

Problems and Opportunities in the Diagnosis and Treatment of Major Depression

KCNI Summer School, July 5th 2021
Brett Jones, MD
Victor Tang, MD

Agenda

1. What is MDD? Definitions, History, Epidemiology
2. Clinical assessment of MDD:
 - What we know
 - Challenges and opportunities
3. Assessment, Management, and Follow-up
4. Discussion Period and Q&A

Major Depressive Disorder

The Old Testament story of King Saul describes a depressive syndrome, as does the story of Ajax's suicide in Homer's *Iliad*. About 400 BCE,

The first English text entirely related to depression was Robert Burton's *Anatomy of Melancholy*, published in 1621

In 1854, Jules Falret described a condition called *folie circulaire*, in which patients experience alternating moods of depression and mania

In 1899, Emil Kraepelin, building on the knowledge of previous French and German psychiatrists, described manic-depressive psychosis using most of the criteria that psychiatrists now use to establish a diagnosis of bipolar I disorder.



Depression

A major depressive episode must last at least 2 weeks, and typically a person with a diagnosis of a major depressive episode also experiences at least four symptoms from a list that includes changes in appetite and weight, changes in sleep and activity, lack of energy, feelings of guilt, problems thinking and making decisions, and recurring thoughts of death or suicide.

Mania

A manic episode is a distinct period of an abnormally and persistently elevated, expansive, or irritable mood lasting for at least 1 week or less if a patient must be hospitalized. A hypomanic episode lasts at least 4 days and is similar to a manic episode except that it is not sufficiently severe to cause impairment in social or occupational functioning, and no psychotic features are present.

Mood Disorders

Depressive Disorders

- **Major Depressive Disorder (MDD)**
- Persistent Depressive Disorder (Dysthymia)
- Disruptive mood and dysregulation disorder (DMDD)
- Premenstrual dysphoric disorder (PMDD)

Bipolar Related Disorder

- Bipolar 1
- Bipolar 2
- Cyclothymia

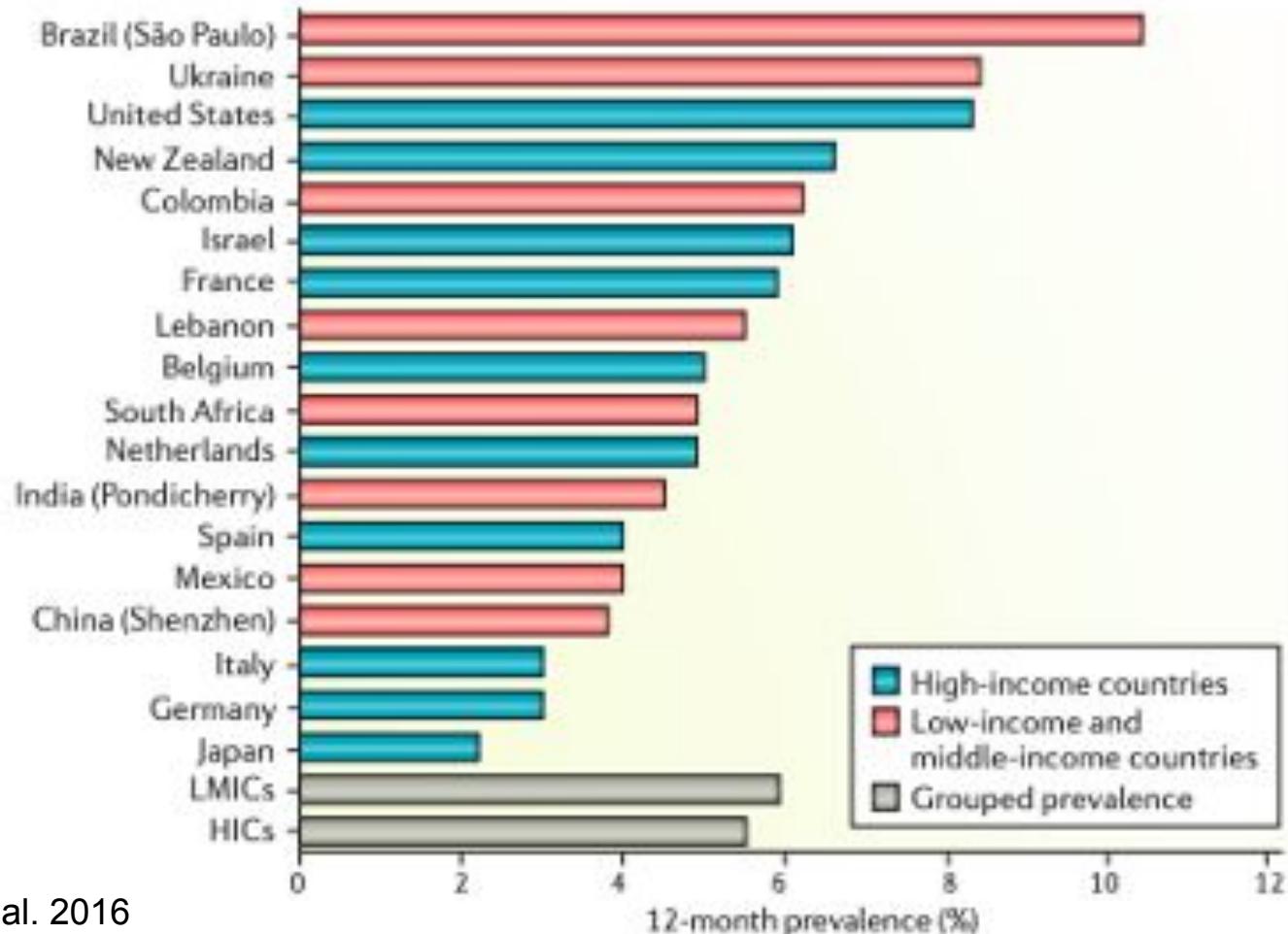
Epidemiology

Sex: almost universal observation, of twofold greater prevalence of major depressive disorder in women than in men.

Age: The mean age of onset for major depressive disorder is about 40 years, with 50 percent of all patients having an onset between the ages of 20 and 50 years.

Social: Major depressive disorder occurs often in persons without close interpersonal relationships and in those who are divorced or separated.

Comorbidity: Individuals with major mood disorders are at an increased risk of having one or more additional comorbid disorders. The most frequent disorders are alcohol abuse or dependence, panic disorder, obsessive-compulsive disorder (OCD), and social anxiety disorder.

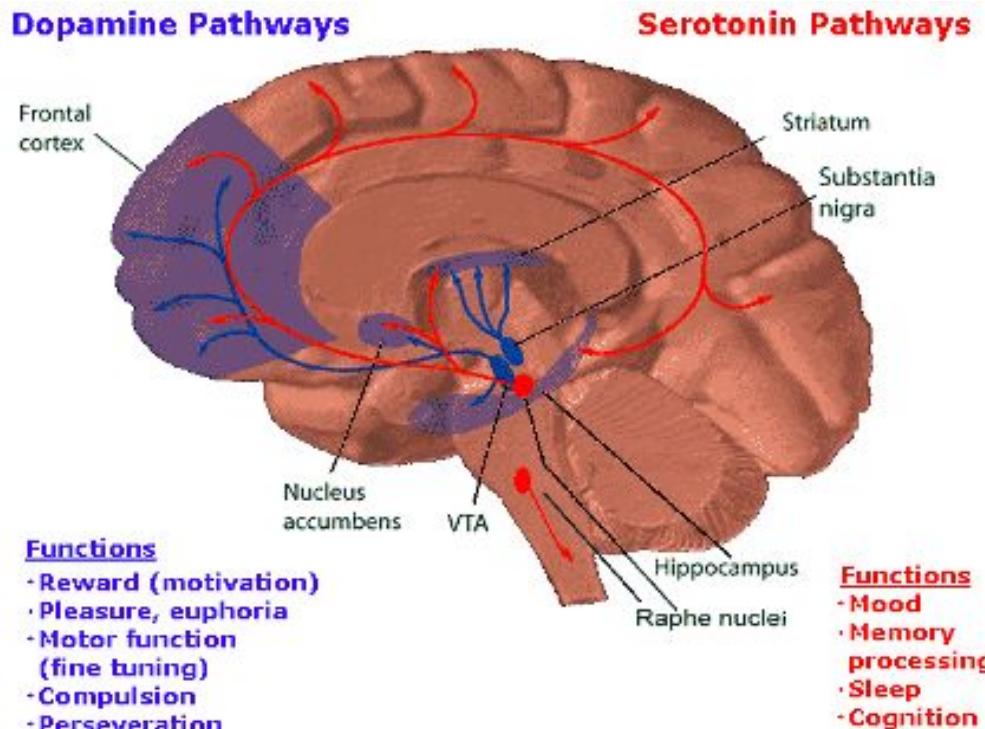


Biological factors

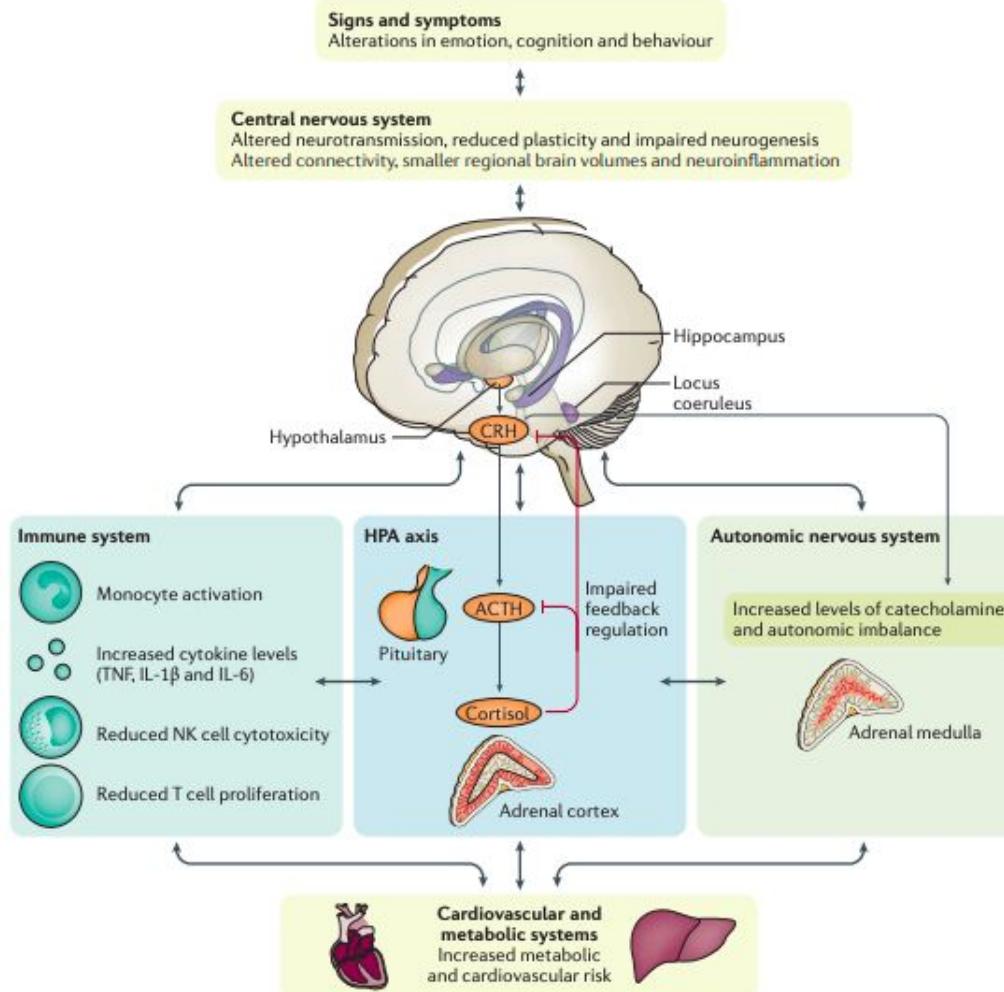
Many studies have reported biological abnormalities in patients with mood disorders.

Until recently, the monoamine neurotransmitters—norepinephrine, dopamine, serotonin, and histamine—were the main focus of theories and research about the etiology of these disorders.

Biogenic amines - predominant target for mood disorder treatments

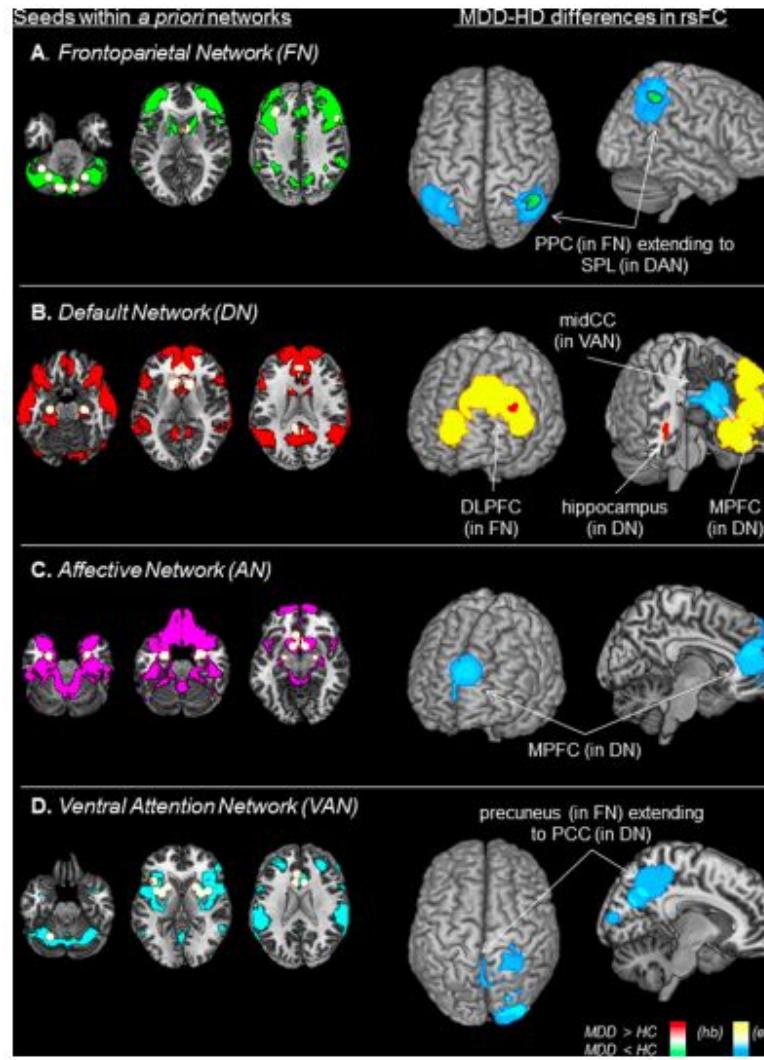


Biological Factors



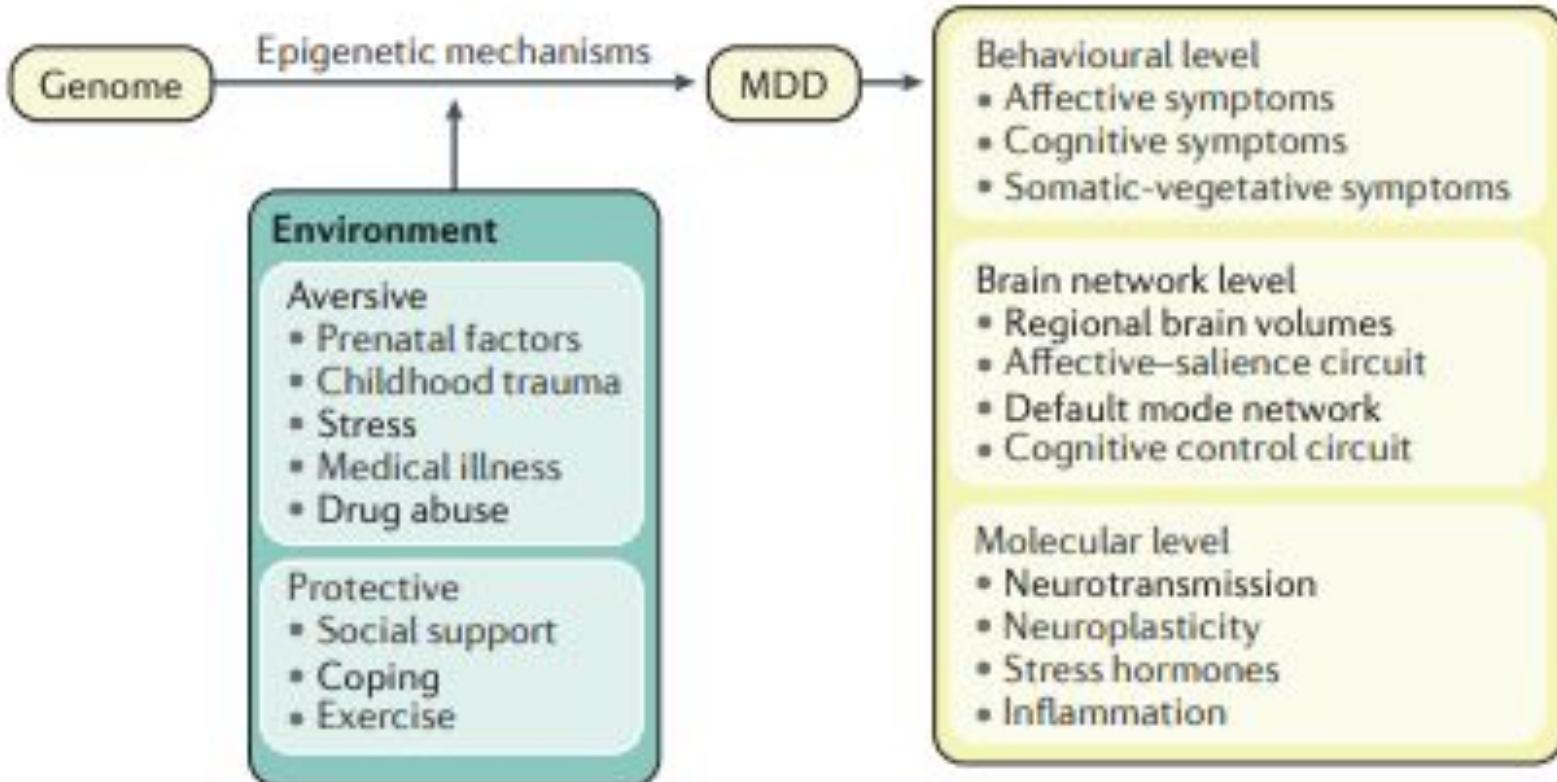
Biological Factors

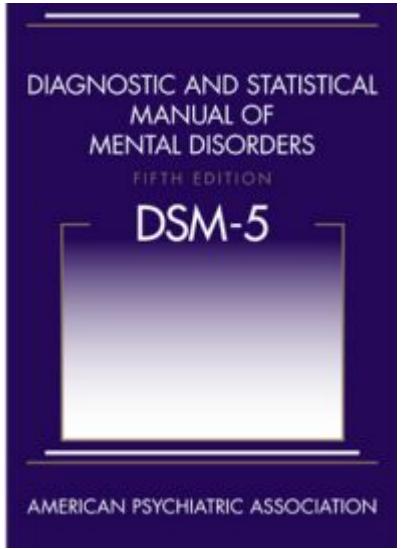
New(ish) emphasis
on networks and
connectivity



Kaiser et al. 2016

Social Factors





Major Depressive Disorder

Diagnostic Criteria

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

- 5/9 symptoms
- 2 “core” symptoms
- Duration ≥2 weeks
- Distress/Impairment
- Exclusion of other psych/medical disorders
- Recurrent or single episode
- Minimal change over past 40 years

Specifier	Key features
Melancholic	Non-reactive mood, anhedonia, weight loss, guilt, psychomotor retardation or agitation, morning worsening of mood, early morning awakening and excessive or inappropriate guilt
Atypical	Reactive mood, over-sleeping, over-eating, leaden paralysis, interpersonal rejection sensitivity
Psychotic	Hallucinations or delusions; mood-congruent or -incongruent
Catatonic	Stupor, catlepsy, waxy flexibility, etc (uncommon in clinical practice)
Anxious distress	Feeling keyed up or tense, unusually restless, difficulty concentrating because of worry, fear of something awful happening, feeling of losing control
Mixed features	Elevated expansive mood, grandiosity, over-talkative, racing thoughts, increased energy / hyperactivity
Cognitive dysfunction	Disturbances in attention, psychomotor speed, memory, executive function, emotion-dependent cognition
Physical symptoms	Lack of energy, fatigue, reduced libido, pain
Sleep	Insomnia, hypersomnia, circadian sleep-wake disturbances

Part 2

Sam is referred to the mood disorders clinic at CAMH by her family doctor.

She has reported low mood for the past 6 months including loss of pleasure, fatigue, difficulty sleeping and suicidal thoughts.

She has a history of physical abuse as a child, a family history of bipolar disorder. She drinks 10-15 standard drinks/week. She takes escitalopram but doesn't find it helpful.

Request for assessment and treatment recommendations

Clinical Assessment of MDD

- History of presenting current depressive episode
- Full psychiatric review
- Past psychiatric treatments
- Medical and physical health
- Family history
- Personal and social history
- Developmental history
- Mental Status Exam/Physical Exam
- Medical Investigations
- Measurement-based care
- Collateral history
- Longitudinal assessment

Problems & Opportunities

- How can we understand variability in symptom presentations?
- Are there subtypes of depression?

FIGURE 2. Modified Schematic Presentation of the Final Common Pathway Model of Depressive Disorders, as Depicted by Akiskal and McKinney (1, 2)

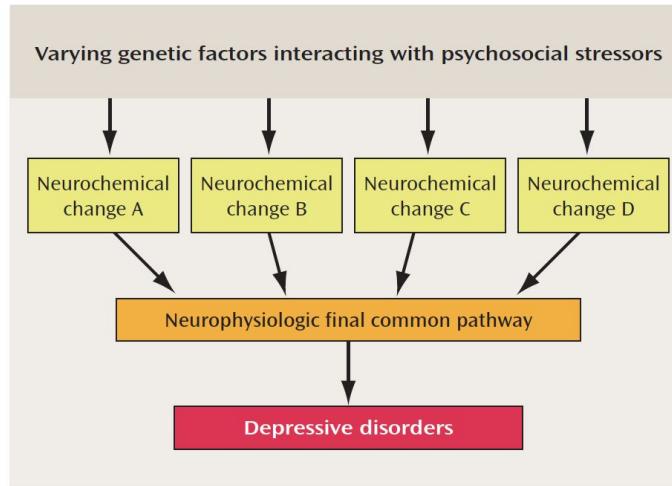
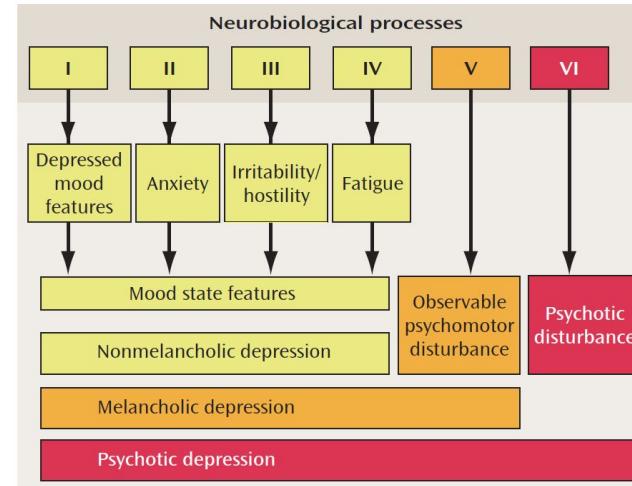
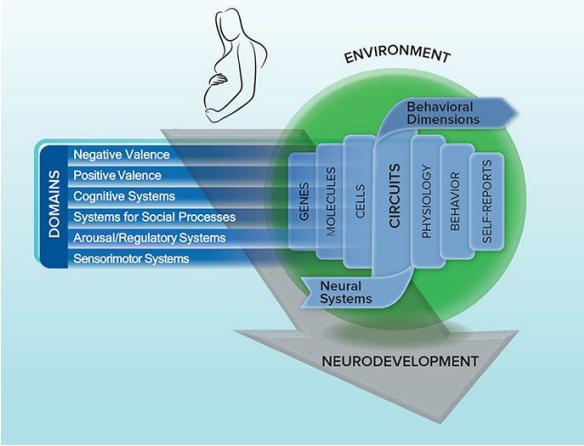


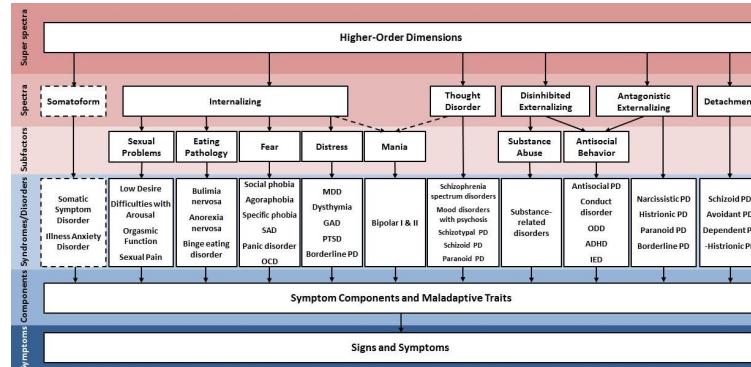
FIGURE 3. Schematic Presentation of a Model of Depressive Disorders in Which Differing Neurobiological Processes Generate Differing Clinical Features and Differing Activation of Components Determines Three Classes of Disorders



Problems & Opportunities: Reinventing Psychiatric Classification



NIMH Research Domain Criteria
(RDoC)



Hierarchical
Taxonomy Of
Psychopathology
(HiTOP)

Table 1. Comparison of ANA and Related Initiatives

	ANA	RDoC	iRISA	IMAGEN	PhenX	CNTRICS
Neuroscience Domains	✓	✓	✓	✓	✓	✓
Standardized Assessment Package	✓		✓	✓	✓	✓
Disseminate Package to Various Settings	✓		✓	✓	✓	✓
Identify Meaningful Subtypes of Disorder	✓	✓			✓	
Describe Individualized Treatments		✓			✓	✓

Kwako et al. (2016) *Biological Psychiatry*

ANA, Addictions Neuroclinical Assessment; CNTRICS, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia; iRISA, Impaired Response Inhibition and Salience Attribution; RDoC, Research Domain Criteria.

Assessing the depressive “episode”

- Onset:
 - Healthy to depressed
 - Depressed to more depressed
 - Abrupt vs insidious onset
- Stressors
 - Precipitating events
 - Perpetuating factors
- Number of episodes
- Length of episode
- “Double Depression”
 - Dysthymia + MDD

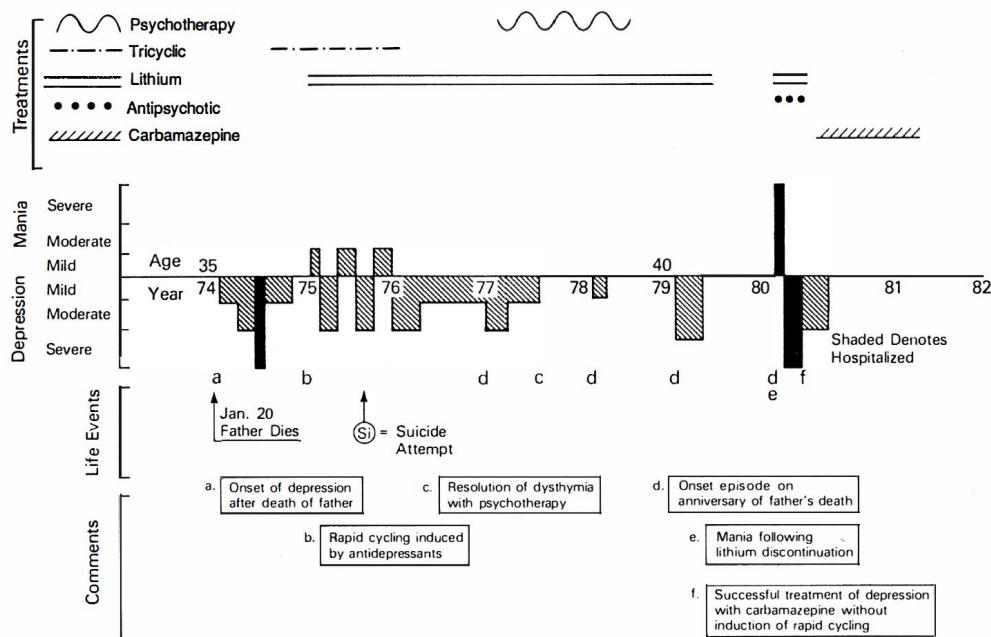


FIGURE 8.1-6

Graphing the course of a mood disorder. Prototype of a life chart. (Courtesy of Robert M. Post, M.D.)

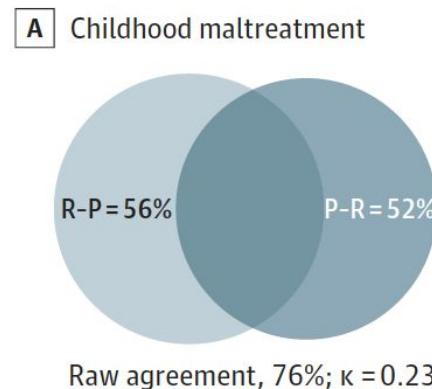
Problems & Opportunities

- When a patient reports their symptoms and history, what are the effects of:
 - Recall bias
 - Emotional state
 - Lack of insight
 - Subjective appraisal of life stressors

JAMA Psychiatry | Original Investigation

Agreement Between Prospective and Retrospective Measures of Childhood Maltreatment A Systematic Review and Meta-analysis

Jessie R. Baldwin, PhD; Aaron Reuben, MEM; Joanne B. Newbury, PhD; Andrea Danese, MD, PhD



Heterogeneity...

National Comorbidity Survey Replication (NCS-R)

Table 7. Distributions and Correlates of Symptom Severity by Quick Inventory of Depressive Symptomatology Self-Report of 12-Month CIDI/DSM-IV Major Depressive Disorder in the Weighted Part 1 NCS-R*

	MDD Cases, Mean (95% CI)				
	Mild (n = 51)	Moderate (n = 194)	Severe (n = 204)	Very Severe (n = 65)	Total (N = 514)
Symptom severity, %	10.4 (7.3-13.4)	38.6 (34.5-42.7)	38.0 (34.1-42.0)	12.9 (9.6-16.3)	
Correlates of symptom severity					
Duration, wk†	15.3 (11.5-19.1)	13.8 (11.9-15.7)	16.6 (14.7-18.4)	23.1 (17.9-28.4)	16.2 (15.1-17.3)
Days out of role‡	6.1 (1.8-10.4)	15.7 (7.8-23.6)	44.8 (33.2-56.5)	91.4 (48.9-134.0)	35.6 (27.0-44.1)
Role impairment, %§	19.6 (8.7-30.5)	41.5 (33.4-49.7)	77.3 (71.1-83.6)	90.0 (82.4-97.7)	59.1 (53.7-64.6)
Comorbidity, %¶	34.9 (20.8-49.1)	58.0 (48.4-67.7)	77.3 (71.6-83.2)	82.1 (73.6-90.5)	66.1 (60.6-71.6)

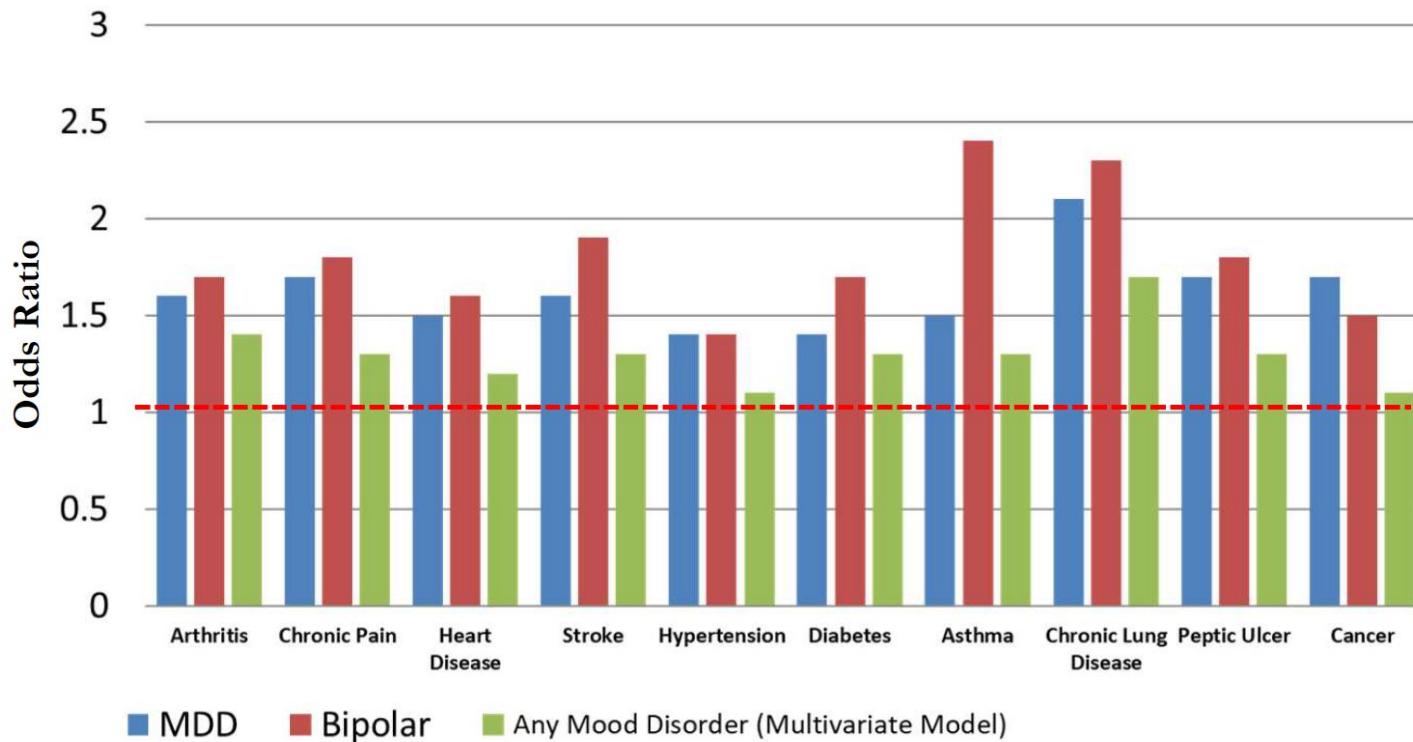
Psychiatric Comorbidity

National Comorbidity Survey Replication (NCS-R)

Table 4. Comorbidity of CIDI/DSM-IV Major Depressive Disorders With Other NCS-R Disorders in the Weighted Part 2 NCS-R*

	MDD Cases With Comorbid Disorders, % (95% CI)			
	Anxiety	Substance Use	Impulse Control	Any
Lifetime comorbidity†				
Lifetime (n = 1530)	59.2 (56.2-62.1)	24.0 (21.8-26.2)	30.0 (27.9-32.1)	72.1 (69.8-74.4)
12-Month (n = 622)	67.8 (63.6-72.0)	27.1 (23.1-31.1)	37.3 (33.8-40.8)	78.5 (74.8-82.3)

Medical History



Casual, bidirectional effects? Reciprocal effects?

Circulation

Volume 132, Issue 10, 8 September 2015; Pages 965-986
<https://doi.org/10.1161/CIR.0000000000000229>



AHA SCIENTIFIC STATEMENT

Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease

A Scientific Statement From the American Heart Association

Benjamin I. Goldstein, MD, PhD, Mercedes R. Carnethon, PhD, Karen A. Matthews, PhD, FAHA, Roger S. McIntyre, MD, Gregory E. Miller, PhD, Geetha Raghubeer, MD, FAHA, Catherine M. Stoney, PhD, Hank Wasiak, BA, MBA, Brian W. McCrindle, MD, MPH, FAHA, and on behalf of the American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young

Medical vs. Psychiatric: Challenges & Opportunities

- Medical disease “masquerading” as syndromes of depression
 - Endocrine (e.g. hypothyroid), infectious (e.g. HIV), neurodegenerative (e.g. dementia), etc.
- Treatments for medical and psychiatric disorders overlap
 - E.g. “Antidepressants” used for pain, “Mood stabilizers” used for epilepsy
- Medical comorbidities frequently direct & narrow treatment options
- Are we ignoring medical comorbidities when studying the “biology” of depression?

Important to look at all information about the patient...

Table 1. Prevalence in Use of Prescription Medications With Depression as a Potential Adverse Effect in Prior 30 Days Among US Adults, 2005-2014

	No. of Participants (%) ^a	No. (%) [95% CI] Taking Medication With Depression as an Adverse Effect ^a		P Value ^b
		None	Any	
Overall	26 192 (100)	17 042 (62.8) [61.7-64.0]	9150 (37.2) [36.0-38.3]	<.001
No. of medications with depression adverse effects				
1	5089 (21.0)		5089 (56.4) [55.2-57.7]	
2	2175 (8.7)		2175 (23.5) [22.3-24.7]	
≥3	1886 (7.5)		1886 (20.1) [19.1-21.2]	

Past Psychiatric History

- Psychiatric hospitalizations
- Previous psychiatrists, therapists, counsellors
- Medication trials - dose, duration, efficacy, tolerability
- Psychotherapy trials
- Previous diagnoses
- Treatment programs - day programs, rehab, support groups

Side Effects

Efficacy vs. tolerability balance

Side effects vs. depression exacerbation?

Table 1: Anticholinergics in the Top 100 (BC Data, 2016)

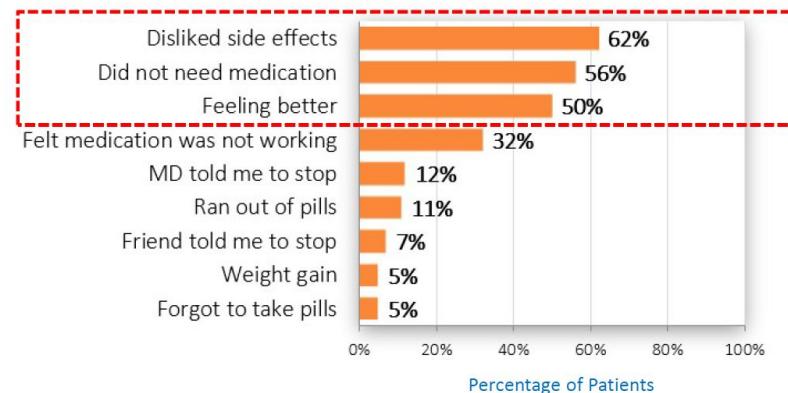
Antidepressants: amitriptyline*, bupropion, citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine
Antipsychotics: aripiprazole, clozapine, olanzapine, quetiapine, risperidone
Drugs for insomnia: trazodone, zopiclone
Drugs for pain: amitriptyline*, cyclobenzaprine

* nortriptyline and other TCAs are similar to amitriptyline

Why are some treatments effective and others are not?

- Poor adherence
- Stopped prematurely
 - 42% stop antidepressant in 30 days
- Wrong diagnosis, ignoring comorbidities
- Pharmacogenetic differences
- “True” treatment resistance

Patient-Reported Reasons for Discontinuation of Antidepressant Therapy¹



Challenges & Opportunities: Episodes of Depression & Treatment

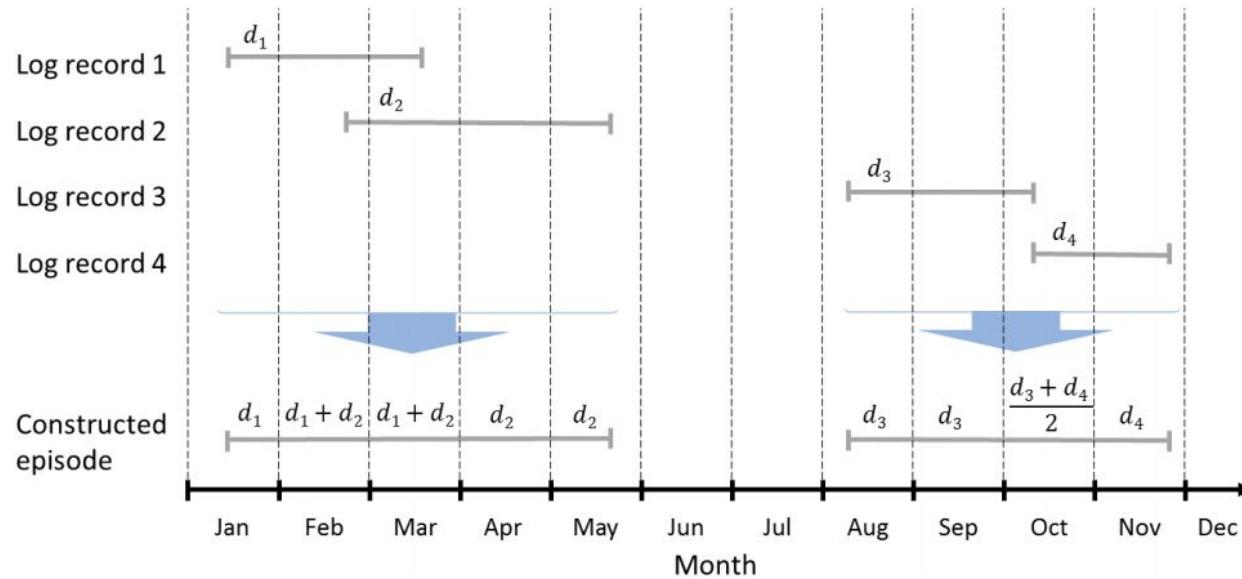


Figure 1 Treatment episodes constructed from overlapping log records for the same medication. The log records have varying durations and different daily doses with common units, d_1 , d_2 , d_3 and d_4 . Log records 1 and 2 belong to a treatment episode with simultaneous regimens of the same medication. Log records 3 and 4 belong to another treatment episode with a change in dose regimen. Constructed episodes show total daily dose for each month.

Necessary/sufficient components of treatment?

Table 3 Network meta-analyses: response in psychotherapies compared with each other and with control conditions

CBT	BAT	PST	3WV	IPT	DYN	SUP	LRT	CAU	WL	PLA
1.20 (0.90-1.61)										
0.99 (0.75-1.31)	0.83 (0.57-1.20)									
1.02 (0.76-1.38)	0.85 (0.58-1.25)	1.03 (0.70-1.51)								
1.00 (0.76-1.31)	0.83 (0.57-1.22)	1.00 (0.70-1.44)	0.98 (0.66-1.45)							
0.89 (0.62-1.29)	0.74 (0.47-1.17)	0.90 (0.58-1.40)	0.88 (0.55-1.40)	0.90 (0.58-1.39)						
0.58 (0.45-0.75)	0.49 (0.34-0.70)	0.59 (0.42-0.82)	0.57 (0.39-0.84)	0.59 (0.42-0.83)	0.65 (0.43-0.99)					
1.47 (0.87-2.49)	1.23 (0.68-2.20)	1.48 (0.85-2.60)	1.45 (0.81-2.60)	1.48 (0.83-2.63)	1.65 (0.88-3.10)	2.52 (1.43-4.45)				
0.43 (0.37-0.50)	0.36 (0.26-0.48)	0.43 (0.33-0.57)	0.42 (0.31-0.58)	0.43 (0.33-0.56)	0.48 (0.33-0.69)	0.73 (0.56-0.96)	0.29 (0.17-0.49)			
0.28 (0.24-0.34)	0.24 (0.17-0.32)	0.29 (0.21-0.38)	0.28 (0.21-0.38)	0.28 (0.21-0.39)	0.32 (0.21-0.47)	0.48 (0.36-0.65)	0.19 (0.11-0.32)	0.66 (0.54-0.81)		
0.53 (0.34-0.83)	0.44 (0.26-0.74)	0.53 (0.34-0.85)	0.52 (0.30-0.89)	0.53 (0.32-0.88)	0.59 (0.33-1.05)	0.91 (0.55-1.50)	0.36 (0.18-0.71)	1.24 (0.78-1.97)	1.87 (1.17-3.00)	

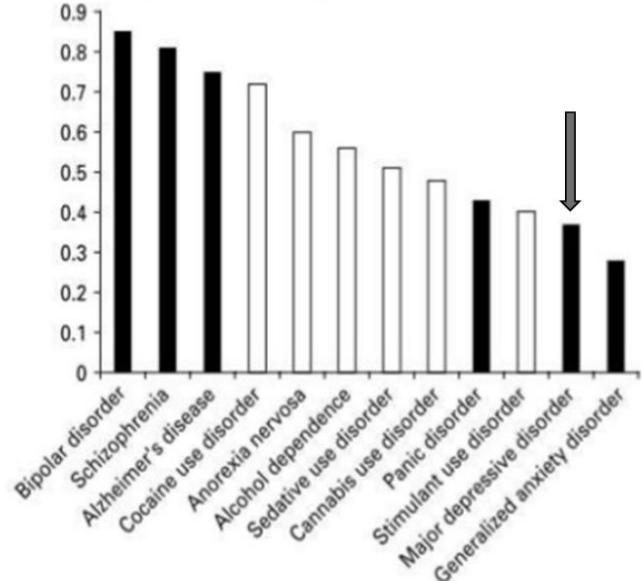
Table 2

Task Force Conclusions Regarding the Evidentiary Strength of Elements of the Therapy Relationship and Methods of Adapting Psychotherapy

Evidentiary strength	Elements of the relationship	Methods of adapting
Demonstrably effective	Alliance in individual psychotherapy Alliance in child and adolescent psychotherapy Alliances in couple and family therapy Collaboration Goal consensus Cohesion in group therapy Empathy Positive regard and affirmation Collecting and delivering client feedback	Culture (race/ethnicity) Religion/spirituality Patient preferences
Probably effective	Congruence/genuineness Real relationship Emotional expression Cultivating positive expectations Promoting treatment credibility Managing countertransference Repairing alliance ruptures Self-disclosure and immediacy	Reactance level Stages of change Coping style
Promising but insufficient research Important but not yet investigated		Attachment style Sexual orientation Gender identity

Family History

Heritability of Psychiatric Disorders



Bienvenu et al. Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence.
Psychological Medicine 2011;41:33–40.

Challenges in clinical practice:

- Recall issues
- Stigma in previous generations
- Lack of validity of diagnoses

Opportunities:

- More useful in prevention?
- More useful in certain disorders (e.g. schizophrenia)?

Shared Heritability In Common Brain Disorders

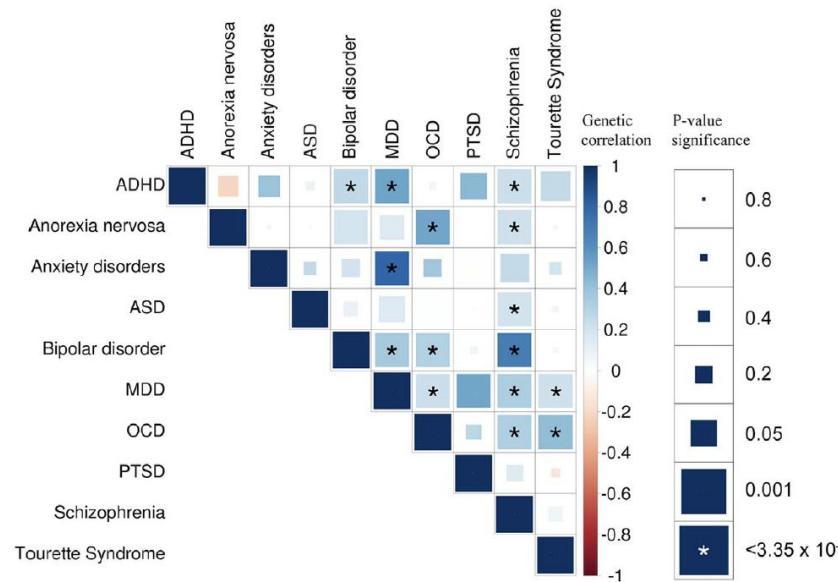
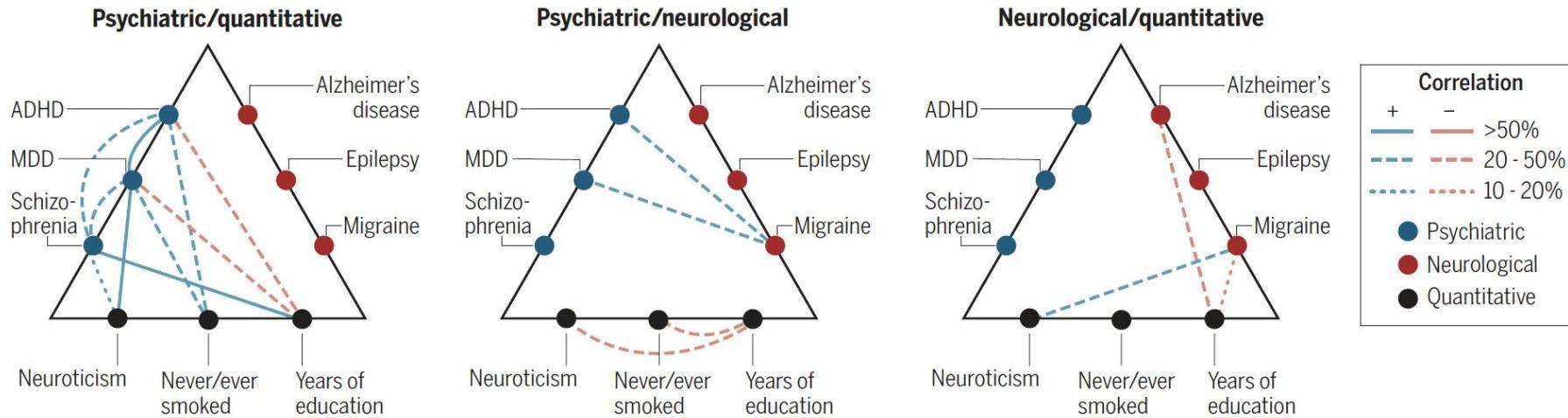


Fig. 1. Genetic correlations across psychiatric phenotypes. The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

Shared Heritability In Common Brain Disorders



It is illegal to post this copyrighted PDF on any website. What Should a Psychiatrist Know About Genetics?

Review and Recommendations From the Residency Education Committee of the International Society of Psychiatric Genetics

John I. Nurnberger Jr, MD, PhD^{a,*}; Jehannine Austin, PhD^b; Wade H. Berrettini, MD, PhD^c; Aaron D. Besterman, MD^d;
Lynn E. DeLisi, MD^e; Dorothy E. Grice, MD^f; James L. Kennedy, MD^g; Daniel Moreno-De-Luca, MD^h;
James B. Potash, MD, MPHⁱ; David A. Ross, MD, PhD^j; Thomas G. Schulze, MD^k; and Gwyneth Zai, MD, PhD^g

**Table 2. Why Do Today's Psychiatric Residents Need to
Understand Genetics?**

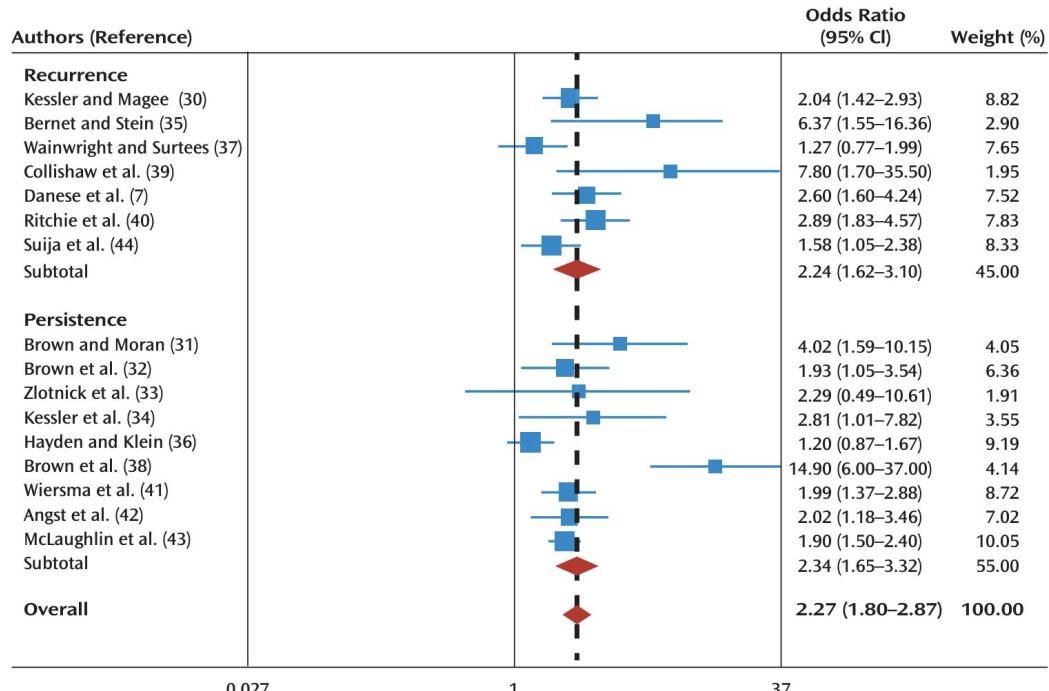
- | | |
|--|--|
| <p>A. Clinical situations in which genetic knowledge is already required</p> <ol style="list-style-type: none">1. Estimating empirical risk for psychiatric illness from family structure information and epidemiologic studies2. Ordering and interpreting genetic tests for autism spectrum disorders and intellectual disability3. Evaluating the need for pharmacogenomic testing and interpreting the results4. Addressing the results of direct-to-consumer genetic tests in clinical practice5. Knowing when to consult genetic counselors and medical geneticists | <p>B. Areas in which new applications of genetics may be expected in the next 1–2 decades</p> <ol style="list-style-type: none">1. Estimating empirical risk in the presence of specific copy number variants and single nucleotide variants2. Ordering and interpreting genetic tests for rare variants in schizophrenia and bipolar disorder3. Applying genetic risk scoring in a clinical framework4. Developing personal genetic profiles for patients and interpretation for treatment decisions and personal prognosis |
|--|--|

Social, demographic, cultural, personal, developmental...

- Development
 - Birth, developmental milestones, prenatal complications
 - Childhood home environment, relationship with parents
- Socio-cultural
 - Sex, assigned gender, sexual orientation
 - Ethnicity, culture, places lived
 - Racism, structural oppression, poverty, intergenerational trauma
- Interpersonal
 - Parents, siblings, grandparents, family dynamics
 - Primary caregivers
 - Romantic relationships
 - Friends, personal supports
- Occupational, vocational
 - School, education, work, career, financial support, government assistance

Childhood Maltreatment

FIGURE 2. Meta-Analysis of Epidemiological Studies Investigating the Association Between Childhood Maltreatment and Depression Course (Random Effects)^a



^a The red diamonds show the combined effect sizes for studies concerned with depression recurrence and depression persistence as well as the overall effect size of the meta-analysis (top to bottom).

Childhood Adversity is “Dose Dependent”

Table 3

Associations between childhood adversity and depression indicators in early adulthood. Results from Cox Regression Analyses, presented as hazard ratios (HR) with 95% confidence intervals (CI).

	Clinical diagnosis			Medication		
	Model I ^a	Model II ^b	Model III ^c	Model I ^a	Model II ^b	Model III ^c
	Parental death	1.46 (1.36–1.57)	1.36 (1.27–1.47)	1.06 (0.99–1.14)	1.05 (1.01–1.11)	1.05 (1.00–1.10)
Parental substance abuse	2.09 (1.98–2.20)	1.97 (1.87–2.08)	1.20 (1.13–1.28)	1.20 (1.15–1.24)	1.19 (1.14–1.24)	1.06 (1.00–1.11)
Substantial parental criminality	1.78 (1.69–1.87)	1.68 (1.60–1.77)	1.16 (1.09–1.22)	1.16 (1.12–1.20)	1.16 (1.12–1.20)	1.07 (1.03–1.12)
Parental psychiatric morbidity	2.11 (2.02–2.20)	2.05 (1.96–2.14)	1.62 (1.55–1.70)	1.22 (1.18–1.26)	1.22 (1.18–1.26)	1.17 (1.13–1.21)
Parental separation	1.58 (1.54–1.62)	1.55 (1.51–1.59)	1.40 (1.36–1.44)	1.08 (1.06–1.10)	1.08 (1.06–1.10)	1.06 (1.04–1.07)
Household receiving public assistance	1.95 (1.86–2.04)	1.88 (1.80–1.98)	1.29 (1.22–1.36)	1.15 (1.11–1.19)	1.16 (1.12–1.20)	1.07 (1.03–1.11)
Child welfare intervention	2.79 (2.60–2.99)	2.57 (2.39–2.76)	1.51 (1.39–1.63)	1.24 (1.17–1.31)	1.23 (1.15–1.30)	1.07 (1.00–1.14)
Residential instability	1.89 (1.74–2.05)	1.81 (1.66–1.97)	1.28 (1.18–1.40)	1.10 (1.03–1.17)	1.09 (1.02–1.16)	1.02 (0.95–1.08)
Total number of childhood adversities						
1	1.55 (1.50–1.60)	1.54 (1.49–1.59)		1.08 (1.06–1.10)	1.08 (1.06–1.10)	
2	2.01 (1.93–2.10)	1.98 (1.89–2.07)		1.14 (1.11–1.18)	1.15 (1.11–1.18)	
3	2.48 (2.32–2.65)	2.42 (2.26–2.59)		1.20 (1.14–1.26)	1.21 (1.15–1.27)	
4 +	3.17 (2.94–3.41)	3.05 (2.83–3.29)		1.32 (1.24–1.40)	1.32 (1.25–1.41)	

Reference group: no childhood adversity.

^a Adjusted for birth year and sex.

^b Model I with additional adjustments for parental country of birth and parental education.

^c Model II with additional adjustments for all CAs simultaneously.

Do sociodemographic factors interact with psych history?

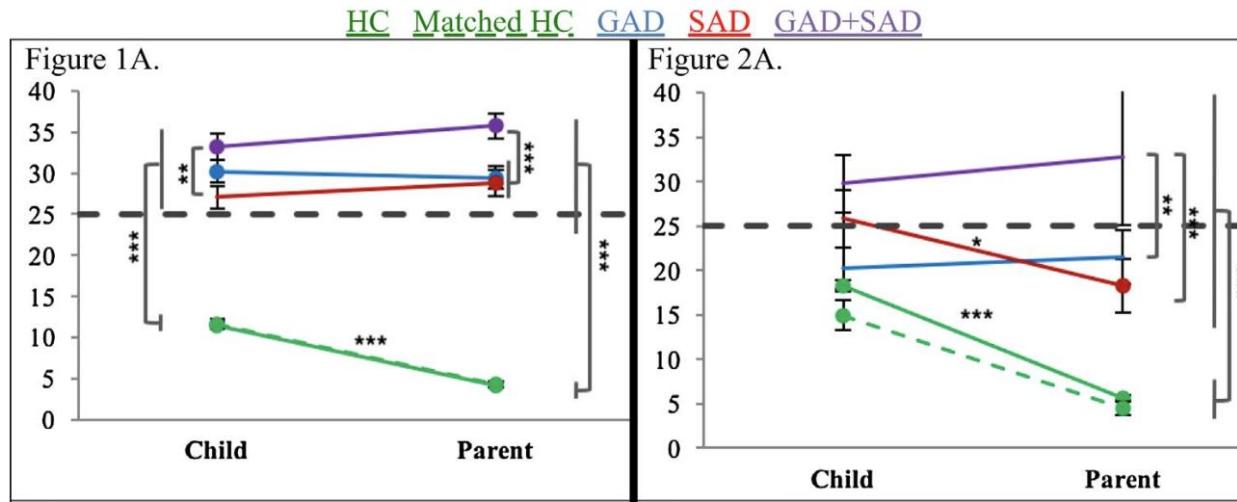
- Gender: More women than men prefer psychological treatment vs medication
 - Minimize exposure of fetus or neonate to ADTs
 - Scope of evidence is broader for postpartum vs during pregnancy
- Age: complications in elderly patients
 - More vulnerable to ADT side effects and drug interactions

Challenges and Opportunities

- Prognostication of social factors is often not clinically useful, especially depending on setting
- Patients that present to mental health care, especially tertiary care centres, especially to ED or inpatient hospitalization selection bias for severity
- Systemic issues, structural issues
 - Marginalized populations

Collateral Information

- Primarily to address limitations in subjective report from patient
- More important in certain populations (e.g. children/adolescents)
- Can be therapeutic to involve family



Medical Investigations

- Not used to directly assess MDD
- Primary purpose is “medical clearance” - ruling out other medical causes
- No recommended standard, but depending on clinical suspicion:
 - Blood work - CBC, electrolytes, thyroid hormone, B12/Folate, iron/ferritin
 - Urine drug screen
 - ECG
 - Head imaging - CT/MRI
 - Specific to comorbidities: e.g. viral load in HIV+ patients

Longitudinal Assessment

- A single assessment is cross-sectional
- Classic issues with longitudinal assessment:
 - MDD diagnosis first → Bipolar Disorder diagnosis after 1st manic episode
 - Mid life depression that evolves into dementia
 - More information becomes apparent later...

Measurement Based Care

- The use of standardized rating scales can help screen for the presence of a disorder, provides an “objective” reference of severity, and can be used to track and monitor progress
- Improves clinical outcomes, improves identification of problems

Measurement Based Care Problems & Opportunities

- Purpose: Screening vs. Diagnosis (PHQ-9 vs. SCID)
- Sensitivity to change
- “Minimal Clinically Important Difference”: MCID
- What does your scale ask? Look at individual items

3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Patient Health Questionnaire (PHQ-9)

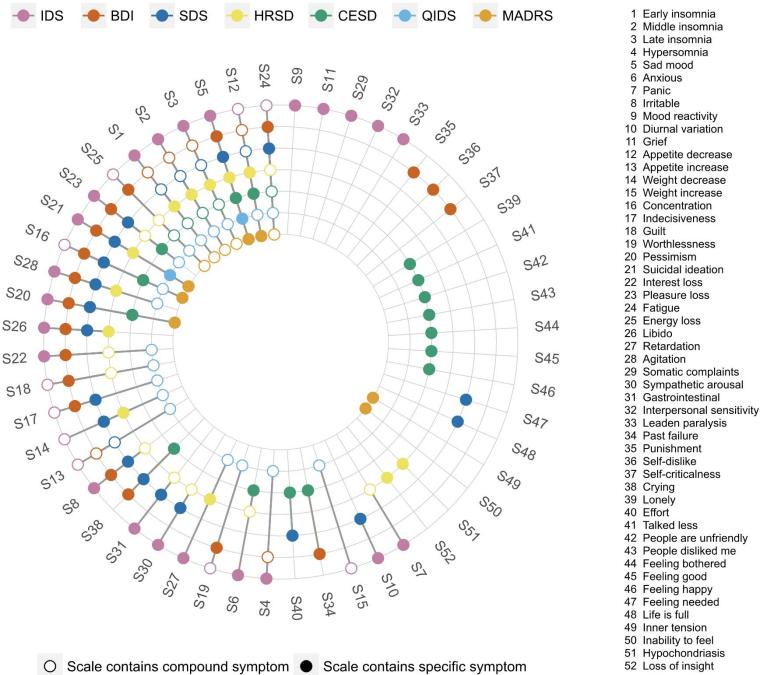


Fig. 1. Co-occurrence of 52 depression symptoms across 7 depression rating scales. Colored circles for a symptom indicate that a scale directly assesses that symptom, while empty circles indicate that a scale only measures a symptom indirectly. For instance, the IDS assesses item 4 hypersomnia directly, the BDI measures item 4 indirectly via a general question on sleep problems; and the SDS does not capture item 4 at all. Note that the 9 QIDS items analyzed correspond exactly to the DSM-5 criterion symptoms for MDD. Please see the online version for colors; in the black and white version, the circles represent (from outer to inner circle): IDS, BDI, SDS, HRSD, CESD, QIDS, and MADRS.

Diagnosis, Assessment, and Management

Diagnosis

- Making the DSM diagnosis with the objective of guiding treatment
- Establish any potential comorbid diagnosis. with a prognosis (risk factors, predictors)
- Establish severity

Assessment

- Formulation: integrating multiple data points and understanding the patients presentation

Management

- First line treatments, second/third treatments (if no response to first treatments)
- determining patient preference
- availability of treatments psychoeducation

MDD Diagnosis - What we know

- Diagnosis guides treatment decision
- Low mood and/or anhedonia
- Sleep, energy, appetite, concentration, psychomotor retardation/agitation, guilt, suicidality
- <5 of 9 symptoms = adjustment disorder or other
- 5 of 9 symptoms = MDD
- >5 of 9 symptoms = MDD
- Subtypes
 - Atypical
 - Melancholic
 - Psychotic features
 - Catatonia

MDD Diagnosis Challenges and Opportunities

- Does not account for common symptoms
 - Anxiety is highly comorbid in depression
 - Degree of anxiety symptoms (not comorbid anxiety) predicts poor response to traditional antidepressants. Specific treatments proven to be more effective in this group
 - Pain is highly comorbid in depression (50% vs 15%)
 - Potential risk for high substance use addiction
 - Specific antidepressants associated with good response in pain syndromes
 - Irritability

MDD Diagnosis Challenges and Opportunities

- Poor biological reproducibility

No Support for Historical Candidate Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples

Richard Border, M.A., Emma C. Johnson, Ph.D., Luke M. Evans, Ph.D., Andrew Smolen, Ph.D., Noah Berley, Patrick F. Sullivan, M.D., Matthew C. Keller, Ph.D.

Objective: Interest in candidate gene and candidate gene-by-environment interaction hypotheses regarding major depressive disorder remains strong despite controversy surrounding the validity of previous findings. In response to this controversy, the present investigation empirically identified 18 candidate genes for depression that have been studied 10 or more times and examined evidence for their relevance to depression phenotypes.

Results: No clear evidence was found for any candidate gene polymorphism associations with depression phenotypes or any polymorphism-by-environment moderator effects. As a set, depression candidate genes were no more associated with depression phenotypes than noncandidate genes. The authors demonstrate that phenotypic measurement error is unlikely to account for these null findings.

MDD Diagnosis Challenges and Opportunities

- Does not fully account for cluster of symptoms

	Factor A: atypical symptoms	Factor B: functional impairment	Factor C: insomnia	Factor D: negative cognition
Sleeping too much	0.95	-0.02	-0.06	0.01
Tiredness	0.46	<u>0.26</u>	<u>0.31</u>	0.05
Weight change	0.20	<u>-0.14</u>	-0.03	0.07
Difficulty concentrating	-0.02	0.96	-0.02	0.00
Impact on normal roles	<u>0.14</u>	0.41	0.03	0.10
Waking too early	<u>-0.17</u>	0.00	0.75	0.03
Trouble falling asleep	0.09	0.00	0.70	-0.03
Worthlessness	0.00	0.00	-0.01	1.00
Thoughts of death	0.07	0.02	<u>0.14</u>	0.36

MDD Diagnosis Challenges and Opportunities

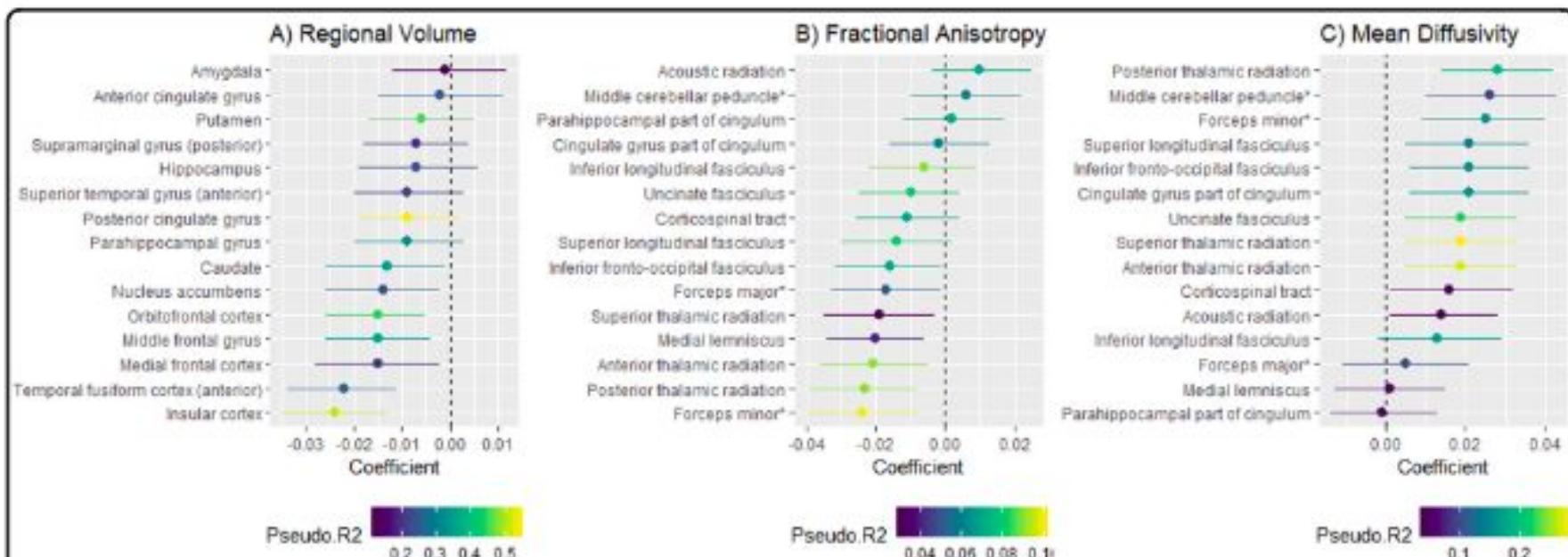


Fig. 2 Plots of associations (regression coefficients and 95% confidence intervals (CI)) between polygenic risk for anhedonia and **a** regional volumes of cortical/subcortical ROIs; **b** tract-specific fractional anisotropy; and **c** tract-specific mean diffusivity.

MDD Diagnosis Challenges and Opportunities

- What symptoms are more likely to improve with what treatments
 - Suicidality - ECT, rTMS, MST, ketamine?
 - Anhedonia - anti-inflammatories, ketamine, wellbutrin?
 - What does this tell us about the underlying pathophysiology
- How does comorbidity influence treatment response
 - MDD with obesity more like to respond to wellbutrin augmentation?
 - What does this tell us about the underlying pathophysiology

Severity - What we know

-Severity assessed by frequency of symptom and number; with many symptoms not accounted for

-More severe more likely to receive antidepressant recommendation over therapy

-In clinical trials more likely to be depressed at end of trial

		Not at all	Several days	More than half the days	Nearly every day
1.	Little interest or pleasure in doing things	0	1	2	3
2.	Feeling down, depressed, or hopeless	0	1	2	3
3.	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4.	Feeling tired or having little energy	0	1	2	3
5.	Poor appetite or overeating	0	1	2	3
6.	Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7.	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8.	Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9.	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Severity - what we know

- May dictate level and frequency of care

Step 4

Severe and complex depression*; risk to life; severe self-neglect

Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multi-professional and in-patient care

Step 3

Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression

Medication, high-intensity psychological interventions, combined treatments, collaborative care[†] and referral for further assessment and interventions

Step 2

Persistent subthreshold depressive symptoms; mild to moderate depression

Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions

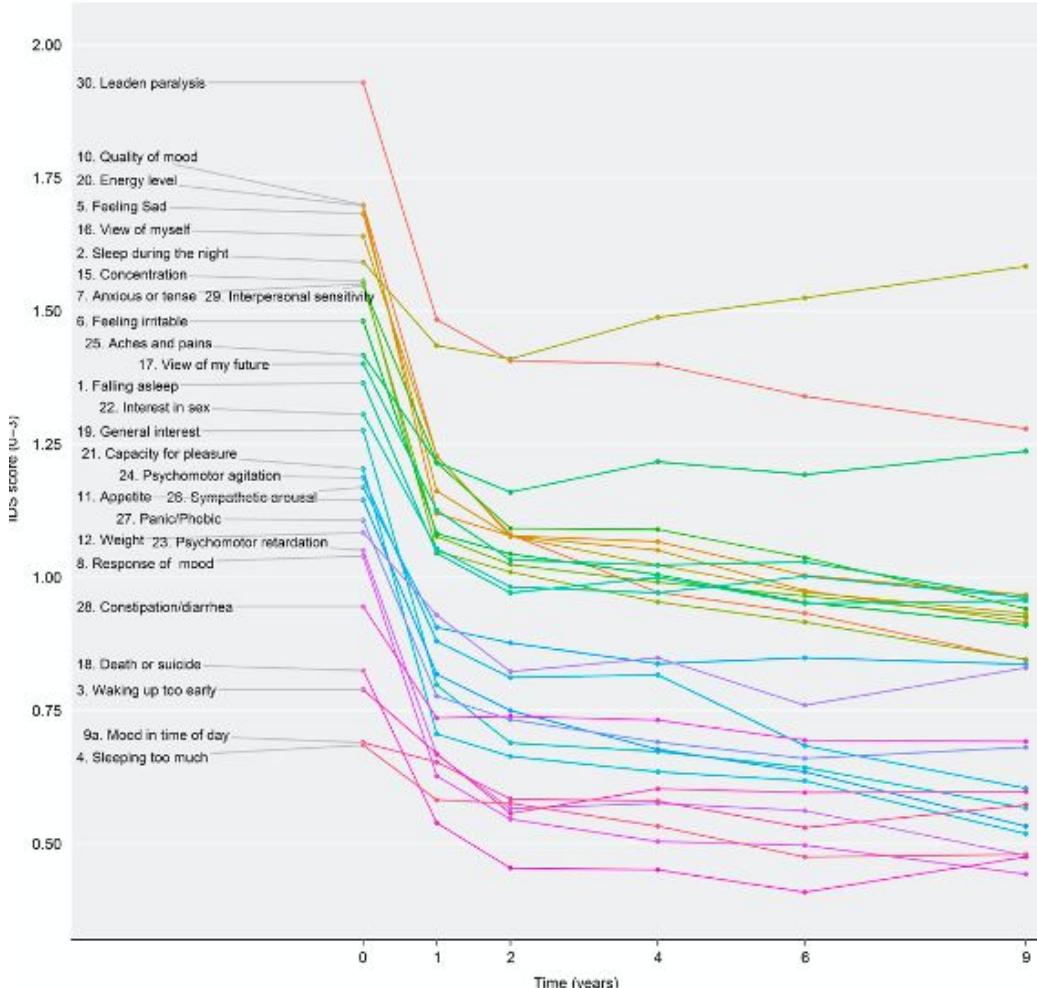
Step 1

All known and suspected presentations of depression

Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions

Severity - Challenges and opportunities

- How does severity of depression influence treatment response
- What symptoms are more likely to improve over time
- What is the rate of specific symptomatic improvement



Severity - Challenges and opportunities

- How does severity influence the treatment we choose

Review article

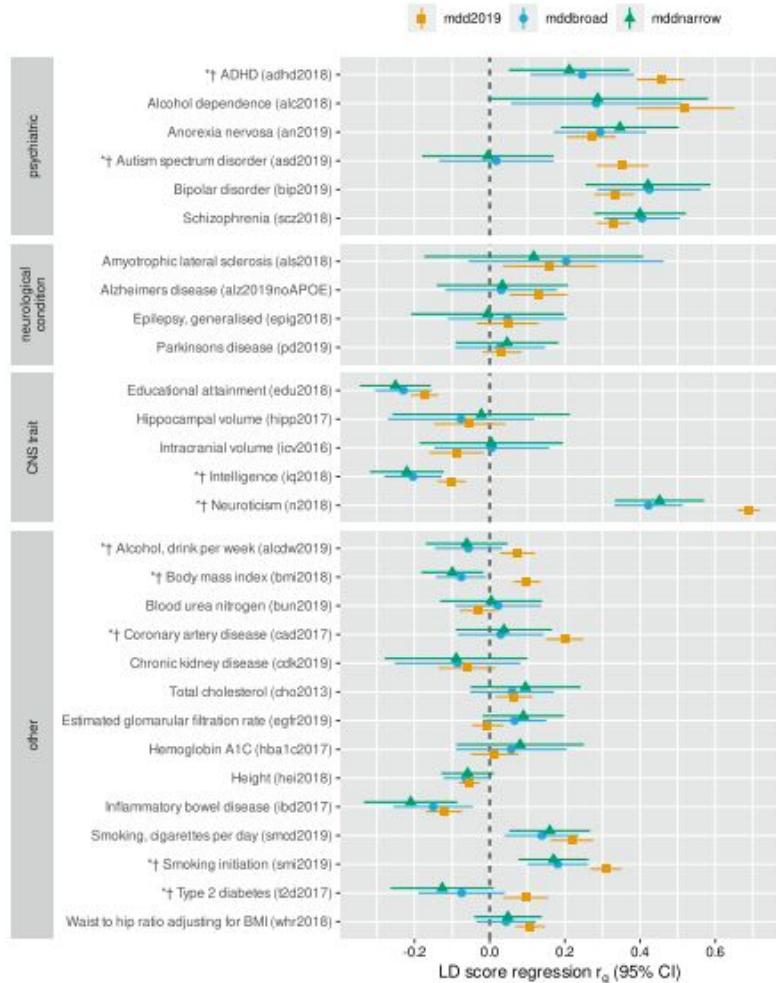
Initial severity of depression and efficacy of cognitive-behavioural therapy: individual-participant data meta-analysis of pill-placebo-controlled trials

Toshi A. Furukawa,* Erica S. Weitz,* Shiro Tanaka,* Steven D. Hollon, Stefan G. Hofmann,
Gerhard Andersson, Jos Twisk, Robert J. DeRubeis, Sona Dimidjian, Ulrich Hegerl, Roland Mergl,
Robin B. Jarrett, Jeffrey R. Vittengl, Norio Watanabe and Pim Cuijpers

Severity - Challenges and opportunities

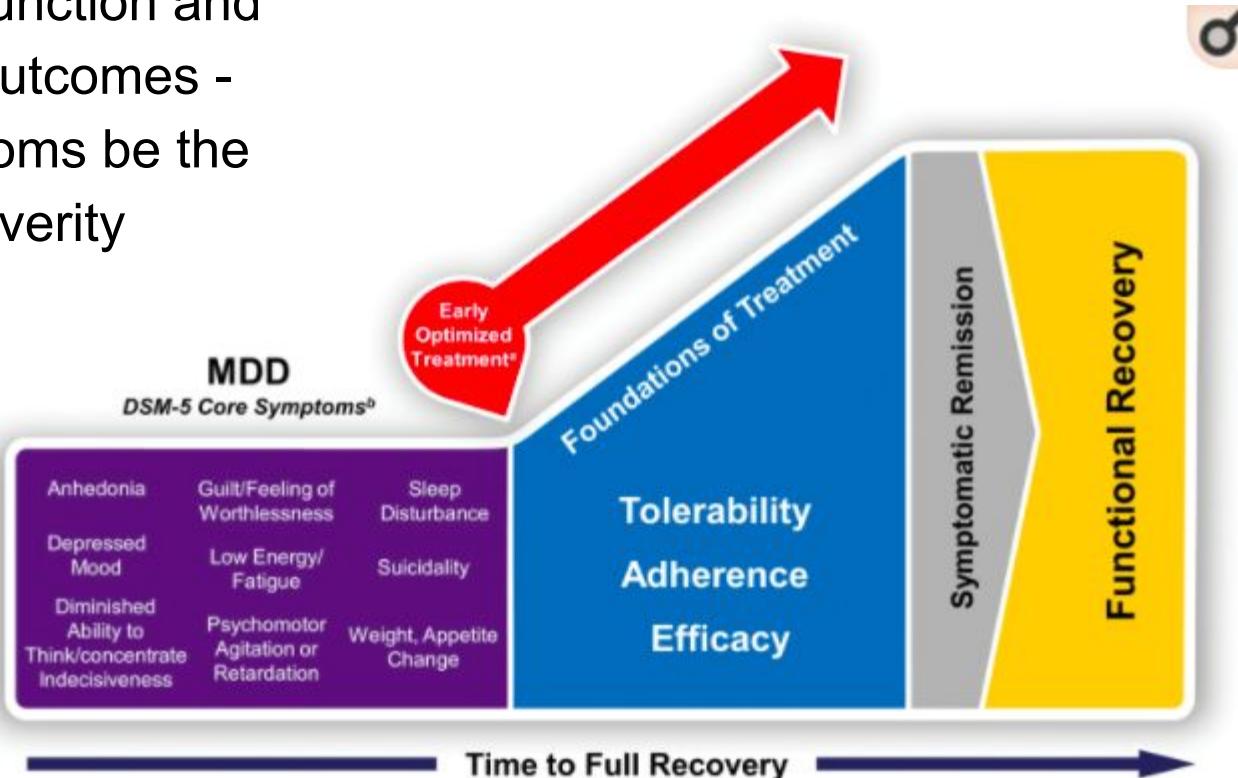
- Is severe MDD the same biological disorder as moderate MDD?

Clements et al. 2021



Severity - Challenges and opportunities

- How to factor in function and patient oriented outcomes - i.e. should symptoms be the best marker of severity



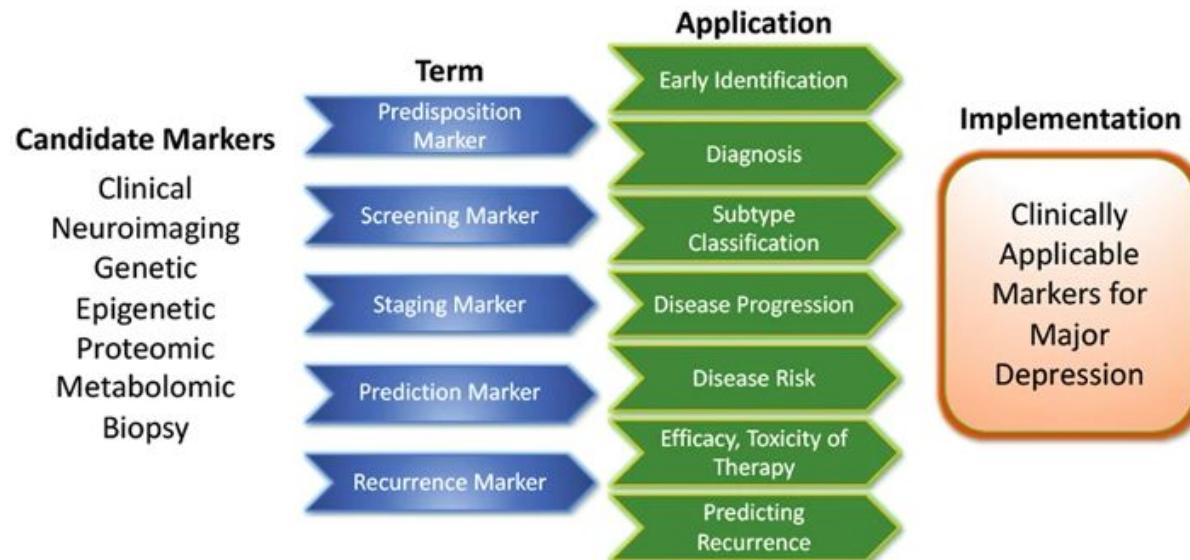
Prognosis - what we know

- Attempt to determine likelihood of someone doing well on a specific treatment
- duration of untreated depression correlates with worse outcomes
- Early improvement is associated with response and remission,
- comorbidities prolong course of illness
- Limited utility on an individual level

Prognosis - Challenges and opportunities

- Multiple putative biomarkers have been explored with little integration

Categories and Applications of Disease Markers in Major Depression



ORIGINAL ARTICLE

A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression

JA van Waarde¹, HS Scholte², LJB van Oudheusden¹, B Verwey¹, D Denys³ and GA van Wingen³

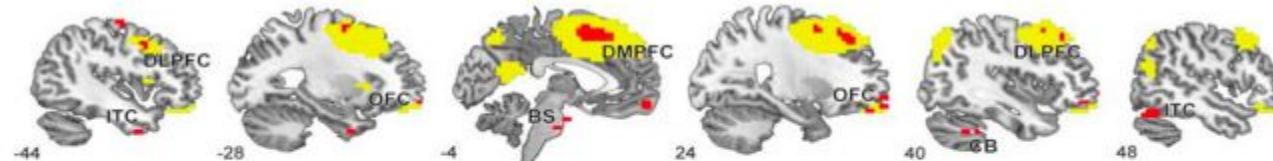


Figure 2. The first resting-state network that predicted remission from depression. The features that showed accurate classification of remitted and non-remitting patients are shown in red, superimposed on the network that was used for classification in yellow ($z > 2.3$). The panels present the results from the left side of the brain to the right side (x coordinates in Montreal Neurological Institute space). BS, brainstem; CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ITC, inferior temporal cortex; OFC, orbitofrontal cortex.

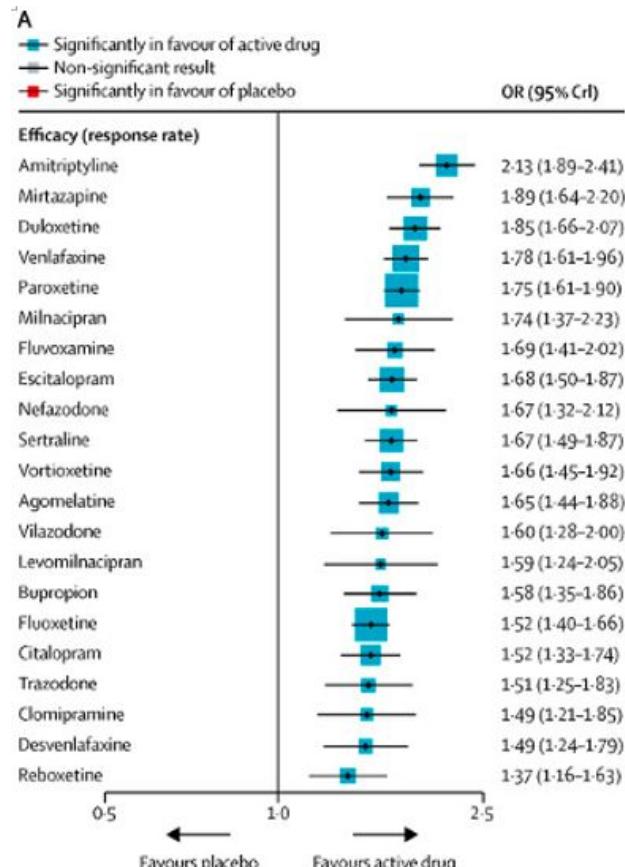
Management (Treatment) of MDD - What we know

- Treatment consists of addressing the contributing factors to the depressive episode
 - Biological - Medication, brain stimulation, addressing medical concerns, diet, exercise
 - Psychological - Therapy
 - Social - Increased physical activity, social engagement
- Decision based primarily on available guidelines with consideration of patient preference, comorbidity, clinical features, response/side effects in previous treatment
- With some exceptions, first line treatments do not typically target specific symptoms
- Secondary medications (augmentations) can often be used to target residual symptoms

Treatment Decision - What we know

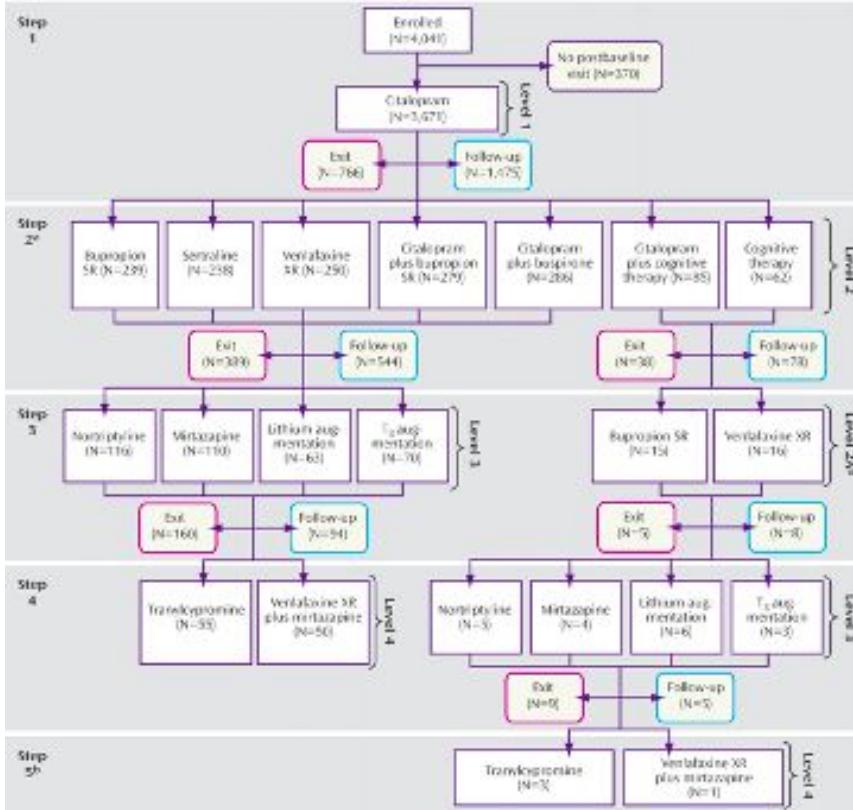
Table 1. Criteria for Level of Evidence and Line of Treatment.

	Criteria
Level of evidence^a	
1	Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled
2	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size
3	Small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies
4	Expert opinion/consensus
Line of treatment	
First line	Level 1 or Level 2 Evidence, plus clinical support ^b
Second line	Level 3 Evidence or higher, plus clinical support ^b
Third line	Level 4 Evidence or higher, plus clinical support ^b

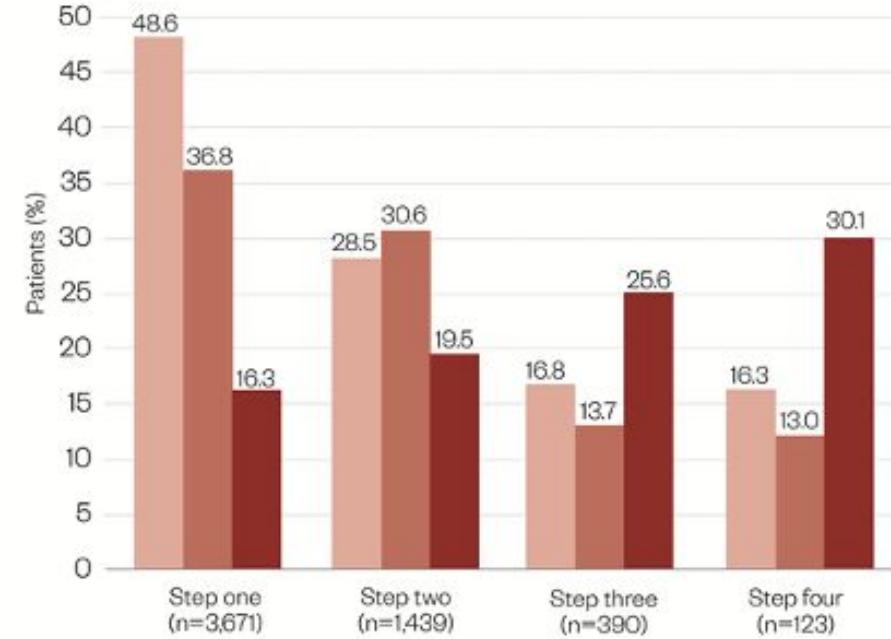


Cipriani et al.

Treatment Decisions - What we know

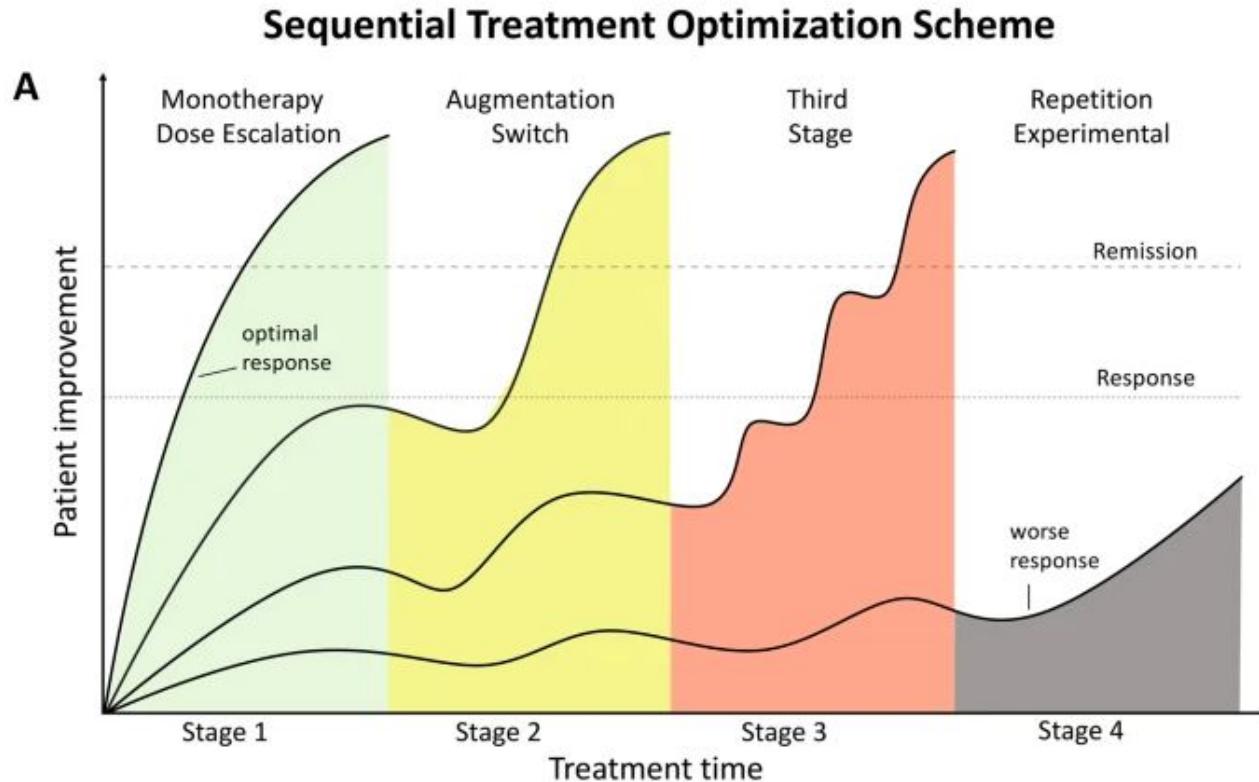


■ Response
■ Remission
■ Intolerable side effects



Treatment - Challenge and opportunities

Fig. 3: Sequential treatment optimization scheme for major depression.



Treatment - Challenge and opportunities



The Canadian Biomarker Integration Network in Depression (CAN-BIND) is a national program of research and learning. CAN-BIND is discovering ways to identify the right treatment for the right person in order to help individuals with depression get well quickly, and stay well.

Original Investigation | Psychiatry

January 3, 2020

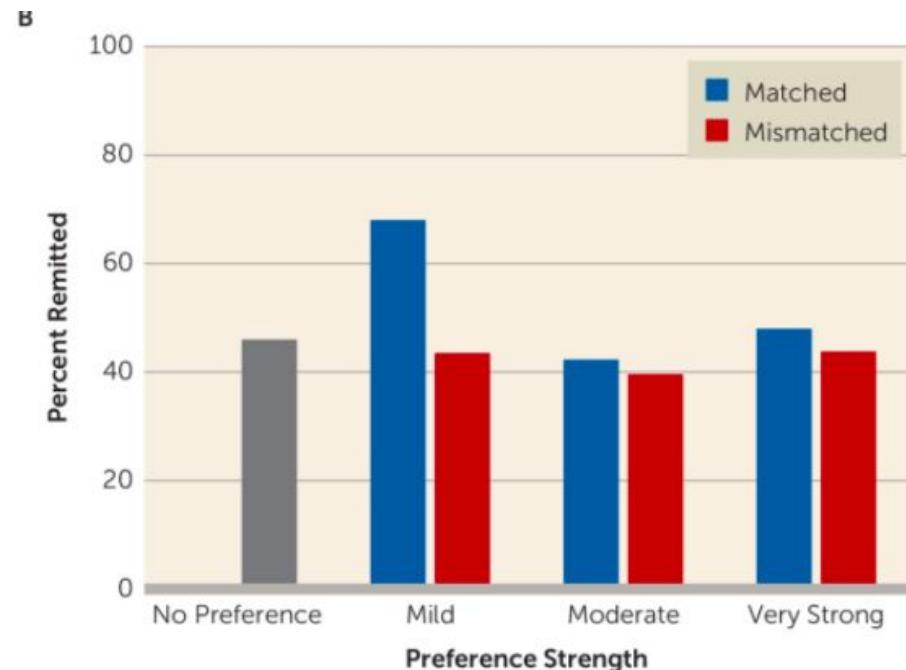
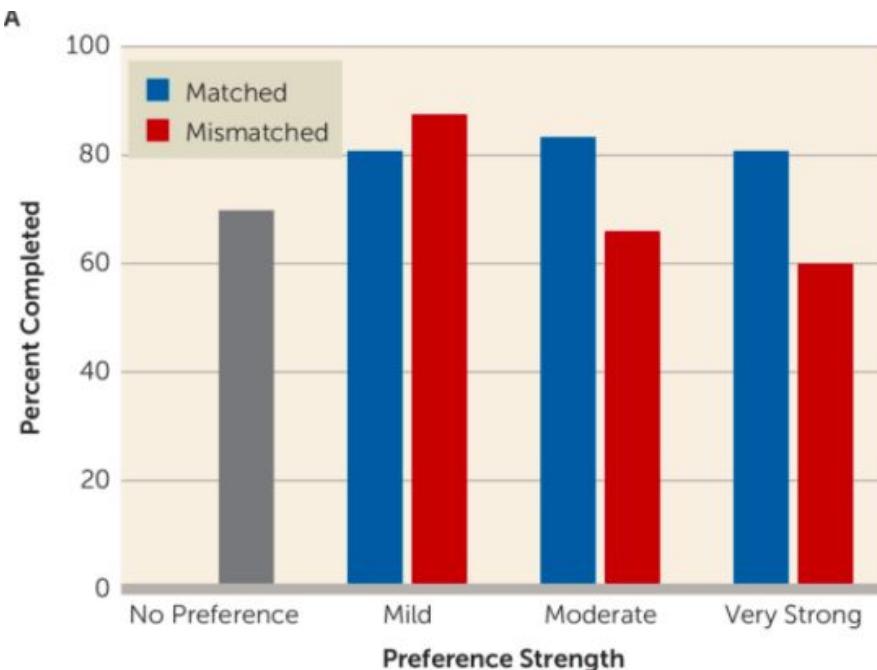
Use of Machine Learning for Predicting Escitalopram Treatment Outcome From Electroencephalography Recordings in Adult Patients With Depression

Andrey Zhdanov, PhD^{1,2}, Sravya Atluri, PhD^{3,4}, Willy Wong, PhD⁵, et al

Symptom Dimension of Interest-Activity Indicates Need for Aripiprazole Augmentation of Escitalopram in Major Depressive Disorder: A CAN-BIND-1 Report

Treatment - Challenge and opportunities

- How does patient preference contribute to overall outcome?



Dunlop 2017 et al.

Follow-up and monitoring - what we know

- Antidepressants take 6-8 weeks to take full effect
- Current practice is to see patients 2 to 4 weeks after initiation of treatment and as needed afterwards
- Great opportunity to capture serial data through methods such as actigraphy, passive monitoring

ORIGINAL RESEARCH article

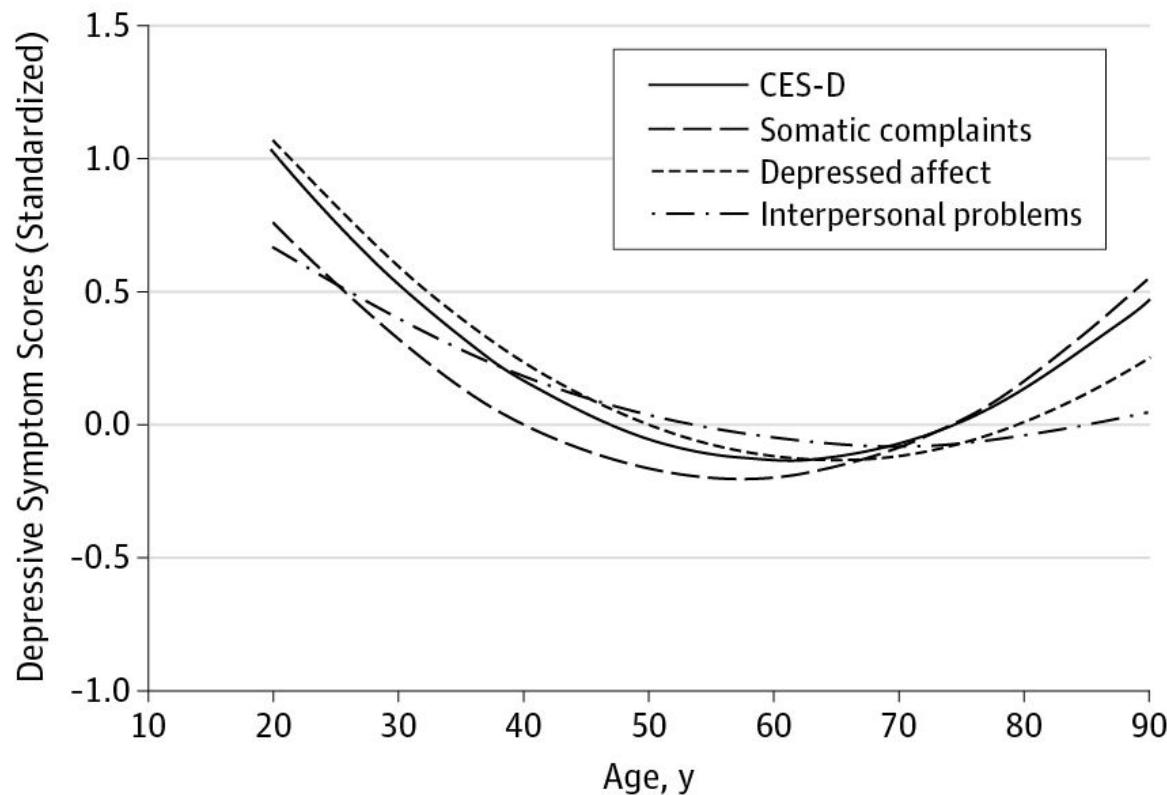
Front. Psychiatry, 18 December 2020 | <https://doi.org/10.3389/fpsyg.2020.584711>



Monitoring Changes in Depression Severity Using Wearable and Mobile Sensors

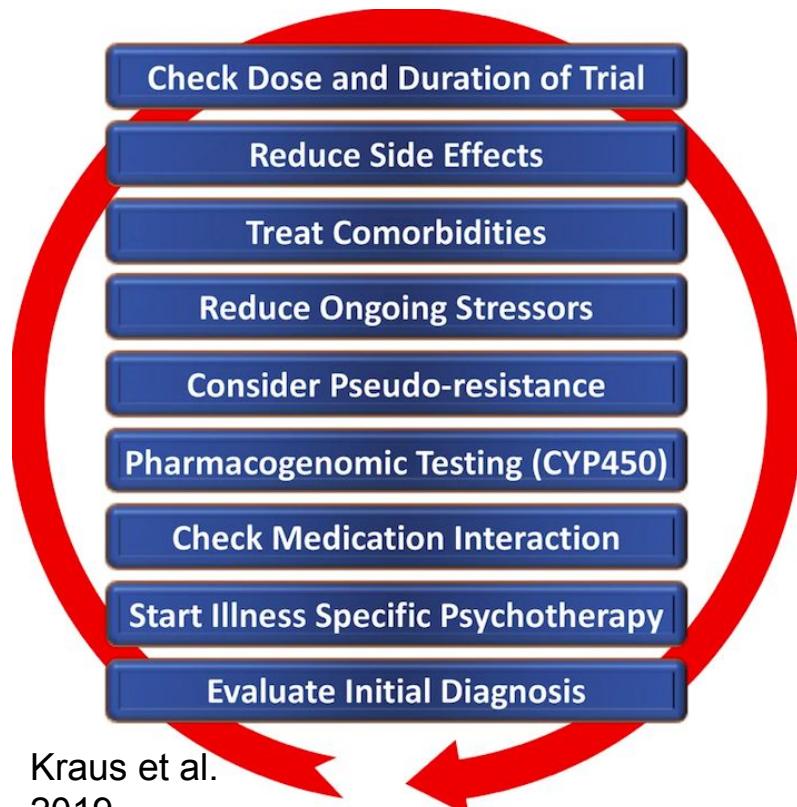
Follow-up and monitoring - challenges and opportunities

- Long-term trajectory of depression can differ across the life span.
- Who to follow and for how long?
-



Sutin et al.
2013

Treatment resistance - Challenges and opportunities



- Candidate clinical, neuroimaging, blood, and genetic markers exist but need to be improved for routine clinical care
 - Establishing a diagnosis, determining treatment, monitoring outcome
- Early identification and treatment facilitate better outcomes
- Establishing standard sequential care
- Investigating mechanisms and effectiveness of novel and rapid antidepressants including brain stimulation

Diagnosis vs. Formulation

Diagnosis (DSM-5 coding):

- Major Depressive Disorder, Current Episode Depressed, Recurrent, Moderate Severity.
 - Comorbid: Borderline Personality Disorder
 - Medical: Diabetes Type II

Formulation:

	predisposing	precipitating	perpetuating	protective
biological	Previous h of MDD Fam hx? Rx/substances Gender (F) Medical hx?	Rx non adherence Subst Menopause Season Peripartum	Rx non adherence Ongoing subst Psych comorbidities	Taking rx Lack of family hx If it was 1 st ep Early response to rx? Healthy Intelligent
psychological	Trauma/ACE leads to insecure attachment, poor coping Slide below for details	Perception of event below activating shame leading to 2 nd emotions of anger etc	Emotional dysregulation, interpersonal difficulties, challenge to engage in care	Ability to present for help, reflect, engage, cope
social	Interpersonal sensitivity, SES, education, isolation	Role transition, role dispute, death, moving, migration, Financial stress	Isolation/ withdrawal	Family, friends, community supports

Challenges and Opportunities: Combining Multiple Sources of Information



Psychiatric Evaluation And Treatment

<http://real-psychiatry.blogspot.com/>

Thank You!

Contact Information

victor.tang@camh.ca @victormarktang

brett.jones@camh.ca @jonesbdm

Acknowledgements

Dr Erin Dickie and the entire KCNI Summer School Team

Research Collaborators: Drs. Dan Felsky, Shreejoy Tripathy, Joanna Yu, Stefan Kloiber, Sean Hill, Marta Maslej, Robert Levitan