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Chapter Six

PSYCHIATRIC DRUGS AND COMMON FACTORS:

AN EVALUATION OF RISKS AND BENEFITS FOR CLINICAL PRACTICE

Daring as it is to investigate the unknown, even more so it is to question the known.

Kaspar

According to the Agency for Healthcare Research and Quality, the number of people using psychiatric drugs in the US increased from 21 million in 1997 to 32.6 million in 2004, and spending climbed from $7.9 billion to $20 billion during the same period (Stagnittie, 2007). A 2004 review of prescription data for 300,000 children concluded that, for the first time, spending for medications for childhood behavior problems eclipsed expenditure for any other drug category, including antibiotics (Medco Health Solutions, Inc., 2004). While psychotropic drug use has risen, community behavioral intervention has remained flat or declined (Case, Olfson, Marcus, & Seigel, 2007). More and more, treatment means medication.

But are the skyrocketing rates of prescription justified by clinical trial evidence? This chapter addresses this fundamental question via a risk/benefit analysis of the major drug classes for all age groups and provides a template for clinicians to both evaluate the drug literature and facilitate medication decisions with their clients. This chapter also places medication treatment, like other interventions, within a common factors context, asserting that, like psychotherapy, pantheoretical elements are unacknowledged linchpins behind improvement.

ANTIDEPRESSANTS

According to a recent study of 5.5 million private health insurance enrollees, antidepressants account for the greatest single expenditure for any form of mental health care and 66.7% of all

psychotropic drugs (Larson, Miller, & Fleming, 2007). The National Institute of Mental Health's (NIMH) website asserts that, while a variety of antidepressants and psychotherapies are useful treatments for depression, "people with moderate to severe depression most often benefit from antidepressants. Most do best with combined treatment. . ." (http://www.nimh.nih.gov/publicat/depression.cfm#ptdep5). The NIMH also states that "antidepressants may cause mild and, usually, temporary side effects…Typically these are annoying, but not serious" (p. 5). In short, according to the government agency tasked with researching and disseminating state-of-the-art treatment information, antidepressants are the treatment of choice for all but mild depressions and are both effective and safe.

Empirical evidence paints a different picture. The only large-scale population-based study of antidepressants found that, for users of antidepressants compared to non-users, the duration of depression episodes was longer and the number of episodes was higher for users (Patten, 2004). Kirsch and Sapirstein (1998), in a meta-analytic review of nineteen studies involving 2,318 people, showed that 75 percent of the response to antidepressants was duplicated by placebo. They speculated that the remaining 25 percent of the positive antidepressant effect may be attributable to the un-blinding power of side effects. Adding to the critique, Kirsch, Moore, Scoboria, and Nichols (2002) analyzed the efficacy data submitted to the US Food and Drug Administration (FDA) for the six most widely prescribed antidepressants approved between 1987 and 1999. Approximately 82% of the response to medication was duplicated by placebo control groups—57% of the studies failed to show a drug-placebo difference. When a difference was found, the drug/placebo difference was only, on average, *1.8 points* on the clinician-rated Hamilton Depression Rating Scale (HDRS). FDA memoranda intimated that the clinical significance of such a small difference was questionable (Laughren, 1998).

In a review of antidepressant trials involving 12,564 persons (Turner, Matthews, Eftihia Linardatos, Tell, & Rosenthal, 2008), 94% of published trials had favorable results whereas the percentage of positive results for published and unpublished trials together drops to 51%. The authors warn that publication bias of this magnitude dramatically distorts reported effect sizes and has serious implications for researchers, health care professionals, and clients. Kirsch et al. (2008) provide further evidence that the belief in antidepressant efficacy is scientifically unfounded. Meta-analytically examining all trials submitted to the FDA for the licensing of four popular SSRIs, the authors found no clinically significant differences between placebo and the drugs, with the exception of the most distressed in the severely depressed group. Even this negligible difference was found to be due not to the drug, but to a decreased response to placebo.

"Treatment resistant depression" prompted the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) (Rush et al., 2004), a -6-year, $35 million NIMH-funded study with nearly 2,900 participants (complete data available for analysis) at level one examining the impact of sequenced augmentation or drug switching strategies on depression when a traditional regimen of a single SSRI failed. STAR*D was an un-blinded, non-placebo-controlled trial designed to simulate conditions faced in daily practice. The sample, however, did not represent a general clinical population since it excluded those with a history of intolerance or non-response to any SSRI and included only those who preferred a medication intervention. Due to the lack of a placebo and double blind, the authors acknowledge that, "Nonspecific treatment effects [e. g., the expectation of improvement] undoubtedly accounted for some unknown proportion of the acute response or remission rates" (Trivedi et al., 2006a, p. 37).

Even though the design favored a drug response, the results were disappointing. In the STAR*D, the average remission rate based on the primary outcome measure was 28% and 25%

on the first two levels, and 14% and 13% on the last two—particularly unimpressive considering the typical 30% placebo response in antidepressant trials (Thase & Jindal, 2004). At Level 1, 28% experienced moderate to intolerable side effects (Trivedi et al., 2006a). At Level 2 (participants augmented or switched), 51% experienced side effects ranging from moderate to intolerable (Rush et al., 2006a; Trivedi et al., 2006b). For all levels, 24% exited due to drug intolerability (Rush et al., 2006b). Data from the 12-month follow-up of those who either remitted or responded indicated a relapse rate of 58% (Rush et al., 2006b).[1]

The conventional assumption that both psychotherapy and pharmacotherapy combined produce better outcomes for depression also garners scant empirical support. Early reviews demonstrated no advantage for combining approaches (e.g., Antonuccio, Danton, & DeNelsky, 1995), but Thase et al. (1997) found that combining the two offered some added benefit for the minority suffering with severe, recurrent depressions. Support for a combined regimen for more chronic depressions is also found in the Keller et al. (2000) trial. The combined group improved more than the medication or psychotherapy groups at 12 weeks. Results were weakened by the lack of a placebo control group and the use of only a single clinician-rated outcome measure.[2]

The negligible advantage of SSRIs over placebo underlines the importance to detect their adverse effects. Common side effects, including agitation, sleep disruption, gastrointestinal complications, and sexual problems reach upwards of 40% of SSRI takers (Antonuccio et al., 1999). SSRI induced mania (Preda, MacLean, Mazure, & Bowers, 2001) and suicidality (Healy, 2003) have been concerns since the early nineties. The FDA reviewed 295 antidepressant trials of over 77,000 adults to examine the risk of suicidality (FDA, 2007, May 2) and found that the relationship between antidepressants and reported suicidality is strongly related to age. The risk associated with drug treatment relative to placebo was elevated for those under age 25. As a

result, the FDA proposed that manufacturers update the existing “black box” warning (which currently warns about the higher risk with youths taking antidepressants) to include the increased risks of suicidal thinking and behavior in young adults during initial treatment.

ANTIPSYCHOTICS

Antipsychotic use has expanded beyond hospital wards and after-care clinics to include the young and old, in all walks of life, many diagnosed with bipolar disorder, irritability, disruptive behaviors, and other non-psychotic problems (Aparasu, Bhatara, & Gupta, 2005; Moreno et al. 2007). Prescription rates for second generation antipsychotics (SGAs) tripled in a 5-year time frame from 1998 to 2002 (Aparasu et al., 2005). According to Aparasu et al., the shift from first to second generation agents is not “unambiguously supported by extant safety and efficacy data [but] is endorsed by guidelines based on expert-consensus and limited data” (p. 147).

Antipsychotic medication is viewed not as a choice, but a requirement (Thase & Jindal, 2004)—those diagnosed with severe psychiatric disorders purportedly need continuous medication to manage a presumed lifelong struggle with mental illness. However, studies discredit the medication-necessity myth, indicating improved outcomes (e.g., lower rates of relapse, better overall global functioning) for persons either never on drugs, or weaned from them, than for those continually medicated (e.g., de Girolamo, 1996; Harrow & Jobe, 2007).

Even with evidence that recovery need not entail drugs, diagnoses such as schizophrenia and bipolar disorder are generally considered “untreated” unless the person is compliant with an antipsychotic regimen. SGAs are often credited as presenting fewer side effects than first generation antipsychotics (FGAs), thereby improving both compliance and treatment longevity. Indeed, medication compliance, inextricably tied to client experiences of side effects, is widely considered the benchmark of successful treatment. The degree to which this factor defines

outcome is reflected in the largest study of these medications to date, the NIMH funded Clinical Antipsychotic Trials of Intervention (CATIE) (Lieberman et al., 2005). In CATIE, the primary outcome measure was not clinical improvement or remission—it was simply discontinuation of treatment for any reason. CATIE enrolled 1,400 participants at 57 US sites and used a triple blind—clinicians, raters, and participants did not know which drug participants were taking. However, CATIE had no placebo group, allowed clinicians to make flexible dosing decisions, and permitted multiple additional drugs (excluding antipsychotics). The goal of CATIE was to valuate how well SGAs (olanzapine—Zyprexa, quetiapine—Seroquel, resperidone—Respidal) compared with one another and a FGA (perphenazine—Etrafon) in real world conditions.

Results from the CATIE trials confirm what many clients report anecdotally—antipsychotics do not improve general life domains and carry a significant side effect burden. Overall, a disconcerting 74% of CATIE participants discontinued before 18 months, largely due to inefficacy and intolerable side effects (Lieberman et al., 2005). The authors note that these rates are consistent with those observed in previous antipsychotic drug trials. Psychosocial functioning improved only modestly for the one third of CATIE participants who reached the primary Quality of Life Scale endpoint at 12 months (Swartz et al., 2007). Rates of moderate to severe adverse events revealed through systematic inquiry ranged from 42 to 69% (Zyprexa the worst) (Stroup et al., 2007). Hospitalization rates ranged from 11 to 20% over the study period, while a weight gain of over 7% occurred in 14 to 36% of participants (Zyprexa worst). The lead author of the CATIE studies admitted: "…the claims of superiority for [SGAs] were greatly exaggerated. This may have been encouraged by an overly expectant community of clinicians and patients eager to believe in the power of new medications. At the same time, the aggressive

marketing of these drugs may have contributed to this enhanced perception of their effectiveness in the absence of empirical information" (Lieberman, 2006, p. 1070).

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), another major investigation funded by the NIMH, examined the effectiveness of SGAs and anticonvulsants for persons diagnosed with bipolar disorder (Sachs et al., 2003). In one of two outcome reports, only 30% experienced no recurrences of symptoms (Perlis et al., 2006); the second (Nierenberg et al., 2006) found even lower rates of recovery (just under 15%). Furthermore, results of the Work and Social Adjustment Scale evaluated during a period of remission revealed "considerable functional impairment" (Fagiolini et al., 2005, p. 284). Similar to CATIE findings, remission from clinically defined symptoms, even for the few who achieved this, did not mean adequate social functioning. Of note, in both STEP-BD outcome publications, no details are provided regarding treatment-induced adverse effects.

CHILDREN AND ANTIDEPRESSANTS

STAR*D, CATIE, and STEP-BD substantially weaken the position that antidepressants, antipsychotics, and anticonvulsants are "effective" for adults. Several large trials, often cited as evidence justifying child psychotropic prescription, follow suit. Consider, for example, two randomized, placebo-controlled trials of fluoxetine (Prozac) (Emslie et al., 1997; Emslie et al., 2002). The "Emslie trials" gained FDA approval for Prozac for young people aged 8-17 diagnosed with depression (FDA, 2003, January 3). Given the failure of tricyclic antidepressants to show efficacy for this age group (Fisher & Greenberg, 1997), Prozac's approval was widely considered a breakthrough for the treatment of youth depression. However, both Emslie studies failed to find a statistical difference between Prozac and placebo on primary outcome measures.[3]

Additionally, in both trials, manic reactions and suicidality were notably higher in the drug group compared with placebo (see Sparks & Duncan, in press for an analysis of the Emslie trials).

The NIMH funded Treatment of Adolescent Depression Study (TADS) (TADS Team, 2004), again evaluated Prozac for the youth age group. TADS compared the efficacy of four treatment conditions: Prozac alone, cognitive behavioral therapy (CBT) alone, CBT plus Prozac, and placebo. Despite media claims, (*The New York Times* front page headline, "Antidepressant Seen as Effective in Treatment of Adolescents," Harris, 2004), the good news seems less so upon examination. The FDA did not count TADS as a positive study for SSRIs due to the negative findings on its primary outcome measure. Other end-point comparisons in TADS favored the combined medication/CBT arm. However, treatment was unblind, and only the combined group received all intervention components (drug, psychotherapy, psychoeducation and family therapy, and supportive pharmacotherapy monitoring), creating a significant disparity in favor of the combination arm. Adding to the bad news, the TADS recorded 6 suicide attempts by Prozac takers compared to 1 by non-Prozac takers, with more than double the incidence of harmful behavior in the Prozac conditions compared to placebo groups (despite the exclusion of youths deemed at high risk for suicidal behavior). Nevertheless, the authors recommended that "medical management of MDD with fluoxetine, including careful monitoring for adverse events, should be made widely available, not discouraged" (TADS Team, 2004, p. 819), a challengeable conclusion given its inconsistency with the study's own harm data.

The long-term TADS efficacy and safety trial contains similar problems. In this 36-week study, partial and non-responders to placebo, and responders and partial responders to Prozac, CBT, and combination treatments in the 12-week trial were openly treated (The TADS Team, 2007). As in phase 1, Prozac and combination groups received additional encouragement and

contact (medication management). Despite this, all treatment conditions converged by 30 weeks and remained so by week 36, with significantly more suicidal ideation in the Prozac alone group. The percentage of suicidal events for those on Prozac, whether in combined or alone groups, was nearly 12%, double the 6% in the CBT group. Despite the convergence of efficacy and continued risks, TADS is often cited as evidence that combining psychotherapy and medication produce superior results (e.g., http://www.nimh.nih.gov/healthinformation/tads.cfm).

Jureidini et al. (2004) questioned the clinical significance of results that show no gains on primary or client/parent-rated measures and highlight other design weaknesses, including reliance on the last observation carried forward, an emphasis on secondary endpoints, and transforming continuous into categorical outcomes thereby inflating small differences. Moreover, publication bias—studies finding in favor of the investigative drug are published whereas unfavorable studies are not—clouds the picture of SSRI efficacy for youth depression. An independent analysis by the FDA concluded that only 3 out of 15 published and unpublished trials of SSRIs showed them to be more effective than placebo on primary outcome measures (Laughren, 2004). None of the 15 found differences on client or parent rated measures.

The risks noted in published and unpublished data prompted the FDA to issue a black box warning on all antidepressants for youth for increased risk of suicidality and clinical worsening (FDA, October, 15, 2004). Further support of the warning emerged from an analysis of placebo-controlled trials of nine antidepressants, a total of 24 trials involving over 4,400 children and adolescents (Hammad, Laughren, & Racoosin, 2006). The investigation revealed an average risk of suicidality of 4% in drug treated youth, twice the 2% placebo risk.[4]

CHILDREN AND STIMULANTS

In the first three years of this decade, spending for ADHD drugs, including amphetamine (Adderall), methylphenidate (Concerta, Ritalin), and atomoxetine (Strattera) increased 183% for children overall and 369% for children under 5 (Medco Health Solutions, Inc., 2004). While the US continues to lead the world, global use of ADHD drugs has increased by 274% (Scheffler et al., 2007). The empirical literature, however, is equivocal regarding stimulant benefits. A review of forty years of trials supporting stimulant prescription (primarily Ritalin) found overall effect sizes in the moderate range, with low to moderate ranges for academic productivity and in the zero range for academic achievement (Conners, 2002). The American Psychological Association (APA) Report of the Working Group on Psychoactive Medications for Children and Adolescents (hereafter Working Group) (Working Group, 2006) noted the lack of data supporting long term efficacy or safety. Further highlighted was that stimulants, while reducing symptoms, show minimal efficacy in general life domains of the child, including social and academic success.

Stimulant advocates, however, point to the Multimodal Treatment Study of Children with ADHD (MTA) (MTA Cooperative Group, 1999), the largest, most complexly designed trial of interventions for ADHD, as proof that stimulants are more effective than behavioral approaches. Much like the Emslie studies are used to justify antidepressants for youth, the MTA is the virtual infrastructure of stimulant prescription. Yet, just like the Emslie trials, the MTA is far from persuasive. Only 3 of 19 measures, all un-blinded, found differences favoring Ritalin. Neither blinded classroom observers, the children themselves, nor their peers found medication better than behavioral interventions. Moreover, 14-month endpoint assessments compared those actively medicated and those who had ended therapy (4 to 6 months after the last, face-to-face, therapeutic contact) (Pelham, 1999). Given this unfair comparison, the fact only 3 un-blinded

measures found an advantage for Ritalin is telling. At the same time, 64% of MTA children were reported to have adverse drug reactions: 11% rated as moderate and 3%, severe.

A 24-month follow-up showed that group differences were even smaller; the medication and combined groups lost much of their effect (up to 50%) while behavioral treatment and community groups retained theirs (MTA Cooperative Group, 2004). At 36 months, treatment groups did not differ significantly on any measure (Jensen et al., 2007). Decreases in growth in medicated children averaged 2.0 cm and 2.7 kg less than not medicated groups, without evidence of growth rebound at 3 years (Swanson et al., 2007).

To address concerns about the use of stimulants without FDA approval with children under 6, the Preschool ADHD Treatment Study (PATS) investigated the efficacy and safety of Ritalin for preschoolers aged 3 to 5.5 (Greenhill et al., 2006). Only 21% of the children achieved MTA-defined criterion for remission. In addition, rates of adverse events, including irritability, repetitive behaviors, tics, and emotional outbursts were significantly higher in the Ritalin group. Annual growth rates for the children who remained on medication were 20.3% less than expected for height and 55.2% less for weight (Swanson et al., 2006).

In March of 2006, a safety advisory committee of the FDA urged stronger warnings on ADHD drugs, citing reports of serious cardiac risks, psychosis or mania, and suicidality. Despite this recommendation, the FDA elected to forgo a black box warning for most ADHD drugs,[5] choosing instead to highlight risks on the label and include information with each prescription.

CHILDREN, ANTIPSYCHOTICS, AND OTHER PSYCHOTROPICS

Prescriptions for children do not stop with antidepressants or stimulants. Prescribers increasingly select from antipsychotics, anticonvulsants, hypertensives, and novel agents (Zito & Safer, 2005). A 2007 study compared the rates of diagnosis of bipolar disorder for ages 0-19 for the

years 1994-1995 and 2002-2003 (Moreno et al., 2007). Investigators found a 40-fold increase in this diagnosis. Of these, more than 90% were treated with psychoactive drugs, approximately one half an antipsychotic and one third, an anticonvulsant. Most of the children were prescribed more than one medication, and only 4 out of 10 received psychotherapy. According to another study of a large national sample, diagnoses of ADHD or conduct disorder were frequently associated with antipsychotic prescription, suggesting the use of these drugs for control of aggression, irritability, and other unwanted behaviors (Cooper, Arbogast, Hickson, Fuchs, & Ray, 2006). Two diagnostic categories, ADHD and bipolar disorder, accounted for 50% of all antipsychotic use in this sample (age 2-18), despite the fact that use of these drugs for these disorders are a far cry from the psychotic symptoms that have traditionally justified prescription.

The APA Working Group found that studies supporting the use of antipsychotics to treat children were plagued with methodological limitations, including small sample sizes, open trials, and lower tier evidence (e.g., retrospective chart reviews and case reports). Nevertheless, based on a series of industry-sponsored studies, the FDA recently issued an approval for Risperdal for children diagnosed with autism and exhibiting irritability or aggression, even though these studies were limited in design and scope and indicated significant rates of somnolence, weight gain, and movement disorders (see Constructing Evidence, for an analysis of these studies).

Moreover, in August, 2007, the FDA also approved Risperdal for the treatment of adolescents aged 13 -17 diagnosed with schizophrenia and for children and teens aged 10-17 diagnosed with bipolar disorder (FDA, August 22, 2007). The approval was based on four Janssen (maker of Risperdal) conducted trials: a 6-week double-blind placebo-controlled trial (for schizophrenia), a 3-week double-blind placebo-controlled trial (for bipolar I), an 8- week comparison of two Risperdal doses, and a 6-month open-label safety trial. Information regarding

these trials was located in a memorandum written by the FDA Deputy Director of the Division of Psychiatry Products (Mathis, 2007, June 18) and documents faxed by Janssen in response to a request for information. *All the trials are unpublished poster presentations*.

The decision to approve Risperdal is cause for concern. The number of serious adverse events (SAEs) for youths on Risperdal in the short-term trials was more than 6 times that of placebo—and, in at least 2 instances, hospitalization was required. In the 3-week trial, there were 6 suicide attempts for Risperdal takers compared to 1 in the placebo group. Also in this study, the incidence of EPS was 23% and 12% for the high and low dose Risperdal, respectively compared to 5% for placebo. Adverse events occurring with rates at least twice those of placebo in the two placebo-controlled trials included somnolence, anxiety, hypertonia, dizziness, and EPS. In the 6-month open label study, 32% dropped out (reason not given); one third of participants experienced EPS, 27%, somnolence, and 15%, weight increase. A significant increase in body weight also occurred in the 6-week trial (16% Risperdal, 2% placebo) and 8-week comparison study (39% high dose, 16% low dose). Ninety seven percent of youths had prolactin levels above normal in the high-dose group and 64% in the low dose group.

The approval of Risperdal expands SGA prescription for a wide spectrum of child behaviors. For young people falling under the popular bipolar umbrella, a 3-week trial sufficed as evidence of efficacy. Of the 10-17 year-olds in this study, only 36% were enrolled due to manic episodes. The remaining 64% were described as experiencing a behavior disorder—fifty percent had a diagnosis of ADHD. The use of this antipsychotic as a behavior management tool warrants examination of the boundary between treatment and control. The memorandum reassures the regulatory agency that Risperdal is “reasonably safe” (Mathis, 2007, June 18, p. 16). Yet evidence from safety assessments contradicts this conclusion. The conclusion that “there

were no unexpected adverse events" is ironic—the troubling side effect profile of this drug is well publicized in the child and adult literature. The FDA's decision to approve Risperdal is a risky and potentially harmful action not supported by the data.[6]

Finally, consider the NIMH funded Treatment of Early Onset Schizophrenia Spectrum Disorders (TEOSS) (McClellan et al., 2007). This landmark trial, initially compared in scope to the MTA and TADS, sought to examine the efficacy, tolerability, and safety of two SGAs (Risperdal and Zyprexa) for youths diagnosed with early-onset schizophrenia spectrum disorder and to compare these to a FGA (molindone or Moban). Of the 119 participants, 41% withdrew either as a result of adverse effects or inadequate efficacy. A 17-year old boy committed suicide and an unspecified number of participants were hospitalized due to suicidality or worsening psychosis. These events are particularly disturbing in light of the fact that youths considered at risk for suicide were excluded from the study. Weight gain (not specified) was deemed serious enough to warrant suspension of the Zyprexa arm. By 2007, reports on TEOSS are scant. The NIMH does not describe this study on its website, nor list it as an on-going or completed trial. No published reports for those responders who continued into the 44-week phase are available.

A CRITICAL FLAWS ANALYSIS

The fact that a for-profit industry plays a role in fashioning what counts as evidence may no longer surprise many. The former editor of the *New England Journal of Medicine* called attention to the problem of "ubiquitous and manifold . . . financial associations" authors of drug trials had to the companies whose drugs were being studied (Angell, 2000, p. 1516). The result is a direct correlation between who funds the study and its outcome. For example, Heres et al. (2006) looked at published comparisons of five antipsychotic medications. In 9 out of 10 studies, the drug made by the company that sponsored the study was found to be superior.

Government agencies and academic advisory panels, presumably the watchdogs over industry-sponsored research, are not the firewalls many assume. In a Pulitzer Prize winning report, Willman (2003) investigated the National Institute of Health and found widespread ties to pharmaceutical money. Financial conflicts of interest among FDA advisory members are common (Lurie et al., 2006). Cosgrove, Krimsky, Vijayaraghavan, and Schneider (2006) noted "strong financial ties between the industry and those who are responsible for developing and modifying the diagnostic criteria for mental illness" (p. 154). Experts who formulate practice parameters often serve as consultants for drug companies (Choudhry, Stelfox, & Detsky, 2002).

Antonuccio, Danton, and McClanahan, (2003) detail the vast reach of the pharmaceutical industry—from Internet, print, and broadcast media, direct-to consumer-advertising, "grassroots" consumer-advocacy organizations, and professional guilds to medical schools, prescribing physicians, and research—even into the board rooms of the FDA. They conclude, "It is difficult to think of any arena involving information about medications that does not have significant industry financial or marketing influences" (p. 1030). Given the infiltration of industry influence, reliance on press reports, web pages, and even the academic literature as a basis for sound decision-making is unwise. Discerning good science from good marketing requires a willingness to engage primary source material, and a critical flaws analysis.

Flaw # 1: Compromises to the Blind

Fisher and Greenberg (1997) assert that the validity of studies, in which a placebo is compared to an active medication, depends upon the "blindness" of participants who rate the outcomes. They note that inert sugar pills, or inactive placebos, do not produce the standard side effect profile of actual drugs—dry mouth, weight loss or gain, dizziness, headache, nausea, insomnia and so on. Since study participants must be informed of the possibility and nature of side effects in giving

consent, they are necessarily alert for these events, enabling them to correctly identify their study group. In addition, interviews that listen for or elicit side effect information easily reveal active versus inactive pill takers, effectively un-blinding the study for clinical raters and skewing results. Moreover, many trial participants in placebo groups have previously been on drug regimens, even some just prior to entering the trial, and are therefore familiar with medication effects. In support of this theory, a meta-analysis of Prozac found a significant correlation between reports of side effects and outcome (Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994). A meta-analytic review of studies using active placebos (side effects mimic active drug) also supports this hypothesis, finding negligible differences between medication and placebo groups (Moncrieff, Wessely, & Hardy, 2004).

Maintenance versus withdrawal trials can also compromise double blinds. Consider, for example, a recent study of long-term use of Risperdal for children and adolescents diagnosed with disruptive behavior disorders (Reyes, Buitelaar, Toren, Augustyns, & Eerdekens, 2006). All children (ages 5-17) who had responded to the drug in an open label, 12-week trial prior to the study's start were randomized to 6 months of double-blind treatment of either Risperdal or placebo. There was no down-titration of medication for those switched to placebo. At the end of the study, the groups were evaluated based on time to symptom recurrence. As might be expected, time to recurrence was significantly shorter for those who were abruptly withdrawn than for those who continued without change. In this trial and others like it, not only does the design ensure an outcome favorable to the drug, the blind between groups is likely compromised due to the predictable responses of those experiencing a precipitous withdrawal.

Flaw # 2: Reliance on Clinician Measures

Fisher and Greenberg (1997) demonstrate that clinicians and clients often differ substantially in their judgment of improvement in clinical trials. A meta-analysis of 22 antidepressant studies involving 2230 persons found that both tricylics and SSRIs showed an approximate 20% advantage over placebo on clinician-rated measures, but *none* on client-rated measures (Greenberg, Bornstein, Fisher, & Greenberg, 1992). In the Emslie studies, the MTA, and TADS, client-rated measures found no difference between the placebo and SSRIs and among the conditions in the MTA. The lack of endorsement of efficacy by clients in clinical trials begs the question: If clients don't notice improvements, how significant can those rated by others be?

In addition, clinician-rated scales are often categorical, allowing a subjective range of responses to participant interviews and potential bias due to compromised blind conditions. Continuous measures are often converted into discrete categories of responder and non-responder further magnifying differences. Finally, some clinician-rated measures tilt toward specific domains of discomfort that favor the investigative drug, potentially distorting findings. For example, the HDRS contains 6 points that favor medications with sedative properties and many trials add sedatives or use drugs with sedative effects (Moncrieff, 2001).

Flaw # 3: Time of Measurement

Psychiatric drugs are often prescribed for long periods of time. This suggests that most clinical trials, which last for 6 to 8 weeks, are not measuring how well the drugs do in actual settings. Additionally, differences between medication and placebo groups often dissolve over time (Fisher & Greenberg, 1997). Without longer term follow-ups, conclusions about effectiveness in real life cannot be determined. Authors of many short-term clinical trials fail to discuss time-frame limitations or to modify accordingly claims made in conclusions. For example, Emslie et

al. (1997), an 8-week study, concluded that “fluoxetine in 20 mg/d is safe and effective in children and adolescents,” (p. 1036) without mention of time.

It could be argued that time limitations favor placebo, and, given enough time, antidepressants, for example, will prove their superiority. However, data from the NIMH Treatment of Depression Collaborative Research Project (TDCRP) suggest otherwise. The 18-month follow-up data (Shea et al., 1992) found clients assigned to placebo (plus clinical management) had intent-to-treat outcomes comparable to that in the active drug condition (plus clinical management). Even with maintenance antidepressants, up to 33% of remitted clients experience a return of depressive symptoms (Byrne & Rothschild, 1998). The significant rates of relapse in STAR*D (58%) underscore the inability of antidepressants to provide long term relief for many. Similarly, the MTA and CATIE show that differences with non-drug treatments tend to dissipate over time, and that initial effects of drug treatment must be weighed in terms of long term tolerability and impact beyond symptom remission. Time, therefore, is a principal consideration in assessing clinical trial findings, and claims of superiority for the investigative drug based on results of 8-week (or shorter) trials must be interpreted within the context of what longer-term studies have shown.

Flaw # 4: Minimization of Risks

Many psychiatric drug studies downplay or fail to assess adverse drug reactions. As a result, rates of side effects may be substantially under-reported (Safer, 2002). Moreover, clinical trial publications typically do not give adverse events the same status as efficacy data. Instead of detailed tables, adverse events may be described in a narrative rather than tabulated formats (e.g., Emslie et al., 1997). Statistical significance for safety comparisons, unlike efficacy comparisons,

may not be reported. Authors of trials often confidently assert in abstracts and discussion sections that the drug is safe when the data, in fact, show otherwise.

Consider a 26-week randomized, double-blind placebo-controlled trial designed to evaluate the safety and efficacy of the antipsychotic aripiprazole (Abilify) to prevent relapse of mood episodes for persons diagnosed with bipolar I disorder (Keck et al., 2006). No less than 88% of participants dropped out of the study. Reports of akathisia (pronounced inner restlessness), tremor, and pain in the extremities in the Abilify group were at least twice that of placebo. The authors mention that there were "more" adverse events related to extrapyramidal symptoms (EPSs) for those on Abilify than placebo, but fail to analyze this difference statistically. Significant weight gain was also seen for 13% of those taking Abilify versus none for those on placebo. In their conclusions, the authors blandly state that, during the trial, "aripiprazole exhibited no unusual or unexpected adverse events," and the tolerability profile was consistent with that found in other trials of the drug (Keck et al., 636). On the surface, this sounds reassuring. However, a consideration of the 88% drop out combined with a consistent pattern of increased incidence of akathisia, EPS, and weight gain is anything but reassuring.

Flaw # 5: Conflicts of Interest

Richard Smith, who resigned as editor-in-chief of the *British Medical Journal* because of rampant industry influence in academic research, explains that the number one aim of industry-sponsored trials is to find favorable results for the company drug (Smith, 2003). He notes a host of strategies that help accomplish this goal, including comparing the industry drug against another known to be inferior, comparing a low dose of a competitor's drug to prove efficacy and high dose to prove less toxicity, using multiple endpoints, then picking the one that casts the drug in the best light, or conducting subgroup analyses and selecting for publication those that are

favorable. According to Smith, the design, conduct, analysis, and publication of clinical trials are, essentially, *marketing* issues.

Knowing that a meaningful boundary between science and industry no longer exists is essential for evaluating any study's findings. Most academic journals now recommend transparency regarding funding sources and author affiliations. With these as caveats, readers can approach the study with a warranted skepticism and a more careful analysis of trial methods and conclusions. For example, financial disclosures at the end of the Keck et al. (2006) study of Abilify are telling. Lead investigators Keck and Calabrese are consultants or members of the scientific advisory boards of Bristol-Myers Squibb, the makers of Abilify; the remaining six authors are employees (three also are major stock shareholders) of Bristol-Mayers Squibb/Otsuka. For those studies conducted before disclosure recommendations, an online database published by a non-profit health advocacy group (see Integrity in Science, http://www.cspinet.org/integrity/) documents researcher conflicts.

Flaw # 6: Biased Samples—Unfair Comparisons

Random assignment to either a placebo or drug group attempts to ensure that both groups are relatively equal in important attributes, and differ only in the presence or absence of the drug being tested. Randomization in drug trials, however, does not mean that the groups are representative samples of real world populations or that the groups are equal. Most often, a larger percentage of persons in drug trials are likely to respond favorably to the investigative drug than a sample of the general population. For example, trials that use placebo washouts eliminate short-term placebo responders before the study begins. Thus, both study groups will be skewed toward placebo non-responders. On the face of it, this arbitrary exclusion makes no sense, given that the purpose of the study is to determine whether a drug is superior to placebo. This

systematic bias favoring the drug is compounded in studies that exclude those who have failed to respond to the investigative drug (or one in its class) but allow successful responders.

For example, in the Reyes et al. (2006) study of long-term Risperdal use in children and adolescents, the original pool of participants contained only those determined to be positive responders. The authors note this as a potential source of selection bias. Exclusionary criteria and placebo washouts, common elements of many clinical trials, increase the chances that the medication group will significantly differentiate from the control group on crucial factors bearing on outcomes. At the same time, these criteria create an unbridgeable gap between research and practice—findings cannot be generalized to the real world of practice.

Flaw # 7: Constructing Evidence

Literature reviews are key landscapes for situating a study within a larger body of prior work—earlier research is cited and constructs a rationale for the current investigation. Here, the track record of any given drug can be clouded in a scientific rhetorical fog, building an empirical case for solid backing of the drug even when the data say otherwise. In the Reyes et al. (2006) study of Risperdal with youth diagnosed with disruptive behavior disorders, the literature review asserts that “Risperidone has consistently demonstrated efficacy and safety in both controlled short-term and open-label long-term studies” (p. 402). Five studies are cited to back this claim—two short-term (Aman, De Smedt, Derivan, Lyons, & Findling, 2002; Snyder et al., 2002) and three, longer-term (Croonenberghs, Fegert, Findling, De Smedt, & Van Dongen, 2005; Findling, Aman, Eerdekens, Derivan, & Lyons, 2002; Turgay, Binder, Snyder, & Fisman, 2002).

A review of these studies finds a consistent pattern. The two short-term trials both employed a 1-week placebo washout, eliminating early placebo responders. Given that many participants were experienced with antipsychotic medications and their well-known sedative

effects and placebos were inactive, both participants and clinicians could likely distinguish the actual study groups, compromising the blind. Both of these trials showed significant differences between the Risperdal and placebo groups for key adverse events: somnolence (sedation), elevated serum prolactin (for boys), and weight increase. Aman et al. did not report adverse events in tabulated format for these key events, with the exception of prolactin elevation.

The three longer-term studies were open-label extensions of the shorter term trials and examined the long-term efficacy and safety of Risperdal in children ages 5 to 12 with lower than average IQ scores. In all three trials, the top reported adverse event was somnolence, ranging from 20.6% to 51.9%. Weight gain was another frequently reported problem (from 17.3% to 36.4%). Only one study analyzed this effect in light of normative development, determining that 50% of the increased weight was above normal growth expectancies for the age group (Croonenberghs et al., 2002). The pattern of increased prolactin levels was observed across the three trials and, although EPSs were less common than other adverse events, they nonetheless occurred. Five participants in Croonenberghs et al.'s large study required antiparkinsonan medications, six withdrew due to EPS, and two developed tardive dyskinesia, while 26% of participants in Turgay et al. experienced EPSs. *Overall, 76 of the 77 participants in Turgay et al. reported adverse events, close to 92% in Croonenberghs et al., and nearly 91% in Findling et al.*

Even with minimal safety data reported in these trials, it is not hard to discern a pattern of serious adverse effects. Yet, over and over, the authors of all 5 studies (cited in support of the drug in the Reyes et al., [2006] literature review) revel in the drug's safety; "generally safe" and "well tolerated" are found in every abstract and conclusions section for all the studies. Efficacy findings of improved behavior across studies are virtually unanimous, though the authors fail to adequately account for the inevitable confounding of high rates of sedation with improvements

on measures sensitive to this effect. In sum, the claim that "risperidone has consistently demonstrated efficacy and safety" (p. 402), with the five studies reviewed here as evidence is, at best, misleading, and at worst a rhetorical construction revealed only via examination of the data.

The funding of all five of the cited Risperdal studies is by Janssen (or Johnson & Johnson, Janssen's parent company), manufacturer of the investigative drug, and authorship by researchers financially entwined with this pharmaceutical. Disclosures reveal that two lead authors were paid to "participate" in the study (see Turgay et al., 2002) and two authors were employees of Johnson & Johnson (see Croonenberghs et al., 2002). In both short-term studies, authors' financial disclosures are omitted, though both reveal primary funding from Janssen. Disclosures in other publications authored by these studies' investigators, however, reveal that Aman and Findling have significant ties to this company, and De Smedt is an employee.

Meanwhile, with a presumed track record for safety and efficacy, Risperdal has become a drug of choice for children of sub-average IQ with disruptive behaviors and is widely used with young persons diagnosed with autism. Studies have also been conducted for non-autistic diagnosed youths whose IQ's fall within normal ranges, indicating that it is increasingly viewed as a ready option for the behaviorally difficult youth in general (Armeteros, Lewis, & Davalos, 2007; Reyes et al., 2006). The problems of sedation, weight gain, increased serum prolactin, and movement disorders have been effectively swept under the rhetorical rug, preventing a thorough scientific investigation of their import as well as funding and momentum for other forms of treatment that may prove effective and less toxic. Instead, the efficacy and safety case, over time, becomes undisputed fact, its accuracy no longer in question.

RISK/BENEFIT PROFILE FOR ALL AGE GROUPS

Psychiatric drugs, clearly, help some adults. An examination, however, of clinical trial research—especially in light of fatally flawed methodologies—fails to provide the definitive proof of efficacy so often cited in professional and lay press. Based on the FDA's meta-analytic review and without regard to methodological problems, the entire scientific case for antidepressants rests on the observation that, in 189 clinical trials with 53,048 adult subjects, "50% of subjects who received active drug and 40% of subjects who received placebo were designated as responders" (Stone & Jones, 2006, p. 31)

For those who had hoped to show that persistence (trying more of the same or switching to a new drug) would overcome SSRI limitations, the STAR*D offers little support. Nor is there evidence for the widely accepted belief that a combination of drugs and therapy works best for most of those diagnosed with depression. Further, while comparable efficacy between drugs and psychotherapy is the rule in the short run, antidepressants (Shea et al., 1992) as well as other psychotropics, fall short of psychotherapy in the long run (Holon, Stewart, & Strunk, 2006). Meanwhile, the extensive CATIE study reaffirms that antipsychotics present an unacceptable side effect profile with minimal efficacy beyond the temporary amelioration of psychotic symptoms. Both CATIE and STEP-BD highlight the limited results achieved with antipsychotics and the persistence of problems in social domains left untouched. In sum, based on a review of evidence supporting the efficacy and safety of psychiatric drugs with adults, a risk/benefit analysis suggests that psychotherapy be considered first, based on client preferences.

Pharmacotherapy helps some children and adolescents. However, the preponderance of empirical research indicates that the risk may not be worth it. The Working Group asked: ". . . how many children should benefit from an antidepressant to justify one extra child harmed. . .?" (Working Group, 2006, p. 114). They further noted that, despite evidence for all ADHD

treatments, the data indicate that the benefits of medication do not maintain over time and the long term adverse effects are unstudied and unknown. Given this, the group determined that "with regard to use over a period of 2 to 3 years, "*the risk–benefit analysis of stimulant medication does not appear to be favorable* because beneficial effects appear to dissipate while side effects (e.g., growth) do not" (p. 52, italics added). The Working Group's report omitted the controversy surrounding the risks for adverse cardiovascular events and mania associated with ADHD drugs (the report was in press before the FDA's analysis). Adding this into the equation, confidence in stimulants as best practice for childhood behavior problems further erodes, tilting the risk/benefit analysis toward more risk free behavioral interventions.

While pharmacotherapy involves considerable risk for young people, psychosocial interventions have a strong track record with virtually no adverse associated medical events (Working Group, 2006), prompting the authors to conclude:

> For most of the disorders reviewed herein, there are psychosocial treatments that are solidly grounded in empirical support as stand-alone treatments. Moreover, the preponderance of available evidence indicates that psychosocial treatments are safer than psychoactive medications. Thus, *it is our recommendation that in most cases, psychosocial interventions be considered first*. (p. 16. Italics added)

In sum, the automatic prescription of psychotropic medications for adults and children, based on known risks and equivocal efficacy, is unwarranted. Where children are concerned, the stakes are higher. They are, essentially, mandated clients—most do not have a voice to say no to treatments or devise their own, and depend on adults to safeguard their wellbeing (Sparks &

Duncan, in press). Clients, caretakers, and practitioners need to discern science from spin to arrive at an informed analysis of the evidence.

COMMON FACTORS AND PSYCHIATRIC MEDICATIONS

Similar to psychotherapy, common factors loom large in medication effectiveness. As Greenberg (1999) points out, the argument that drugs "work" because of their active chemical properties (specific factors) rests on the ability to demonstrate the superiority of the drug over placebo in controlled randomized trials. However, despite study designs that actively favor the investigative drug, the placebo has shown, time and again, a robust potency. As we have seen, the difference in outcome between antidepressants and placebos is small, at best, and the superiority of drugs over placebo across all classes loses ground under critical scrutiny. The case for medication efficacy due to specific, biochemical properties that target neural substrates of diagnosed disorders remains dubious (Moncrieff & Cohen, 2005). How, then, might the common factors provide an explanatory framework for the positive effects of psychiatric medications?

Wampold's (2001) meta-analysis assigns as much as 87% of the variance of psychotherapy outcome to extratherapeutic factors (including error and unexplained variance). These variables are incidental to the treatment and idiosyncratic to the specific client—part of the client and his or her environment that aid in recovery regardless of participation in therapy (Asay & Lambert, 1999). Extratherapeutic factors can explain the phenomenon known as "spontaneous remission." Here, diagnosable conditions remit over time without treatment (Posternak & Miller, 2001)—even schizophrenia (de Girolamo, 1996; Harrow & Jobe, 2007). Whether attributed to biology, personal resources, or the result of inevitably changing life circumstances, clients tend to resolve difficulties that would be diagnosed and medicated in standard practice. Given that client factors comprise the largest portion of variance in outcome, it is reasonable to consider

how clients use medications to their benefit—what is it about any given client's personal, social, and contextual resources that promote a favorable response to medication? How does asking this question shift the conversation to identify and amplify potent client attributes in the interest of not only immediate change, but change over time? Here, focus is on how clients take the offered intervention, whether medical or otherwise, and fashion unique solutions for even the most daunting dilemmas (Sparks, Duncan, & Miller, 2007).

Client factors intimately relate to other common factors: therapist effects, the alliance, and the treatment delivered (including placebo/expectancy/allegiance effects). Who administers the medication (therapist effects), and the relationship he or she establishes with the client play determinant roles in whether the treatment is effective. The TDCRP revealed large psychiatrist effects—7-9% of the variability in outcomes was due to the psychiatrist (McKay, Imel, & Wampold, 2006), up to triple the variance attributable to antidepressant treatment. The McKay et al. analysis revealed that clients of the most effective psychiatrists (top one-third) who received a placebo had better outcomes that those of the least effective psychiatrists (bottom one-third) receiving medication. In addition, the top psychiatrists in the placebo condition also had the best outcomes in the drug condition. Further highlighting the power of therapist effects, a study of 6000 therapists (Wampold & Brown, 2005) found that when clients of more effective clinicians were medicated, the medication was more successful than for clients of less effective therapists. Medication was not helpful for the clients of the least effective psychotherapists.

Researchers in drug trials often view the alliance as a factor related to compliance rather than actual change (Greenberg, 1999). The TDCRP, however, upheld what researchers repeatedly have found—a positive alliance is one of the best predictors of outcome. Data from the TDCRP revealed that the alliance was predictive of success for all conditions (Krupnick et

al., 1996), with no difference between drug and non-drug treatments. The alliance accounted for 21% of the variance across treatments.

The placebo response in psychiatric drug trials, as noted, has long been the bane of researchers, exhorting them to take extraordinary measures (largely unsuccessful) to counteract its effects. Expectancy accounts for significant portions of drug response and often match the effects of the investigative drug (Kirsch et al., 2002). Any medication intervention, therefore, must be considered in concert with placebo and expectancy effects—i.e., the treatment delivered. The belief by clients that they are getting a powerful healing agent and the hope for improvement this engenders, play powerful roles in outcome. In part, this class of therapeutic factors refers to the portion of improvement deriving from client's knowledge of being treated and assessment of the credibility of the therapy's rationale and related techniques. Outcome is enhanced when both client and therapist believe in the restorative power of the treatment (Frank & Frank, 1991).

For example, a clinical trial of antidepressants found that 90% of depressed participants who reported high expectancies for improvement responded to treatment, compared with 33% of those who expected the medications to be "somewhat effective" (Krell, Leuchter, Morgan, Cook, & Abrams, 2004). TDCRP data also indicated that expectancies significantly predicted response across both the psychotherapy and pharmacotherapy conditions (Sotsky et al., 1991). Moreover, in the TDCRP, clients' perceptions of treatment fit with their beliefs about their depression and what would be helpful (psychotherapy or medication) contributed modestly to early engagement, continuation in therapy, and the development of a positive alliance (Elkin et al., 1999). Finally, a study of persons diagnosed with bipolar disorder treated with medication (Gaudiano & Miller, 2006) found that both expectancies and the alliance were predictive of outcome. The authors

conclude that expectancy and alliance factors are not just important predictors in psychotherapy—prescribers should ask clients about expectations, and attend to the alliance.

Understanding expectancy further contextualizes positive findings in drugs trials, especially when those treated with drugs receive greater attention and time. In the limitations section of the TADS study comparing combined Prozac and CBT, Prozac alone, CBT alone, and placebo for the treatment of adolescent depression, the authors acknowledged that variations in knowledge of treatment received existed across the four groups as well as inequities in contact time with the clinicians. A pharmacotherapist was assigned to each participant in the combined, medication alone, and placebo groups. This person monitored drug dosage and "offered general encouragement about the effectiveness of pharmacotherapy for MDD" (TADS Team, 2004, p. 809). The combined group adolescents also received contact with a cognitive behavioral therapist for 15 sessions. Parents in the combined group participated in psychoeducation groups about depression along with conjoint family sessions. Only the combined group received all of these "extra" components. The authors admit that, because of the inequality in conditions and lack of blinding, the "specific ingredients" of improvement could not be determined.

Expectancy factors, including therapist allegiance, are fueled by media and advertising wooing consumers to view drugs as virtual guarantees of symptom relief and, even more, "the good life." Faith in psychiatric medications, at the same time, rests comfortably within a social context in which medical explanations and solutions hold great sway. When therapists have allegiance to medication, they likely reinforce expectancy for improvement. Similarly, the ritual of medicine—the diagnostic interview, the formal explanation (diagnosis), and the prescriptive treatment (medication) holds all the allure of healing rituals that are part of the cultural scripts characteristic of human societies. In sum, medical "scripts," both from doctors' pads and the

medical narrative, have the power to create potent placebo effects (evidenced by their prominence in the drug trial literature) that then can translate into improved outcomes.

> Greenberg (1999) summarizes the common elements in psychiatric drug therapy: Medication response can be readily altered by who delivers the drug, how its properties are described, the degree of familiarity with the setting in which it is presented, and the ethnic identity or socioeconomic status of the person ingesting it. (p. 301)

Based on the evidence, the specific ingredients of medication and their alleged biochemical impact are secondary to common factor effects in producing desired outcomes.

CLINICAL IMPLICATIONS

Two conclusions emerge from this chapter: First, when clinical trials are critically examined—does the study have a true double blind, are outcome measures clinician or client-rated, how long did the study last, who funded the study and what are the authors' affiliations, are the groups representative of the general population and offer a fair contest, and is it rhetoric or evidence—it is clear that psychiatric drug treatments should not be privileged over psychosocial options. And second, when effects to treatment are noted, who provides the treatment, the quality of the alliance, and the clinician and recipient's expectations for success provide a better explanation of the results than any presumed specific effects due to the medication.

These conclusions, however, do not eliminate medication as one choice among many, particularly when clients believe their problems to be biological and that drugs might be helpful. What is not supported is the *automatic* trigger to recommend medication without considering client preferences and a full range of options. The efficacy of psychotherapy has been irrefutably supported across all domains of symptom distress, with few, if any instances indicating superior

outcomes for medication, especially in the long run. Knowing that there is no irresistible scientific justification to medicate, therapists are free to put other options on the table and draw in the voices of their clients—to engage in an informed risk/benefit analysis to help clients choose treatments in concert with their values, preferences, and cultural contexts. Practitioners need not fear these conversations or feel timid in the face of medical opinion. The Working Group (2006) clearly defines the clinician's role:

> A clinician's role is to provide the family with the most up-to-date evidence, as it becomes available, regarding short- and long-term risks and benefits of the treatments. (p. 174)

It is not outside the expertise of practitioners of all disciplines to critically examine and be informed about the evidence. Similarly, it is well within the scope of practice of mental health professionals to provide this information to clients in formats consistent with their language and preferred modes of learning, and to make available unbiased sources where additional information can be obtained. Further, it is within our professional bounds to speak clearly about the pervasive conflicts of interest in many media outlets and press materials—not to take the medication option off the table but, as an ethical imperative, not to withhold any information that can help clients make the most informed decision possible. Finally, such risk/benefit conversations seem supported by the APA Presidential Task Force on Evidence-Based Practice definition of evidence-based practice: "the integration of the best available research with clinical expertise in the context of patient characteristics, culture, and preferences" (2006, p. 273). Risk/benefit discussions address the best available research and lean toward client preferences.

In the interest of empowering clients to make informed decisions about medications, we offer the following guidelines that honor client preferences as well as their central and "heroic" roles

in the change endeavor, incorporate the evidence for drug efficacy and safety, and respect the right of all persons to be fully informed in critical treatment decisions:

1. Conduct a thorough and systematic assessment of the problem situation, combining information from all significantly involved persons and networks.
2. Develop a collaborative framework for understanding the problem with the client and significant others that includes developmental, environmental, interactional, and socio-cultural understandings.
3. Develop a plan that follows the assessment and framework of understanding and that is responsive to clients' view of the problem, strengths, cultural context, and preferences.
4. If medication is part of the plan, make sure all involved are aware of potential risks, known adverse events and withdrawal reactions, the meaning of off-label prescription, and the lack of studies supporting combining psychotropic medications. Suggest independent resources for obtaining additional information about risks and benefits, including physicians and unbiased sources.
5. Work collaboratively with clients and significant others to implement the plan, modifying as needed based on systematic client feedback on progress. If medication is part of the plan, assist the client to view positive change as resulting from his or her efforts, and significant others as relevant, in overcoming the problem, and include discussion of a time frame for discontinuation of medication.

The belief in the power of chemistry over social and psychological process—fueled by unprecedented promotion from the drug industry that targets all players in health care—forms the basis of pharmacology's growing centrality in psychotherapy research, training, and practice. While some clients may be helped some of the time with this focus, it misdirects the field away

from an empirically based understanding of what is responsible for change. Additionally, it promotes prescriptive treatments of questionable sustainability, fraught with potentially dangerous effects. We advocate that psychotherapists adopt a critical perspective of psychopharmacology, examine its impact on our clients and our field, and realign ourselves with known processes of change common across psychological and medical models.

QUESTIONS FROM THE EDITORS

1. You present a very different view of drug efficacy and safety that is not often, if ever, reported in the media. Why?

It is not hard to sound like a conspiracy theorist when answering this question. Simply put, there is no mainstream media source that is not under the sway of pharmaceuticals. To appreciate this unnerving fact, one need only to examine primary sources—the actual clinical trial research—and compare it to descriptions in the popular press and websites providing "information" to the public. A good example is the STAR*D study. The pharmaceutical industry regularly releases write-ups announcing drug news (often reprinted without critique) and the STAR*D really hit the big time. The *Los Angeles Times* trumpeted "A Varied Assault on Depression Yields Gains" (Maugh, March 23, 2006), and described mythical results clearly at odds with STAR*D's findings. Moreover, the NIMH—a source most would assume to be beyond the reach of spin—misrepresented STAR*D findings even more grievously. The NIMH webpage omits the significant number of STAR*D drop-outs and claims that roughly 50% achieved remission by taking 2 steps—either a single agent or an augment/switch choice. This figure could only be derived by cumulatively *adding* percentage rates across levels, a practice statistically meaningless and certainly misleading. Since the rates of effectiveness are calculated from the numbers of participants in each level, *average, not cumulative* percentages correctly reflect

overall improvement. For example, in the first two levels, out of a total of 4,168 participants, 1114 achieved remission, a 27%, not 50%, rate. The STAR*D is but one example that demonstrates that primary sources must be consulted to distinguish science from science fiction.

2. The view that medication is necessary for schizophrenia is deeply ingrained, yet you contend that it is not. What evidence supports your seemingly radical position?

The *World Health Organization's* studies of outcomes for schizophrenia in developed versus non-developed countries found that symptoms tend to dissipate within 5 years when medication is never used or when clients wean themselves off. Surprisingly, outcomes were better in non-developed countries, where most individuals did not take medication—people spent less time in hospitals with lower rates of relapse and were more likely to be employed and socially connected (de Girolamo, 1996). Harding, Zubin, and Strauss (1987) tracked 269 clients admitted to Vermont hospitals with a diagnosis of schizophrenia 32 years after their first admission. They found that about two-thirds of these former patients showed no signs of schizophrenia and had long since stopped their medications. In the Soteria Project (1971-1983) persons diagnosed with schizophrenia and randomly assigned to residential treatment with minimal use of antipsychotic medication had better 2-year outcomes than those assigned to "usual hospital" treatment (Bola & Mosher, 2003). More recently, a 15-year follow-up study of persons diagnosed with schizophrenia found that a larger percentage of those un-medicated showed better global functioning and intervals of recovery than their medicated counterparts (Martin & Jobe, 2007)—65% of those taking antipsychotics were experiencing psychosis compared to only 28% of those not medicated. Antipsychotics can remain part of the discussion, but should not be privileged.

3. Given your risk/benefit analyses, what are the implications for training programs?

It is now standard practice that students not only know the DSM, but also the latest compendium of psychotropics—and like the DSM—without accompanying critique. With even the hint of "depression, psychosis, or mood swings," trainees are taught to refer to physicians while forbidden to discuss risks and benefits. But the recommendations of the Working Group (2006) usher a new day. Therapists can engage in critical analysis of the drug trial literature and the role it plays in professional guidelines, training mandates, and media. Such an analysis reveals the blemished underbelly of even the most sophisticated trials and effectively casts doubt on medication superiority and safety. Based on the evidence, a different training mandate emerges:

1) Teach students a critical perspective through an examination of primary research. A seven flaws analysis is a teachable tool to evaluate the science supporting medication prescription and privilege. Teach students that medication is an option not a mandate.
2) Provide students with opportunities to practice medication discussions with clients. Student facility with a range of options, as well as sources of unbiased information, increases the chances of more measured conversations and non-medical alternatives.
3) Bolster student confidence in taking a view likely to be unpopular or discredited. Model respectful professional conversation while instilling a faith in the empirical evidence that justifies a far more conservative approach than currently practiced.
4) Teach students about the common factors—the known contributors to change—thereby increasing their reliance on clients, the therapy relationship, hope and expectancy, and their own abilities to resolve even the more severe life situations and problems.
5) Train students in outcome management—the proof of the pudding is in the taste. Teaching students to collaborate with clients to monitor the benefit of any intervention necessarily opens the door for frank conversations about what is working and what is not.

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Notes

[1] Various other psychotropic medications, aimed to reduce SSRI-induced agitation or sexual dysfunctions, were concomitantly prescribed to an unknown proportion of the participants.

[2] The authors of this study, published in the *New England Journal of Medicine,* were so heavily tied to the pharmaceutical industry, the editors stated "it would have used too much space to disclose them [financial ties to industry] fully in the Journal" (p. 1462). Additionally, the study's investigative drug (nefazadone) has since been recalled, due to unacceptable liver toxicities.

[3] Jureidini et al. (2004) report that the first Emslie trial changed its primary outcome measure between the trial's beginning and final publication, and used secondary measures to show superiority of the investigative drug.

[4] The Medicines and Healthcare Products Regulatory Authority in the UK has banned all antidepressants for those under 18 with the exception of Prozac, which can only be used for those over eight years of age and only in conjunction with continued psychotherapy and when the psychosocial intervention by itself has failed.

[5] Aderall has a black box for cardiac risk and Strattera for suicidality.

[6] Abilify, a second-generation antipsychotic, has recently been approved for adolescents aged 13 to 17 diagnosed with schizophrenia and children aged 10-17 diagnosed with bipolar I, despite commonly observed adverse reactions of extrapyramidal disorder, somnolence, and tremor and documented evidence of additional serious reactions in adult trials (see Minimization of Risks). http://www.fda.gov/cder//foi/label/2008/021436s21,021713s16,021866s8lbl.pdf