion. Wrote Freud:]

His strong need to establish things on a philosophical foundation and to achieve epistemological clarity compelled him to formulate, and seek as well to master, the whole profundity and comprehensive meaning of the very difficult problems involved. Perhaps he sometimes went too far in this direction, in his impetuous urge for investigation. Perhaps the time was not yet ripe for laying such general foundations as these for the young science of psychoanalysis. The psychoanalytic consideration of philosophical problems, for which Tausk showed special aptitude, promise to become more and more fruitful....His clinical activities, to which we owe valuable researches into various

"... I was one of those who witnessed the triumph of one of the greatest ideas of mankind...."

psychoses (e.g., melancholia and schizophrenia) justified the fairest hopes....His passionate temperament found expression in sharp, and sometimes too sharp, criticisms, which however were combined with a brilliant gift for exposition. These personal qualities exercised a great attraction on many people, and some, too, may have been repelled by them. No one, however, could escape the impression that here was man of importance.....

[In a personal letter to Lou Andreas Salomé, who was close to Freud and had briefly had a sexual relationship with Tausk, Freud revealed his more private thoughts:]

Poor Tausk whose you distinguished a while with your friendship, put a thorough end to his life on July 3....His farewell letters...are alike affectionate...blame no one but his own

inadequacy and bungled life - thus throw no light on the final deed. In the letter to me he avers steadfast fidelity to psychoanalysis, thanks me, etc. But how it might have looked behind that is not to be guessed. So he fought out his day of life with the father ghost. I confess I do not really miss him; I had long taken him to be useless, indeed a threat to the future....I never failed to recognize his significant gift, but it was prevented from being translated into correspondingly valuable achievements.

[Tausk's close friend, Paul Federn, who remained close to and loyal to Freud, wrote to his wife as follows:]

If Freud had shown him a human interest, and not simply recognition and support, he might have continued to bear his martyr-like existence....The methodological rigor which Freud teaches makes people hard and alienates them from their fellow men; he who cannot love is defenseless against failure.....

*“...be who cannot love is defenseless
against failure...”*

[Roazen follows up on Federn's fate decades later in 1950:]

...years later Federn too shot himself. He was then a very old man, seventy-nine...suffering from cancer of the bladder....

[Roazen reviews Freud's complex relationship with Tausk, from support to rejection:]

[Freud] had done everything for Tausk as a psychoanalyst - subsidized his medical education, made him editor of a journal, sent him patients. But Freud did this more for the cause than for the man, and when Tausk began to infuriate him, he simply brushed Tausk aside....

[Coda: Roazen ends by tracing the after-history of the forgetting of Tausk.]

In the two decades between Tausk's death and Freud's own in 1939, Tausk's name came up only occasionally. Freud cited Tausk one more time.....In 1938, the old guard around Freud had occasion once more to think of Tausk. The Nazis were driving Freud and his pupils from Vienna, and the analysts now in difficult financial straits had heard that Tausk's son Marius had one well as an endocrinologist and pharmacologist in Holland; so Federn got in touch with him to see if the loans to his father could now be repaid. [Multiple psychoanalysts] had...all helped Tausk through medical school. Once informed of the debt Marius did not hesitate to pay.

Federn also mention to Marius that Freud had been one of Tausk's creditors, so Marius wrote to Freud to ask how much was owed to him. Freud behaved like a correct gentleman. Though suffering from cancer of the jaw...this secluded invalid of eighty-two remained as formidable as ever; retaining all his sense of dignity and punctiliousness, Freud wrote back to say that he could not remember how much he had lent Marius's father, it could not have been much anyway, and it did not matter any more.....

PL Reflection

One ought to distinguish between greatness of achievement and greatness of personality.

Freud

CurbSide Consults

Questions and cases from you

Question:

I consulted on a patient with multiple sclerosis who was put on lamotrigine for bipolar depression. Three months later, she experienced an exacerbation of her MS, with a painful flare of neurological symptoms, which is the worst she has had for the past five years. This flare also is much more difficult to get under control with usual treatments such as steroids. Her neurologists hold that lamotrigine cannot impact autoimmune disease and that it should help neurological pain. PL has stated that lamotrigine can worsen autoimmune conditions. What is the evidence for this concern, and how can her specialists be convinced?

PL:

Lamotrigine is associated with Stevens-Johnson syndrome (SJS), as is well-known. This serious reaction occurs in about 1 in 5000 adults on average. This agent also causes rash in about 5-10% of persons. This non-serious rash risk is higher in persons with known drug allergies. This overall picture is consistent with the view that lamotrigine is triggering an immune system reaction. People who already are sensitive to immune system hyperactivity would be at increased risk of such reactions with medications like lamotrigine.

The perspective that lamotrigine's effects involve broad immune system reactivity is supported by the fact that its serious adverse event risk is not limited to SJS. It also has other effects that are autoimmune in nature. For instance, lamotrigine has been associated with causing or worsening aseptic meningitis. The FDA issued a warning on

this harm in 2010. The FDA reported 40 known cases reported to it, in 15 of which the reaction occurred in an on-off-on paradigm, meaning going away when lamotrigine was stopped and returning when lamotrigine was resumed. This pattern strongly supports a causal relationship. Autoimmune diseases are among the causes of aseptic meningitis.

Lamotrigine also is associated with hemophagocytic lymphohistiocytosis, another serious immune-mediated reaction which can be fatal. The FDA issued a warning on this risk in 2018 after 8 known cases and one death. Cases of lupus-like syndrome caused by lamotrigine also have been reported.

In short, lamotrigine is associated with a range of dangerous autoimmune or immune-mediated hyperreactivity: not just SJS, but aseptic meningitis, lupus, and hemophagocytic lymphohistiocytosis. On top of the very common rash reaction, which also is immune-mediated, it is clear that lamotrigine interacts with the immune system in a fashion which can lead to hyperreactivity of that system. In persons with autoimmune diseases, such overactivity is already present at baseline, which may place such persons at higher risk when exposed to agents which trigger the immune system, such as lamotrigine.

This is the rationale for drawing this link and arguing that lamotrigine should be stopped in a case such as this patient, who clearly has a temporal relationship with worsening of autoimmune disease and use of lamotrigine. If her doctors remain skeptical, one can ask them to do the A-B-A-B paradigm: stopping lamotrigine (tapering off) to see if autoimmune symptoms improve, and then resuming it to see if autoimmune symptoms worsen, and then stopping it again. This would be a pragmatic test

of their belief that it is safe, and there is no reason for them not to put such a belief to the test.

PL might add that this logic would apply to all scenarios where a patient has a side effect and it is unclear if a drug is causing it. PL would urge clinicians to be open to the pragmatic A-B-A-B test. In almost all cases, there is no harm to stopping a drug briefly, before resuming it, to test whether a side effect resolves and recurs in relation to a drug. The temporality of this

association can be shown to be causal by using this test. Clinicians should avoid the mistake of the physicians who are treating this patient: they refuse to test their beliefs, and instead adamantly continue medication based on their abstract theories. Hippocrates taught us millennia ago that this is the harmful way to practice medicine.

PL Reflection

Therapists are always looking for “good” patients. For some a good patient is someone like themselves. Then there are those who seek the worn-out criteria of “YAVIS” cases (i.e., young, attractive, verbal, intelligent, and successful)....YAVIS cases may or may not be such good patients, but they are sought after by therapist because these patients do proceed naturally, gathering momentum. I know for certain that you cannot refer a DOPUR patient (i.e., dumb, old, poor, ugly, on relief) so easily. Beyond this, the selection criteria for patients are pretty much similar for nearly all therapies. These include a good measure of motivation, an interpersonal capacity to relate to others, a certain stability and responsibility in one’s personal life, and some semblance of self-cohesion....Of course, with all these desired qualities, you may wonder why such a person requires treatment. In reality it is a gross misconception that only sick and disturbed individuals need therapy. In fact, as in the “rich get richer” metaphor, the healthier the patient, the more he or she can get from psychotherapy.

The best patient is the one who doesn't need it at all!

T. Bryan Karasu
Life Witness: Evolution of the Psychotherapist

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The Final Issue

We have reached the final issue of PL. With ambivalent feelings, this will be the last introduction to a newsletter issue.

The final special article is devoted to a central question of clinical practice: psychopharmacology versus psychotherapy, and whether one is better than the other, whether they should be combined, and if so by whom. This topic is discussed at length, with the rest of the issue condensed to a final Psychotherapy section on cognitive-behavioral therapy, using an analogy from baseball, and a final note of farewell.

We would like to remind readers that this December 2018 issue is the final subscription issue of PL. The PL website will remain open for questions and curbside consults, and will include commentary on new journal articles. E-books also will be made available there. In the meantime, PL readers also can buy a new psychopharmacology textbook authored by me, to be published by Oxford University Press in January 2019, now available for pre-order, as described in the sidebar.

Thank you for your past support. Without you, we couldn't have achieved our mission.

Nassir Ghaemi MD, Editor

New truths begin as heresies and end as superstitions - T. H. Huxley

Special Article: Psychotherapy versus Psychopharmacology

How to understand the two main approaches to treatment

A general topic of both clinical and conceptual interest is whether clinical practice in psychiatry should involve using drugs or giving psychotherapy. Should one approach be more common than the other? Should they be combined? Is one better or worse?

This final special article of PL will discuss this central topic, with a focus on the viewpoint that psychoanalytically-oriented approaches should be preferred and provided commonly, along with medications, to many patients, and further that MD-psychiatrists should be seen as best positioned to provide this kind of combined psychopharmacology/psychotherapy treatment.

Psychoanalytic (“psychodynamic”) psychotherapy

At first, it may be useful to define terms. Freud's ideas have evolved and the term “psychoanalytic” has been replaced by “psychodynamic.” The latter term implies something very exciting or profound, which it might be, but PL thinks the older term is less misleading. There is an “analysis” that happens in this approach: interpretation of the meaning of psychological experiences. So PL will continue to use the phrase psychoanalytic therapy.

The nature of psychoanalytic therapies involves a common set of methods, despite many differences in content and emphasis. As Leston Havens described well, the core of all aspects of psychoanalytic approaches involves the method of

free association. Patients are encouraged to think about ideas or feelings that they might not think important, or which they might suppress consciously or repress unconsciously. The concept of unconscious emotions is central to this approach to psychotherapy, and despite many years of controversy about this concept, especially during Freud's lifetime, one can say that experimental research has shown that there certainly are unconscious emotional states. Whether those states involve a predominance of sexual and/or aggressive feelings, as Freud held, can be argued still, but it is not unreasonable to make that assertion based on a certain amount of clinical and empirical evidence regarding human psychology.

“Integration” versus “split” treatment

“The nature of psychoanalytic therapies involves a common set of methods, despite many differences in content and emphasis...”

There has been a major change in psychiatric training and practice in the past few decades. Until the 1990s, it was routine for psychiatrists to be trained in psychoanalytic psychotherapy extensively, and to practice it. As drugs became central to practice, many clinicians trained in that era and earlier have taken to the practice of treating with drugs and psychoanalytic psychotherapy at the same time. Younger psychiatrists trained in the last two decades also tend to receive extensive psychoanalytic teaching, and often practice both approaches at the same time as well. They may not necessarily conduct formal psychoanalytic psychotherapy, with once weekly one hour

sessions (or they might), but they will tend to interpret clinical experiences via psychoanalytic inferences, along with or alongside biological judgments.

The perspective for “integrated” treatment where psychotherapy is combined with psychopharmacology has been presented well in a classic paper by the prominent psychiatrist/psychoanalyst Glen Gabbard, called “Whatever happened to the biopsychosocial psychiatrist?”

In that paper, Gabbard made the point that the biopsychosocial model (BPS) should be seen as the basic conceptual structure of psychiatry, and that it inherently supported the provision of care by a MD-psychiatrist as being preferable to all other mental health professionals. The reasons he gave for this view are summarized below.

The argument for MD psychiatrist-integrated treatment

Gabbard takes a psychoanalytic approach to psychotherapy. When he says psychotherapy, he means the kind that originated in Freud’s psychoanalysis and has been further developed from that basic structure. Some basic psychoanalytic concepts that are relevant to the strengths of single-clinician MD-psychiatrist treatment have to do with concepts like splitting, where patients will treat different clinicians differently, often idealizing one and demeaning another. This cannot happen if a single clinician treats them.

Further he supports the view that patients with psychiatric conditions like depressive or bipolar

or anxiety states often have important aspects of care that may grow out of biological problems, but are not themselves biological. The sense of self, of who they are as persons, can be affected. The distinction between the illness and the person who has the illness is central, and can be addressed only in psychotherapy.

Psychiatrists have a special privileged position, in Gabbard’s view, because they can understand biological and psychological aspects of the interplay between a mental illness, and the person who has it, in a way that is beyond the training of non-medical mental health professionals.

“Psychiatrists have a special privileged position, in Gabbard’s view...”

A key component to the benefit of integrated treatment too, according to Gabbard, is the relevance of more frequent and lengthier visits. The combined psychotherapy/psychopharmacology given by a MD-psychiatrist can occur in weekly one hour sessions, or perhaps biweekly one hour sessions. This set-up is much more preferable than the 15-20 minute “med check” which is so frequent in psychopharmacology practice. In pure psychopharmacology, with brief med checks, the psychiatrist does not get to know the patient as a person. This lack of connection can lead to multiple problems: there can be misdiagnosis of the mental illness itself, as the psychiatrist can misinterpret the patient’s experiences. There can be incorrect medication treatment decisions, as the psychiatrist targets symptoms incorrectly. There also can be classic psychoanalytic experiences that arise in the treatment and impede correct diagnosis and/or treatment and/or adherence to treatment. These include, of course, transference and countertransference between

doctor and patient, but also between the patient and the medication, as well as unconscious beliefs or feelings about a diagnosis or a set of symptoms or certain behaviors.

The harm of the med check

The perspective described above has much to commend it, and PL differs little with it in some clinical aspects. It is a major problem in clinical practice that many clinicians provide medications for psychiatric purposes without getting to know their patients well. This problem mostly is related to insufficient time in clinical appointments. The 15 minute medication check is the problem, in many cases. Sometimes these brief visits are driven for structural reasons:

a clinician may work for an organization (hospital, department, clinic, group practice) where salaries are dependent on the number of patients seen. The shorter the visit, the more patients seen, the more one meets one's salary requirements. This may be good for the clinic or practice, but it is bad for patients. Sometimes, clinicians in private practice see more patients in less time because in that setting, time literally is money. More patients means more income. Again, this is good for the clinician, but bad for the patient.

We should be careful then not to lay blame at the feet of clinicians alone; much of this problem in practice is driven by the health care system in the United States, which is organized poorly, and the subject of intense political interference.

Within this poor health care structure, PL would agree with our colleagues that better care is provided by clinicians who see patients for longer

periods of time. 15-20 minutes is too short; 30 minutes is better; longer would be ideal, especially for complex cases or during symptomatic crises. Initial evaluations also should be longer: 45 minutes is too short; one hour is better; longer is ideal, especially for complex cases or consultations.

"This problem mostly is related to insufficient time in clinical appointments..."

attention to identity, or the "self" of the patient, what Havens used to call "the person in the patient."

All this is correct, but the PL view is that only sometimes is a "psychodynamic" approach required or helpful; sometimes it is irrelevant, weak, or even harmful.

Is it "psychodynamic" or existential?

For instance, where is the literature on the "self" in psychoanalysis? Freud wrote nothing about it. His "ego" was part of a tripartite structure of self-conception, not really a "self." In fact, in the psychoanalytic literature, the concept of the self emerges half a century or more after Freud, in writings of people like Heinz Kohut and Erik Erikson and others in the 1960s and later. Psychoanalytically-oriented colleagues often discuss the concept of empathy in relation to Kohut. This is fine, but Kohut is just one of hundreds of prominent thinkers/therapists who have written about empathy, and most of them

are not “psychodynamic” in training or thinking. The concept of “empathy” was invented and used for the first time in psychiatry by the founder of the existential approach to psychotherapy, Karl Jaspers. The perspective of empathy was central to the existential approach to psychotherapy for half a century before Kohut ever wrote a word about it. The concept of self has been described in detail for the past century in the existential tradition, including with Jaspers during Freud’s own life, and even before Freud with William James.

As to what is really important in psychotherapy, our colleagues note the important work of Jerome Frank, whose

Persuasion and Healing, is a classic. Frank tried to show, as many had argued during Freud’s era and before, that psychotherapy really is about persuasion, about agreement between therapist and client/patient. Some have interpreted this view in a postmodernist bent, about creating a joint “narrative.” The test is utilitarian: Does it help the patient? Does the patient like it? There’s no truth to the matter otherwise. Freud would have disagreed: he went to extensive lengths to argue that his psychoanalytic thinking was discovering some truths of reality, not just persuasion to a shared narrative. It is not Freudian, or psychoanalytic, or “psychodynamic”, to argue for non-specificity of therapeutic influence. However, if it is true, it argues for a general impact of the “therapeutic alliance” as key to psychotherapy benefit. There are some systematic reviews of empirical studies that support this view. If this is true, then it would agree with the central position of the existential approach to psychotherapy, which was about empathy between therapist and client, which was all about the relationship and nothing else, not

“...the PL view is that only sometimes is a “psychodynamic” approach required or helpful; sometimes it is irrelevant, weak, or even harmful.”

interpretations or transferences or defense mechanisms or transference. In short, the literature on the therapeutic alliance from Frank onwards contradicts the psychoanalytic/psychodynamic approach to therapy, and completely confirms the central thesis of the existential approach to psychotherapy.

In short, much of what is argued above in favor of a psychoanalytically-inspired psychotherapy instead is found more clearly in existential psychotherapy. The PL view here is not that psychotherapeutic influences are irrelevant, but that the wrong ones are being promoted.

Psychotherapy by the MD-psychiatrist versus other mental health clinicians

We now come to the practical question about whether the MD psychiatrist is privileged to provide psychotherapy along with psychopharmacology in integrated treatment in a way that other mental health clinicians cannot provide, and whether this integrated treatment is the best approach for patients.

As described above, PL would agree that this perspective could be valid for many patients for whom psychoanalytic concepts would be relevant. Sometimes these factors are quite common, like transference and countertransference, or unconscious feelings about medications.

However, also as described above, many of the reasons claimed to support “psychodynamic” approaches instead do not find strong support in Freudian-inspired psychotherapeutic ideas, but rather are supported and advanced more clearly

and more strongly in the existential psychotherapy approach. If readers agree with this view, then one can ask the question whether MD psychiatrists are trained adequately in the existential psychotherapy approach. The answer is obvious. Most psychiatrists know very little about existential psychotherapy, and it likely is true that at least in the United States, the majority could not tell a questioner one useful fact about its key founders, like Karl Jaspers or Ludwig Binswanger. More would know who Heinz Kohut was.

This reality has to do with the fact that the psychiatric profession in the United States was overwhelmed by Freudian psychoanalytic hegemony for most of the 20th century. Outside of biological approaches, almost nothing else was taught but Freudian orthodoxy and its derivatives (object relations, self psychology, etc). Jaspers and the existential school was ignored almost totally. Social psychiatry approaches (such as Harry Stack Sullivan) had limited impact. Cognitive behavioral approaches were much more prominent in PhD psychology schools rather than in psychiatry residences.

Against eclecticism

The basic problem, as described by the PL editor in book format previously, is that American psychiatry has moved from psychoanalytic dogmatism throughout most of the 20th century to biopsychosocial eclecticism for most of the past few decades. After drugs became more prominent in the 1970s and 1980s, the prior psychoanalytic orthodoxy was preserved by the grafting of drugs on top of it. This hybrid was

“... what is argued above in favor of a psychoanalytically-inspired psychotherapy instead is found more clearly in existential psychotherapy.....”

termed the biopsychosocial (BPS) model. This article cannot do justice to the pros and cons of this philosophy, which the PL editor has described at length in book format. Readers are referred there for a fair discussion of the topic and the rationale for what can be provided here only as conclusions, without sufficient premises or explanation. Suffice it to assert, with that important caveat, that the BPS model was developed by the psychoanalyst/gastroenterologist George Engel as a means of preserving a place for psychoanalytic concepts in medicine (and psychiatry). As noted, the PL approach is not that there is no place for psychoanalytic views in psychiatry; there is a place for such views. The PL approach is that there also are many places in psychiatric practice where psychoanalytic views are irrelevant or even harmful.

The contrast here is between an eclectic approach, as with the BPS model, where everyone is recommended to get biological and psychosocial components to the clinical formulation and treatment. This approach naturally tends to end in the recommendation of medications and psychotherapy, with the latter aspect being psychoanalytically-influenced in the US because of the past century of Freudian hegemony. This eclectic perspective is convenient and self-referential; it is not based on empirical studies but rather on a conceptual assumption that more is better.

This is not to say that it is false. There are scenarios where empirical studies show that combining medications and certain psychotherapies (often CBT, sometimes psychodynamic) are more effective than either approach alone. But this is the case only in some

conditions, and some circumstances, not all or most conditions or circumstances. Yet the combination of medications and psychoanalytically-influenced psychotherapy is provided in practice far more frequently than any other approach.

A method-based scientific approach

The PL approach is method-based, which is synonymous with saying it is scientific. The PL view, which was originated by Jaspers, is that psychiatry has a few basic methods, and these methods need to be used when they should be used, and not used when they should not be used, and scientific research should be the main source of evidence to guide us as to when to use them. What are these methods? Again, space precludes a fair and sufficient discussion. Readers are referred to book-length treatments of the topic elsewhere. Again, providing conclusions without sufficient premises, the PL viewpoint is that one could describe these basic methods of psychiatry in different ways. One could start with Jaspers' dichotomy of *Erklären* (causal explanation) and *Verstehen* (meaningful understanding). Many psychiatric conditions or situations involve biological diseases of the body and brain, which can be understood like any medical disease in a physical reductionistic manner (*Erklären*). Other psychiatric situations involve humans dealing with life dilemmas, not diseases of the body, and an approach that is existential and humanistic is needed (the concept of empathy was introduced by Jaspers as part of his exploration of the method of *Verstehen*).

"The PL approach is method-based, which is synonymous with saying it is scientific..."

Or one could use the version of Jaspers modernized by Paul McHugh, and look at four perspectives of psychiatry: disease (as above, for schizophrenia and manic-depressive disease), dimension (continuous biological traits, as with personality), behavior (as with behavioristic theory, applied substance abuse or eating disorders), and life story (inspired by Frank, a shared narrative approach to meaning). Or one could use the version of Jaspers interpreted by Havens, and look at four schools of psychiatry:

the objective/descriptive school (personified by Kraepelin and the medical model, best applied to schizophrenia and MDI), the psychoanalytic school, the interpersonal school (personified by Sullivan, best applied to managing paranoia and borderline personality), and the existential school (personified by Jaspers, applied to all humans). Or one even could just take Engel's simple tripartite division and split it up: there is a biological approach in psychiatry (which is legitimately reductionistic in some conditions), a psychological approach (which can be subdivided further into psychoanalytic, CBT, existential and other methods), and a social approach (which could be interpreted interpersonally, as with social work traditions, or societally, as in social epidemiology).

One can see with the richness of these various methods or schools that the "psychodynamic" approach is only one of a number of methods or schools, with a limited scope where it is helpful and valid, but with many situations or scenarios where it is not as relevant or valid as other approaches.

The argument for split treatment

The PL view is that non-MD psychiatrists often are better trained and able to apply these other methods or approaches that are need in many psychiatric conditions or cases. MD-psychiatrists tend to be trained well in the biological medical approach, of course (although even there PL has argued for an approach to medical/biological aspects to clinical practice that is different from mainstream psychiatry today), and often trained well in psychoanalytically-influenced approaches to psychotherapy.

However, clinical psychologists tend to be much better trained than MD-psychiatrists in cognitive-behavioral methods, and some clinical psychologists are among the few that are trained formally in existential psychotherapy. Social workers are much better trained than MD-psychiatrists or clinical psychologists in interpersonal aspects of clinical practice, and in societal aspects of psychiatric illness, such as poverty and stigma. Epidemiologists are better trained than any of the above clinical groups on the science of social factors as they affect illnesses. Also, it is worth noting that nurse practitioners often have a broader range of medical experience than many psychiatrists do (given the increasingly common limitation of internal medicine training in psychiatric residencies), which can impact beneficially the use of a medically-sound biological approach to practice.

In short, in all these scenarios, better care would be provided by a non-MD psychiatrist for aspects of treatment outside the medical/biological approach. This claim is not made for all

scenarios, but for some, indeed many, clinical circumstances.

The PL Bottom Line

- There is not a strong conceptual or scientific rationale for combining psychopharmacology and psychotherapy in a general way for most people.
- There are benefits to psychoanalytically-oriented psychotherapy that are specific to a certain scope of problems or situations.
- Other psychotherapies, especially existential psychotherapy, provide more benefits than psychoanalytically-oriented therapy, especially around the themes of empathy, identity, and meaning.
 - The view that the MD psychiatrist provides the best integrated treatment of c o m b i n e d psychopharmacology and psychoanalytically-oriented psychotherapy conflicts with the greater benefit found in many patients with existential psychotherapy or with CBT, for which non-MD mental health professionals tend to be better trained.
 - The integration model is based on a Freudian heritage and an eclectic conceptual model of psychiatry.
 - The alternative approach that accepts split treatment in many cases is less Freudian and more Jaspersian and is based on a method-based model of psychiatry, emphasizing the key schools and methods of the profession, each of which with strengths only within a limited scope.

Psychotherapy

Understanding cognitive-behavioral therapy

A baseball metaphor

From Michael Otto: 10-Minute CBT Oxford University Press, New York, 2011, pp 25-27

This is a story about Little League baseball....It starts with Johnny, who is a player in the outfield. His job is to catch fly balls and return them to the infield players. On the day of our story, Johnny is in the outfield and crack! - one of the players on the other team hits a fly ball. The ball is coming to Johnny. Johnny raises his glove. The ball is coming to him, coming to him....and it goes over his head. Johnny issues the ball, and the other team scores a run.

Now there are a number of ways a coach can respond to this situation. Coach A is the type who will come out on the field and shout: "I can't believe you missed that ball! Anyone could have caught it! You screw up like that again and you'll be sitting on the bench! That was lousy!" Coach A then storms off the field.

At this point, Johnny is standing in the outfield, if he is at all similar to me, he is tense, tight, trying not to cry, and praying that another ball is not hit to him. If a ball does come to him, Johnny will probably miss it. After all he is tense and tight and may see four balls coming at him because of the tears in his eyes. If we are Johnny's parents, we may see more profound changes after the game. Johnny, who typically places his baseball glove on the mantel, now throws it under his bed.

"...while we may all select Coach B for Johnny, we rarely choose the voice of Coach B for the way we talk to ourselves..."

And before the next game starts, he may complain that his stomach hurts, that perhaps he should not go to the game. This is the scenario with Coach A.

Now let's go back to the original event and play it differently. Johnny has just missed the ball, and now Coach B comes out on the field. Coach B says: "Well, you missed that one. Here is what I want you to remember: high balls look like they are farther away than they really are. Also, it is much easier to run forward than to back up. Because of this, I want you to prepare for the ball by taking a few extra steps backwards. As the ball gets closer you can step into it if you need to. Also try to catch it at chest level, so you can adjust your hand if you misjudge the ball. Let's see how you do next time." Coach B leaves the field.

How does Johnny feel? Well, he is not happy - after all, he missed the ball - but there are a number of important differences from the way he felt with Coach A. He is not as tense or tight, and if a fly ball does come to him, he knows what to do differently to catch it. And because he does not have tears in his eyes, he may actually see the ball and catch it.

So if we are the type of parent who wanted Johnny to make the Major Leagues, we would pick Coach B, because he teaches Johnny how to be a more effective player....But if we didn't care

whether Johnny made the Major Leagues...we would again pick Coach B because we care whether Johnny enjoys the game.....

Now while we may all select Coach B for Johnny, we rarely choose the voice of Coach B for the way we talk to ourselves. Think about your last mistake. Did you say, "I can't believe I did that! I am so stupid! What a jerk!" These are Coach A thoughts and they have many of the same effects on us as Coach A has on Johnny....During the next

week, I would like you to listen to see how you are coaching yourself. If you hear Coach A, remember this story and see if you can replace Coach A with Coach B thoughts.

PL Reflection

The psychiatric resident has to learn four tasks to become a good psychiatrist:

1. Help someone mourn a loss.
2. Leave people alone.
3. Hang up the phone.
4. Encourage people.

Leston Havens MD

A final farewell

The mission of the Psychiatry Letter

By Nassir Ghaemi

When I started PL, I felt that there was information that I wanted to share with the clinical community in a way that I could not share in scientific articles or books. I realized that many clinicians turned to newsletters for guidance, and after some consideration of the effort in time and cost, I decided to try this mechanism of communication. I had some things I wanted to say. Over the past four years, I have said those things. Now, I'm finished.

Over half a century ago, one of the core founders of psychopharmacology in the United States, Frank Ayd MD, decided to start a newsletter. He described the plan to another key founder of the field, Harvard psychiatrist Gerald Klerman. Klerman predicted the newsletter wouldn't last long, because Ayd would run out of things to say. Ayd recalled this discussion 40 years later, in the 2000s, when his International Drug Therapy Newsletter had outlived Klerman and would soon outlast its founder Ayd too. Klerman's prophecy applied to me, not Ayd.

I wanted to present a new approach to psychiatry, one that was not present in any other newsletter, and in fact not present in any textbook, nor in most books or scientific articles. This is an approach that is disease-oriented, not symptom-oriented, in treatment as well as in diagnosis. It rejects 20th century American psychiatry's emphasis on DSM for symptom-based diagnosis and standard neurotransmitter-based psychopharmacology for symptom-based treatment. It goes back to the 19th century for an

emphasis on disease and forward to the 21st century for an emphasis on non-neurotransmitter-based psychopharmacology.

Four years of PL archives will remain available on the PL website to allow all visitors to find and read the articles that lay out this approach. Further, these PL articles laid the basis for much of the material in my new textbook of psychopharmacology. In that sense, the material of PL will live on. Further, in the website, we plan to make e-books available so that this material is accessible more easily, and I plan to continue to provide analyses and commentary on new scientific articles as they are published.

PL never was destined to continue just for the sake of continuing. It didn't exist, like other newsletters, just to fund itself. Recently, another newsletter approached PL to buy its subscriber base. PL wasn't for sale.

It had a mission.

Mission accomplished.

PL Reflection

When making a decision of minor importance, I have always found it advantageous to consider all the pros and cons. In vital matters, such as the choice of a mate or a profession, the decision should come from the unconscious, from somewhere within ourselves.

In the important decisions of our personal life, we should be governed, I think, by the deep inner needs of our nature.

Sigmund Freud

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