From Resistance to Response: Evolving Strategies in MDD Management

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TOTAL CME

Disclosures

- Research support: Alkermes, Boehringer Ingelheim, Janssen, Karuna, Neurocrine Biosciences, Teva
- Advisory boards or consulting: Alkermes, Boehringer Ingelheim, Clinical Care Options, CME Outfitters, CMEology, Healthcare Global Village, TotalCME, VML Health
- None of the research supported by any of the sponsors above will be discussed today.
- I will describe off-label treatment strategies for depression.

Learning Objectives

- Apply measurement-based care tools to identify patients with treatment-resistant depression or patients with major depressive disorder (MDD) who are suboptimally managed
- Differentiate between depression symptoms caused by MDD and those stemming from bipolar disorder, using evidence-based diagnostic criteria and patient history
- Evaluate the risks and benefits of augmentation versus switching strategies for antidepressant treatments to minimize AEs, focusing on evidence-based treatment strategies
- Develop treatment plans that specifically target the residual symptoms of depression
- Critically evaluate the impact of targeting multiple pathways when treating MDD

Audience Participation

Your mobile device can be used to participate in polling and to download today's presentation. Join in by scanning the QR code!

Complete your pre-test now by scanning the QR code.

Robert Burton (1621)

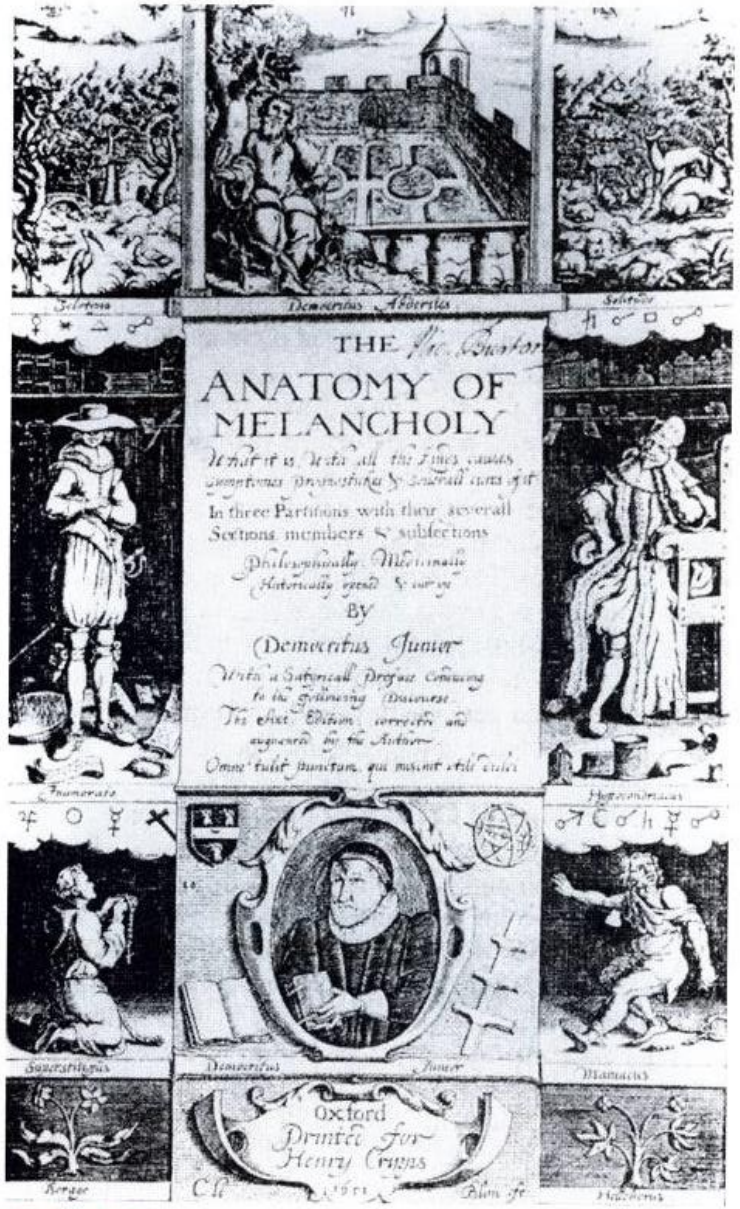
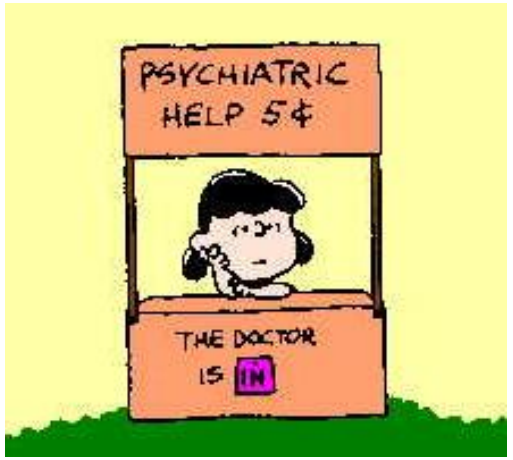
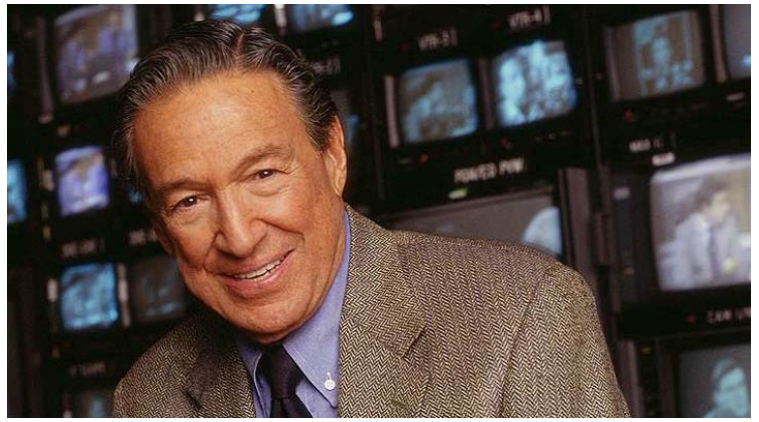


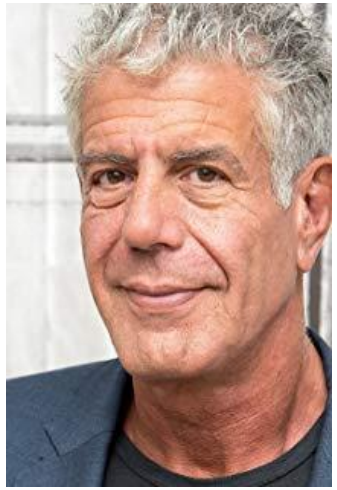
FIGURE 8.1-1
Frontispiece of Robert Burton's *Anatomy of Melancholy* (1621).

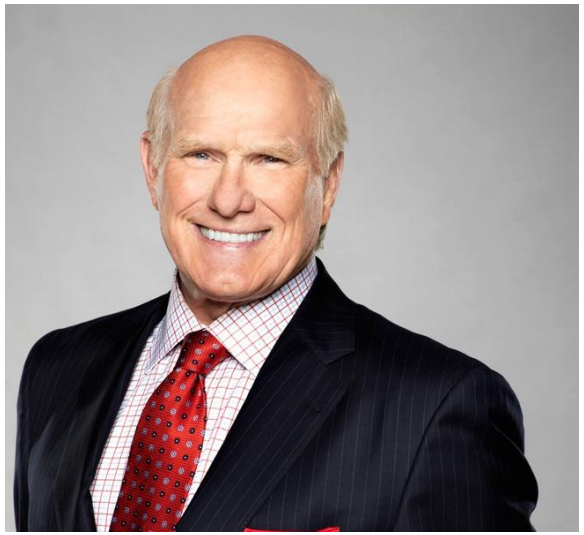

TIME
ROBIN
WILLIAMS
1951-2014

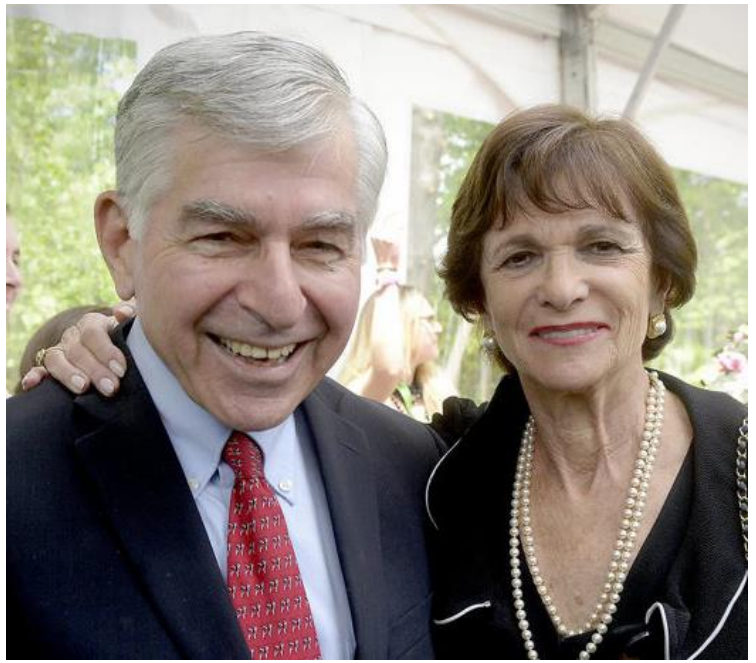

PSYCHIATRIC
HELP 5¢
THE DOCTOR
IS IN


TheBrief
STYLE ICON
Designer Kate
Spade in her
New York City
showroom on
Nov. 2, 2000









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Depression: Definition

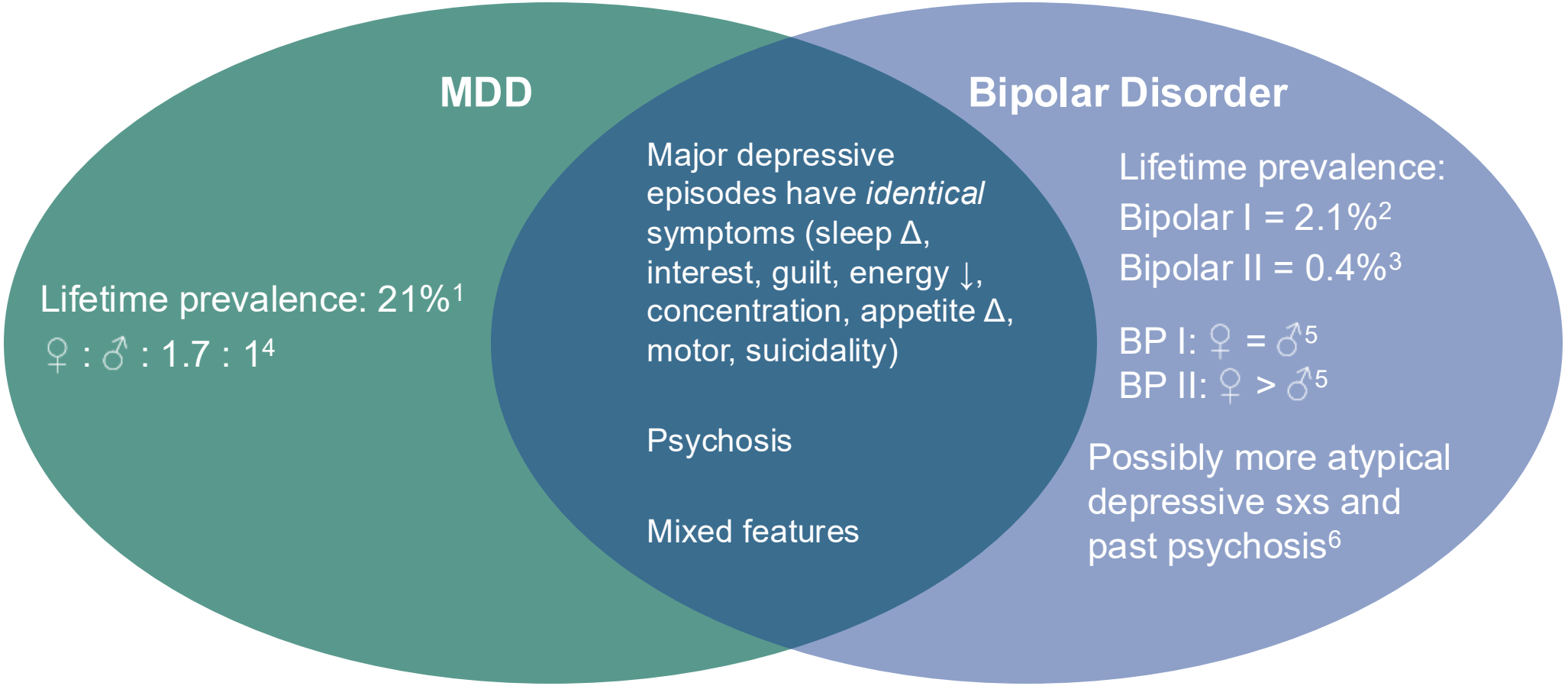
- A term used to describe clinical signs and symptoms
  - Ranging from transient feelings of discouragement, disappointment, sadness, grief, or despondency to a **disorder** with **neurovegetative symptoms**
    - ie, major depression
- To qualify as a disorder, it must cause *"**clinically significant distress or impairment**"* in function
- Need a thorough **biopsychosocial-spiritual** assessment to determine diagnosis and treatment plan

Criteria for Major Depression:

- Sleep disturbance (increased or decreased)
- Interests (diminished)
- Guilt (or feelings of worthlessness)
- Energy (decreased)
- Concentration (decreased)
- Appetite disturbance (increased or decreased)
- Psychomotor (agitation or retardation)
- Suicidal thoughts (or thoughts of death)
    - > 4 or more symptoms with depressed mood or anhedonia for >2 weeks

Diagnostic and Statistical Manual. 5th ed. APA; 2013.

Depression in MDD vs Bipolar Disorder



1. Hasin DS, et al. *JAMA Psychiatry*. 2018;75(4):336-346. 2. Blanco C, et al. *J Psychiatr Res*. 2017;84:310-317.
3. Merikangas KR, Lamers F. *Curr Opin Psychiatry*. 2021;25(1):19-23. 4. Li S, et al. *Ann Gen Psychiatry*. 202312;22(1):53.
5. Altshuler LL, et al. *Am J Psychiatry*. 2010;167(6):708-715. 6. Mitchell PB, et al. *J Clin Psychiatry*. 2001;62(3):212-216.

Risk Factors for Depression

- Family or personal history of depression
- Family or personal history of alcohol or substance abuse
- Having a chronic illness
- Stressful life events
  - Loss of parent, spouse, job
- Adverse childhood experiences

General Facts About Suicide

- Tenth leading cause of death in the USA
- Second leading cause of death in youth ages 10-34
- Results in approximately 49,000 deaths/year in the USA
- Accounts for 1.3% of all deaths
- 1 of every 8-10 attempts is successful
- Average rate is 14.1/100,000
  - When >85 years old, rate is 22.7/100,000
- Rate increases with social unrest
- In severe depression, suicide rates are 10%–25%

Klerman GL. *J Clin Psychiatry*. 1987;48 Suppl:33-38. https://www.cdc.gov/youth-violence/prevention/index.html

High Risk for Suicide

- Those with depression, psychosis, and suicidal thoughts
- Men 20-30 or >50 yo, women 40-60 yo
- Survivors of a violent suicide attempt
- Substance use (alcohol #1, pain killers #2)
- Those who took precautions to avoid rescue
- Those who refuse help, feel hopeless, live alone
- Those without social supports or religion

https://www.cdc.gov/suicide/pdf/ncipc-suicide-factsheet-508_final.pdf

Who Needs Evaluation?

- Anyone who complains of depression or suicidal thoughts or who denies being suicidal but whose actions demonstrate suicidal intent
- Take suicidal statements/notes very seriously
  - Listen/demonstrate concern, observe symbolic communication (giving things away, collecting pills, etc.), emphasize options
- Social supports
  - Engage the help of others, see a professional
  - Call doctor or therapist, go to ER, or call 911/police if needed
  - May need to fill out a “petition” to have person evaluated
- Protection
  - Avoid dangerous situations, hide guns/weapons/keys, ensure safety

Treatment of Depression

- Psychotherapy: first choice for mild depression, add on for moderate-severe depression
- Pharmacotherapy
  - SSRIs/SNRIs/atypical antidepressants
  - Tricyclic antidepressants (TCAs)
  - Monoamine oxidase inhibitors (MAOIs)
  - Lithium
  - Mood stabilizers
  - Psychostimulants
- Somatic therapies: ECT, rTMS, VNS, DBS

The Evolution of Antidepressants

1950s	MAOIs	Lesser Selectivity
1960s	Tricyclics	
1970s	Older heterocyclics	Greater Selectivity
1980s	SSRIs	Lesser Selectivity
1990s	Newer atypicals	
2000s	NMDA antag?	New Target

Adapted from Shelton RC. *J Clin Psychiatry*. 1999;60 Supp 4:57-61.

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Citalopram
- Escitalopram
- Fluoxetine
- Paroxetine
- Sertraline
- Fluvoxamine
- Vortioxetine

- Mechanism of action: inhibition of reuptake of serotonin
- Toxicity: safe in overdose
- Side effects: **nausea**, **diarrhea**, anxiety, sedation, long-term weight gain, **sexual dysfunction**, apathy, treatment-emergent **suicidal thoughts** in patients up to age 25

SNRIs

- **Duloxetine**
- **Venlafaxine**
- **Desvenlafaxine**
- **Milnacipran**
- **Levomilnacipran**
- Dual serotonin and norepinephrine reuptake inhibition
- FDA indication MDD; also data suggesting efficacy for neuropathic pain/chronic pain, fibromyalgia, anxiety disorders, stress urinary incontinence

Antidepressant Warnings and Cautions

- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults (18–24 years) taking antidepressants for MDD and/or other psychiatric disorders
- Worsening of depression, emergence of suicidal thoughts and/or behavior
- Risk of serotonin syndrome during treatment with SSRIs/SNRIs alone or in combination with other serotonergic drugs such as other antidepressants or triptans
- Abnormal bleeding; use caution if used concurrently with other drugs that affect clotting or increase the risk of bleeding, eg, NSAIDS; inform patients of the increased risk and how to respond
- Activation of mania or hypomania
- Discontinuation symptoms after stopping serotonergic antidepressants either abruptly or during dose reduction have been reported
- Hyponatremia has been reported as a result of treatment with SSRIs and SNRIs due to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Atypical Antidepressants

- Bupropion
- Mirtazapine
- Nefazodone
- Trazodone
- Vilazodone

- Bupropion has **no sexual side effects** and is also useful for **smoking cessation**
- Mirtazapine is often used for depression in the elderly
- Trazodone is sedating and often used to treat **insomnia**

Tetracyclic and Tricyclic Antidepressants (TCAs)

- Amitriptyline
- Nortriptyline
- Desipramine
- Imipramine
- Doxepin
- Protriptyline
- Trimipramine
- Maprotiline
- Amoxapine
- Clomipramine

- Side effects: dry mouth, constipation, urinary retention, blurred vision, orthostatic hypotension, increased appetite, weight gain, sedation, fatigue, sexual dysfunction
- **Lethal in overdose** (2-week supply)

Monoamine Oxidase Inhibitors (MAOIs)

- Phenelzine
- Tranylcypromine
- Isocarboxazid
- Selegiline

- Need to adhere to a special "**tyramine-free**" diet—avoid aged cheeses, beer, wine, meats, etc.
- Have to "wash out" SSRIs before starting
- **Lethal in overdose**

Measurement-Based Tools to Quantify Depression Symptom Severity, Response, and Remission

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	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

Scoring:
0-4: None
5-9: Mild
10-14: Moderate
15-19: Moderately Severe
≥20: Severe

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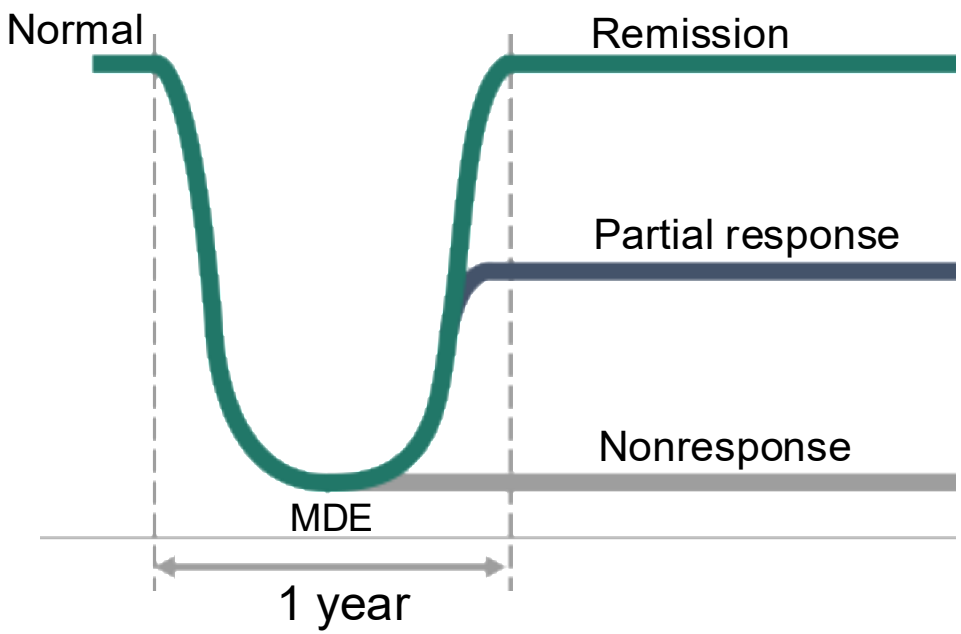
Definitions of Response and Remission

Nonremission Is Common

- 35%–45% remission
- 10%–20% response with residual symptoms
- 15% partial response
- 25%–34% nonresponse
- 7%–15% intolerant



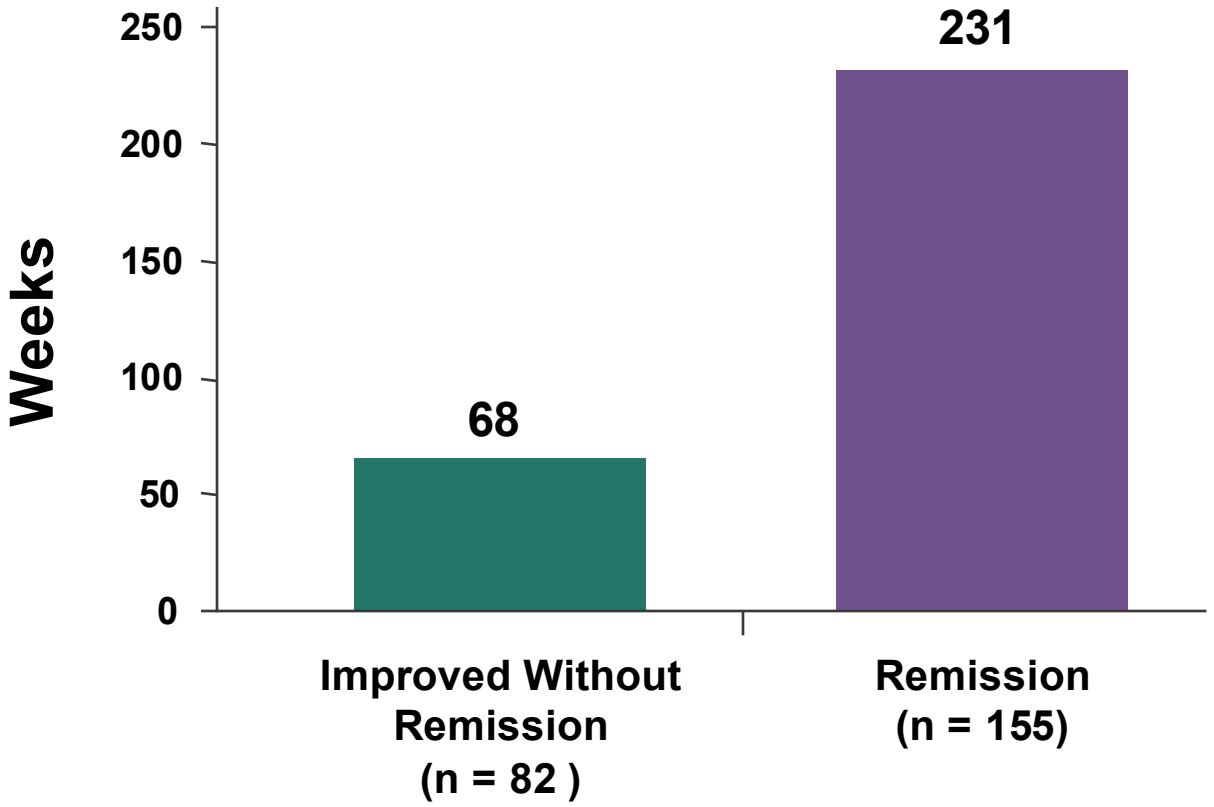
Depression in Primary Care: Vol. 2. Treatment of Major Depression. AHCPR Publication No. 93-0551, 1993.
Fava M, Davidson KG. *Psychiatr Clin North Am.* 1996;19(2):179-200.

Consequences of Nonremission

- Poor function (eg, work, family)
- Poor prognosis (eg, increased recurrence)
- Psychiatric or general medical complications (eg, substance abuse [SA])
- Health service utilization
- Death from:
  - Medical comorbidities
  - Suicide
- Treatment resistance

Simon GE, et al. *Gen Hosp Psychiatry.* 2000;22(3):153-162.
Paykel ES, et al. *Psychol Med.* 1995;25(6):1171-1180.
Judd LL, et al. *Am J Psychiatry*. 2000;157(9):1501-1504.

Median Weeks to Relapse* Following Response



*Relapse defined as onset of new major depressive episode.
Adapted from Judd LL, et al. *J Affect Disord*. 1998;50(2-3):97-108.

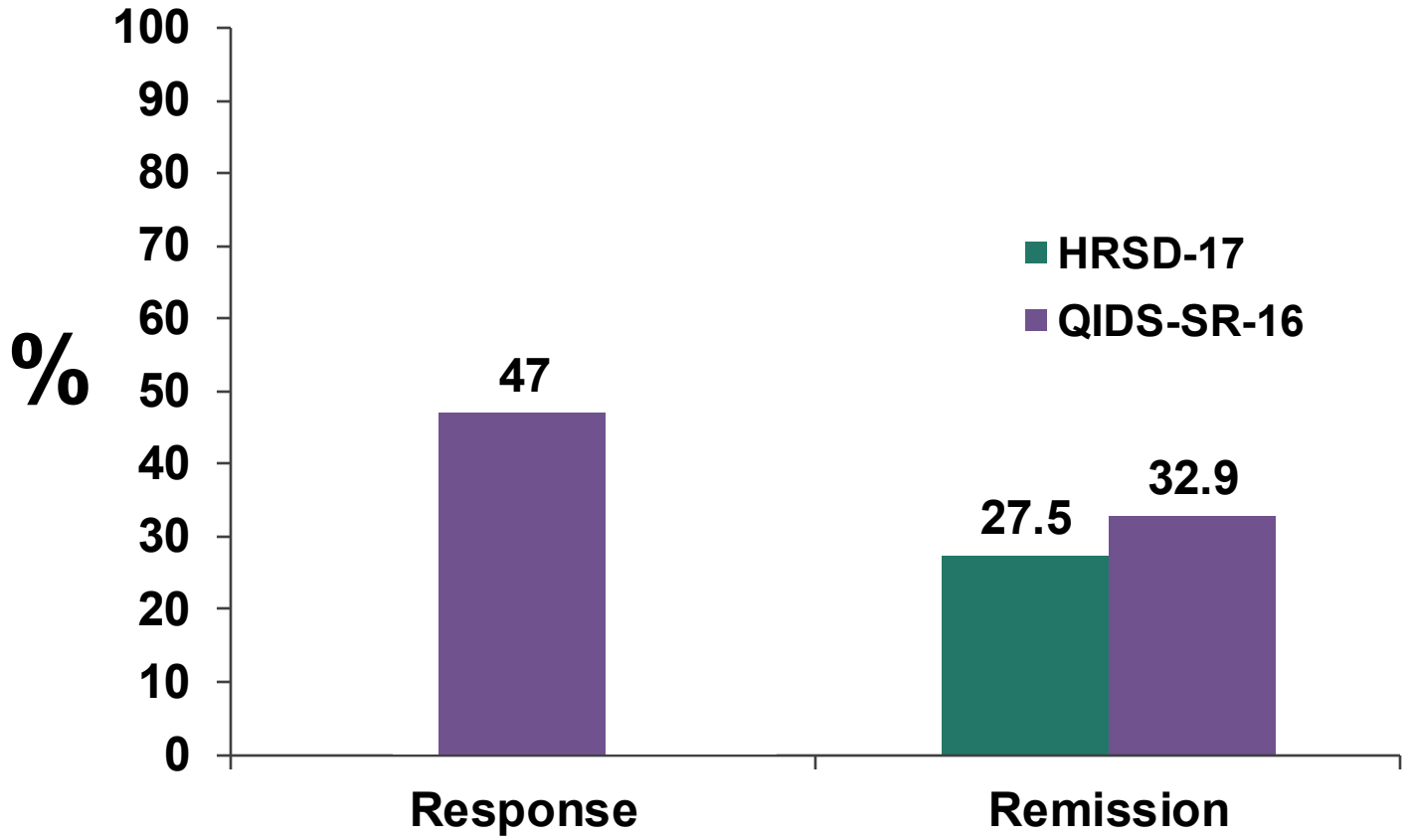
The STAR*D Trial

- STAR*D Trial
- Sequenced Treatment Alternatives to Relieve Depression

Treatment Levels

- Level 1:
  - Citalopram
- Level 2:
  - Switch options:
    - Sertraline
    - Bupropion SR
    - Venlafaxine XR
    - Cognitive psychotherapy
  - Add-on options
    - Bupropion SR
    - Buspirone
    - Cognitive psychotherapy

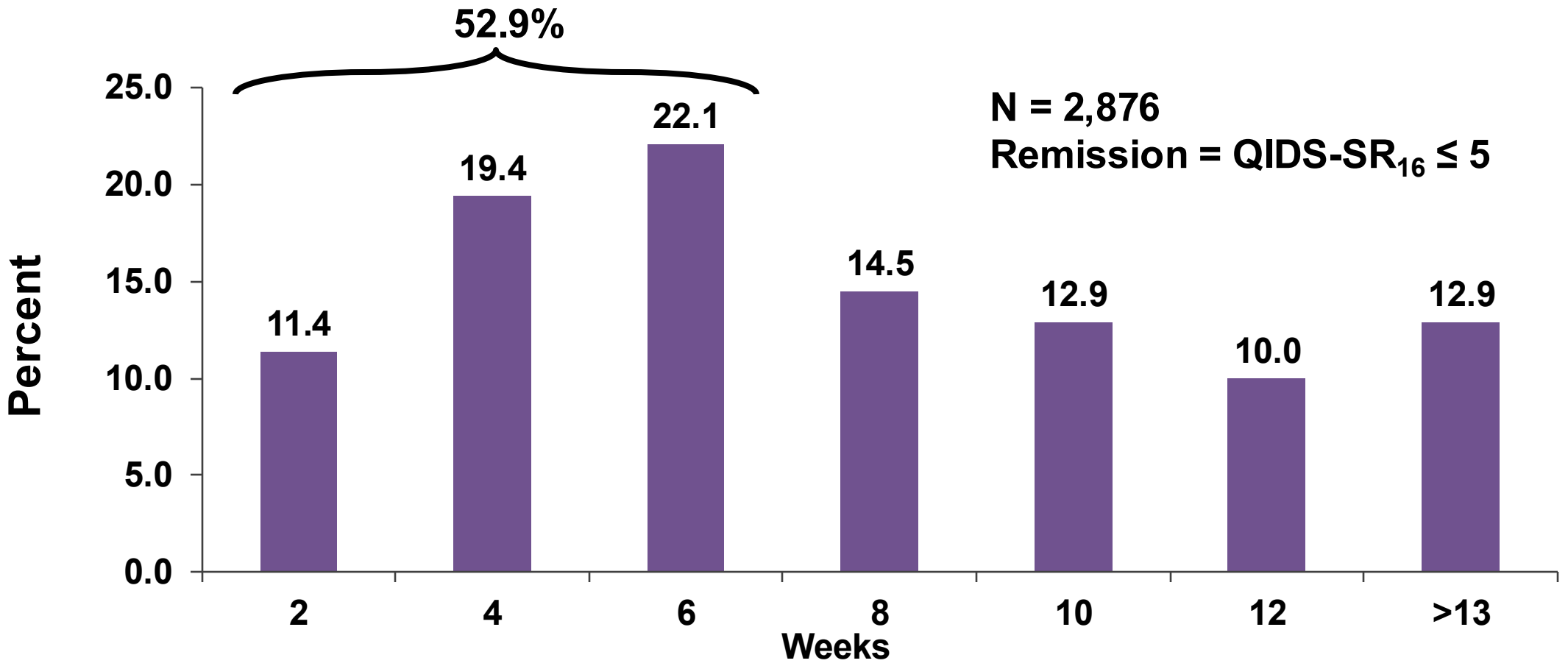
Level 1 Response and Remission With Citalopram (N = 2,876)



HAMD-17, 17-item Hamilton Rating Scale for Depression; QIDS-SR-16, 16-item Quick Inventory of Depressive Symptomatology – Self-Report.

Trivedi MH, et al. Am J Psychiatry. 2006;163(1):28-40.

Of Ultimate Remitters, 1/2 Remitted by Week 6

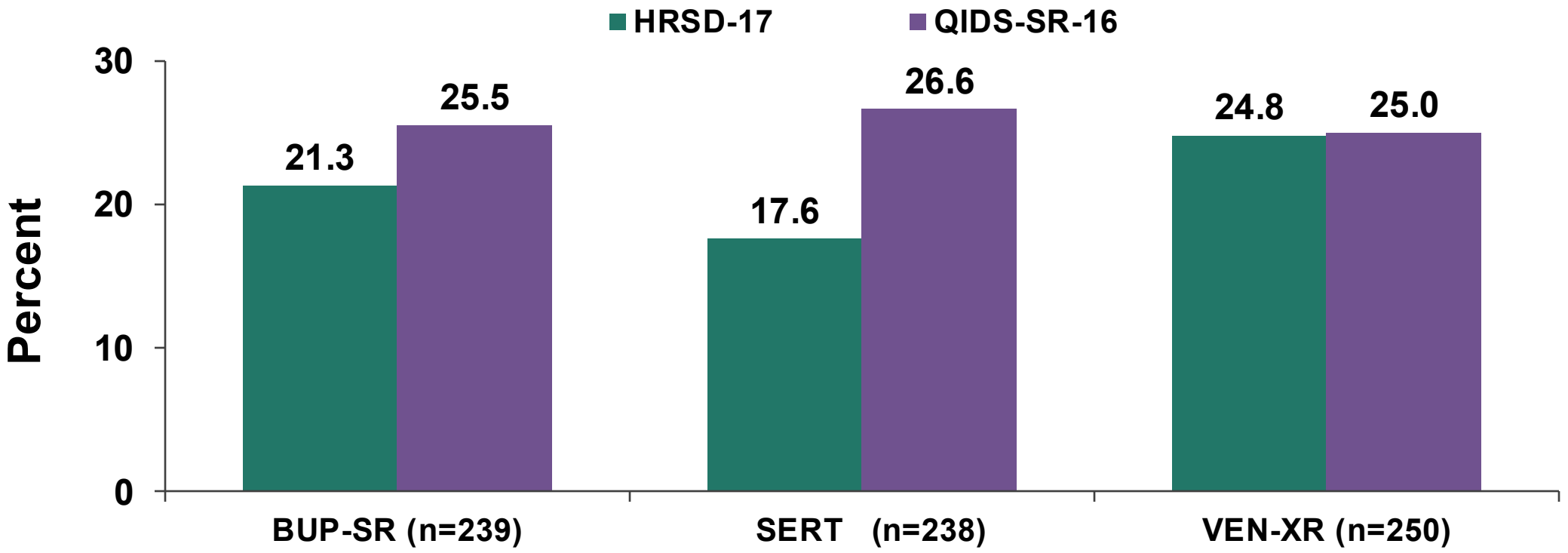


Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

Management of Partial or Nonresponse

- Dose increase (50%–100%)
- Augmentation (antidepressant + other medication to boost effects)
- Combination (2 antidepressants)
- Switching to another antidepressant
- Adding or switching to other treatments (psychotherapy, ECT, phototherapy)

Level 2 Switching: Treatment Outcomes (% Remission)



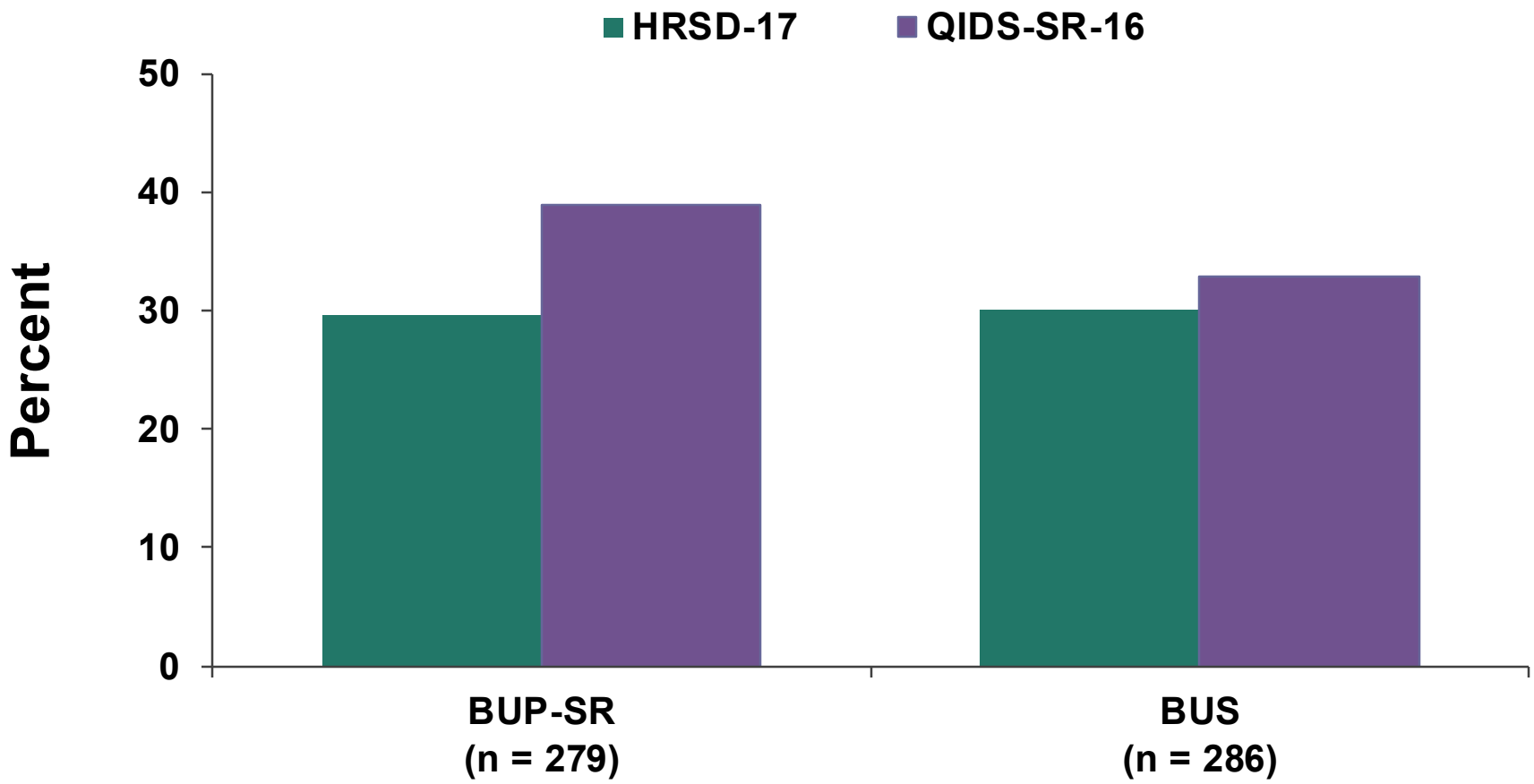
Rush AJ, et al. *N Engl J Med*. 2006;354(12):1231-1242.

Augmentation

- Lithium[1]
- Thyroid hormone (T3 or T4)[2]
- Stimulants (methylphenidate, dexedrine,[3] modafinil)
- Buspirone[4]
- Dopamine agonists (pramipexole,[5] amantadine)
- Pindolol[6]
- Olanzapine, ziprasidone, aripiprazole, risperidone[7,8]

1. Katona CL, et al. *Br J Psychiatry.* 1995;166(1):80-86. 2. Joffe RT, Schuller DR. *J Clin Psychiatry.* 1993;54(7):269-271.
3. Stoll AL, et al. *J Clin Psychiatry.* 1996;57(2):72-76. 4. Dimitriou EC, Dimitriou CE. *J Clin Psychopharmacol.* 1998;18(6):465-469.
5. Sporn J, et al. Poster presented at NCDEU Annual Meeting; 1998. 6. Pérez V, et al. *Arch Gen Psychiatry.* 1999;56(4):375-379.
7. Shelton RC, et al. Poster presented at NCDEU Annual Meeting; 1998. 8. Ostroff RB, Nelson JC. *J Clin Psychiatry.* 1999;60(4):256-259.

Level 2 Augmentation: Treatment Outcomes (% Remission)



Trivedi MH, et al. *N Engl J Med*. 2006;354(12):1243-1252.

Treatment Levels

- Level 3
  - Switch options
    - Mirtazapine
    - Nortriptyline
  - Results: 12%–20% remitted; no clear preference
  - Add-on options
    - Lithium carbonate
    - Triiodothyronine (T3)
  - Results: 24.7% remitted with T3 and 15.9% with Li; T3 had fewer side effects

Treatment Levels

- Level 4
  - Switch options
    - Tranylcypromine
    - Venlafaxine XR + mirtazapine
  - Results: 7%–10% remitted; greater symptom reduction with venlafaxine + mirtazapine; more side effects (and discontinuation) with MAOI
  - Add-on options
    - None

Overall STAR*D Outcomes

- 36.8% remitted at Level 1
- 30.6% of remaining pts remitted at Level 2
- 13.7% of remaining pts remitted at Level 3
- 13.0% of remaining pts remitted at Level 4
- Overall cumulative remission rate was 67%
- Time to remission at each step was ~6.4 wks; most patients require 6 to 12 weeks to exhibit full response at appropriate dose
- Step 2: switching to cognitive therapy had a 41.9% remission rate; augmenting with bupropion led to a 39.0% remission rate
- Steps 3/4: venlafax + Li/mirtaz and bupropion/citalopram + T3 also had slightly better results
- >1/3 of patients left the study early; no placebo/blind

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917.

How Long Should Antidepressants Be Continued?

- Typically, “continuation treatment” should last at least 6-12 months after remission from a single episode of depression
  1. 50% risk of relapse after single episode
  2. 70% risk of relapse after 2 episodes
  3. 90% risk of relapse after 3 episodes
- If 2-3 episodes or more, most patients require long-term “maintenance treatment”

Reimherr FW, et al. *Am J Psychiatry*. 1998;155(9):1247-1253.
Fava M, Kaji J. *Psychiatric Ann*. 1994;42:281-290.
Kupfer DJ. *J Clin Psychiatry*. 1991;52 Suppl:28-34.

Avoid Abrupt Discontinuation of Antidepressants

- TCAs, MAOIs, and SSRIs may be associated with *discontinuation-emergent adverse events* (Discontinuation Syndrome)
- Symptoms include headache, muscle ache, nausea, malaise, low mood, tearfulness, restlessness, unusual symptoms (eg, “zapping”)
- The frequent discontinuation of fixed doses of short-acting SSRIs (eg, paroxetine) without taper can create significant clinical problems

Managing Antidepressant Side Effects

- Some tend to go away over first few days/weeks (eg, jitteriness, nausea)
- Others tend to be longer-term problems (eg, weight gain, sexual dysfunction)
- Behavior modification (eg, avoid caffeine)
- Adjust timing of doses and/or divide doses
- Adjust doses (usually lower; sometimes higher)
- Pharmacologic options

Symptom-Targeted Approach to Managing Residual Depressive Symptoms

Symptom Domain	Viable Targeted Strategies
Anxiety	Adjunctive buspirone, CBT, short-term benzodiazepines
Fatigue	(Ar)modafinil, stimulants, bupropion
Impulsivity, mood instability	Lithium, lamotrigine, divalproex
Insomnia	Z-drugs, trazodone, orexin receptor antagonists, CBTi
Low self-worth/self-esteem	CBT
Sexual dysfunction	Phosphodiesterase inhibitors (eg, sildenafil), bupropion, mirtazapine
Suicidal behavior	Lithium
Suicidal ideation	(Es)ketamine

TOTAL CME

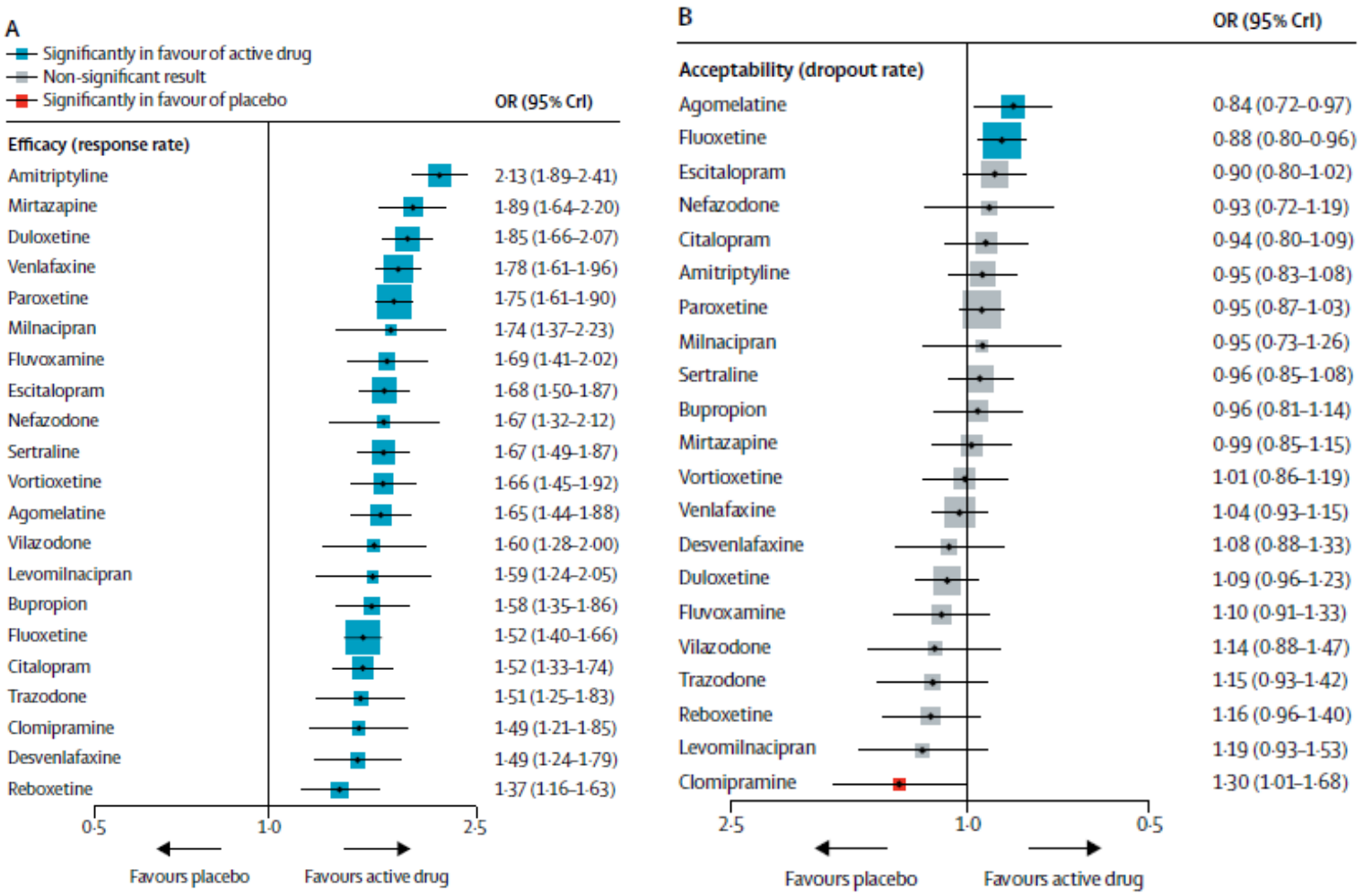
Menza M, et al. *J Clin Psychiatry*. 2003;64(5):516-523.

Does Efficacy Vary Among Antidepressants?

- The “best” antidepressant is the one that works for an individual; sometimes what works for family members may work for you
- There is no evidence that antidepressant or antianxiety effects vary across antidepressants of the same class
- Generics are just as effective as brand name

Quitkin FM, et al. *Br J Psychiatry Suppl*. 1993;(21):30-34.

Efficacy (A) and Acceptability (B) of Antidepressants



Cipriani A, et al. *Lancet*. 2018;391(10128):1357-1366.

Depressive Breakthrough

- Antidepressants are better than placebo in preventing relapses and recurrences
- Yet 10%-30% of depressed patients have relapses or recurrences (“depressive breakthrough”) while on treatment
- Psychosocial stressors, substance abuse, drug interactions, pharmacological and biological changes may contribute to risk of breakthrough

Fava M, Kaji J. *Psychiatr Ann.* 1994;42:281-290.

What to Do if Treatment Fails?

- Assess adherence to recommended treatment
- Comorbidity (ETOH/substance abuse, anxiety disorders, eating disorders, OCD, non-psychiatric comorbidity)
- Drug interactions
- Check diagnosis
  - ? Bipolar disorder
  - ? Major depressive disorder with psychotic features
  - Prodromal phase of psychotic disorder
  - Dementia
  - Non-psychiatric medical condition (eg, thyroid, diabetes, hypercalcemia)

Atypical Antipsychotics That Are FDA-Approved for Add-On Therapy After Incomplete Response to an Antidepressant in MDD (ie, not necessarily TRD)

Agent	Adjunctive Therapy Dosing in MDD
Aripiprazole	2-5 mg/day initially; target = 5-10 mg/day; max 15 mg/day
Brexpiprazole	0.5-1 mg/day; target = 2 mg/day; max 3 mg/day
Cariprazine	Target = 1.5 mg/day; max = 3 mg/day
Olanzapine (+ Fluoxetine)	6 or 12 mg/day
Quetiapine XR	Initially 50 mg/day; target = 150-300 mg/day (max = 300 mg/day)

Off-label and/or unstudied as adjunctive therapy in MDD: asenapine, risperidone, iloperidone, lurasidone, ziprasidone
Under review as adjunctive therapy in MDD: lumateperone (D1 post-synaptic blockage modulates glutamatergic transmission).
Harvey J, Lacey MG. *J Neurosci.* 1997;17(14);5271-5280. Durgam S, et al. *J Clin Psychopharmacol.* 2025;45(2):67-75.

Looking Beyond Poly-Monoaminergic Mechanisms to Target Residual Symptoms

Anti-glutamatergics:

- Original database with IN esketamine was (by design) augmentation to new antidepressant starts; no existing database specifically examining augmentation after partial response to traditional antidepressant

Looking Beyond Poly-Monoaminergic Mechanisms to Target Residual Symptoms

Anti-glutamatergics:

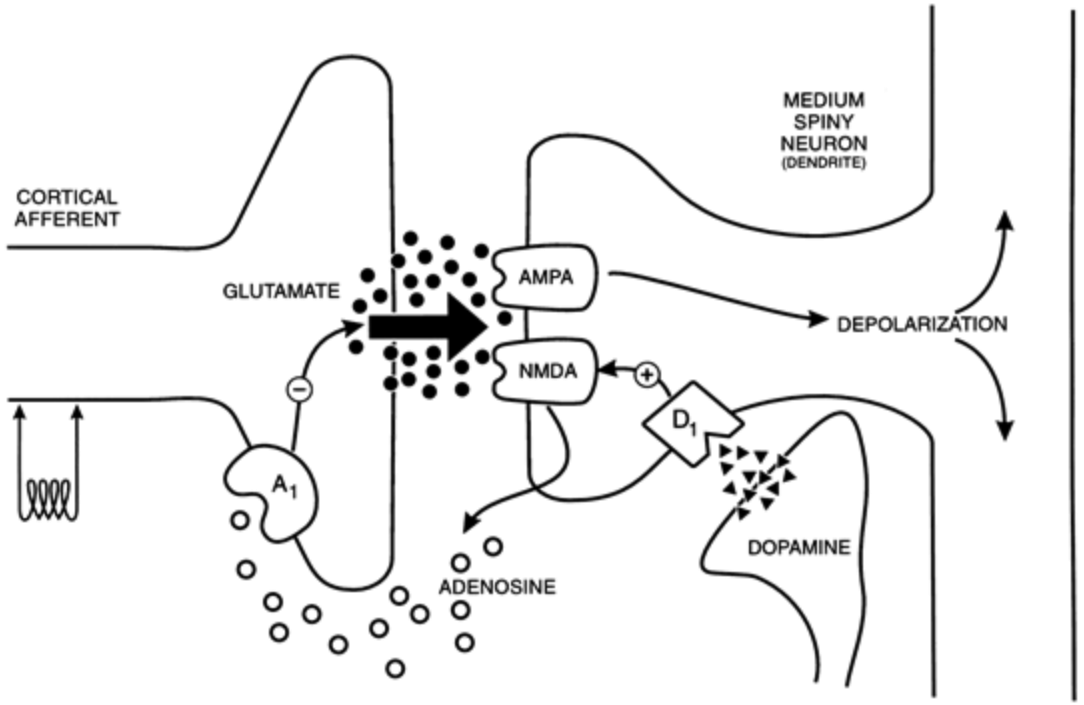
- Original database with IN esketamine was (by design) augmentation to new antidepressant starts; no existing database specifically examining augmentation after partial response to traditional antidepressant
- Bupropion + dextromethorphan as an uncompetitive NMDA receptor antagonist + sigma-1 receptor agonist
- In real-world practice, >70% of treatment initiations occur “off label” as add-on therapy to an SSRI or SNRI (claims database N = 22,288)[1]

1. Muzyk A, et al. *J Med Econ.* 2024;27(1):1003-1010.


ReachMD

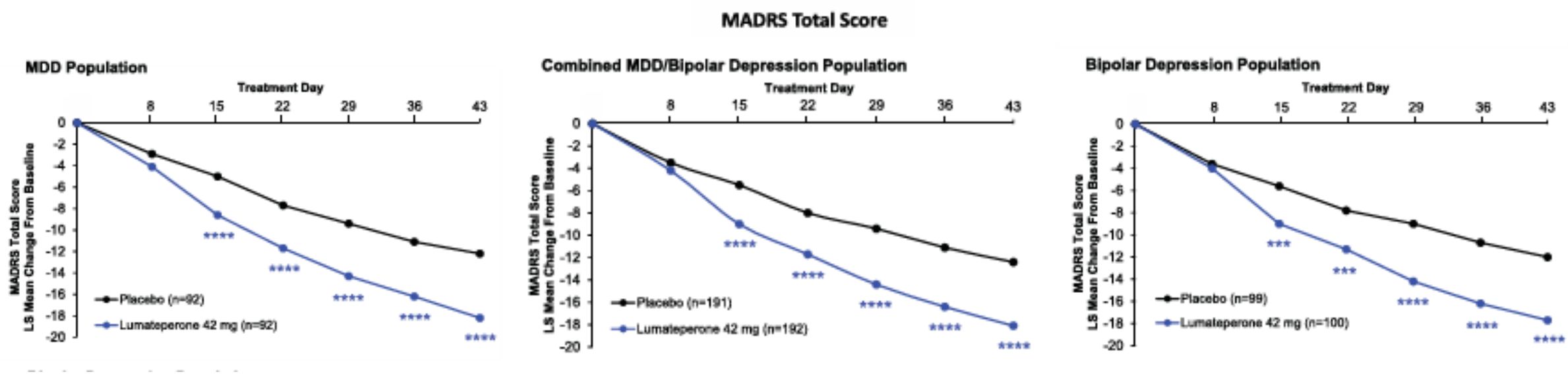
Looking Beyond Poly-Monoaminergic Mechanisms to Target Residual Symptoms

- Anti-glutamatergics:
- D1 post-synaptic blockade indirectly modulates glutamatergic transmission[1] (ie, lumateperone)



1. Harvey J, Lacey MG. *J Neurosci*. 1997;17(14):5271-5280.

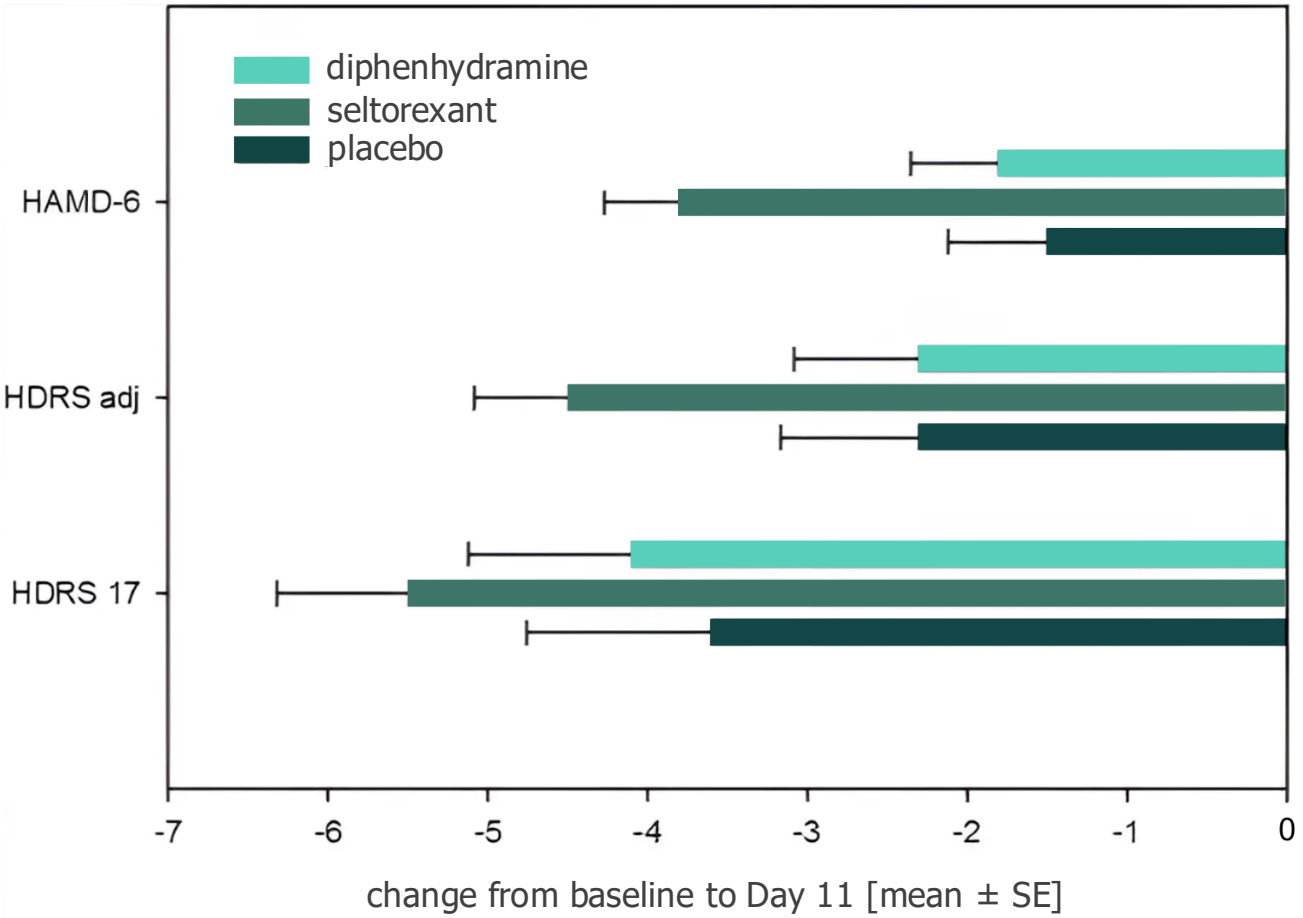
Adjunctive Lumateperone in Major Depressive Disorder With Mixed Features



Durgam S, et al. *J Clin Psychopharmacol.* 2025;45(2):67-75.

Looking Beyond Poly-Monoaminergic Mechanisms to Target Residual Symptoms

Selective Orexin-2 Receptor Antagonist: Seltorexant



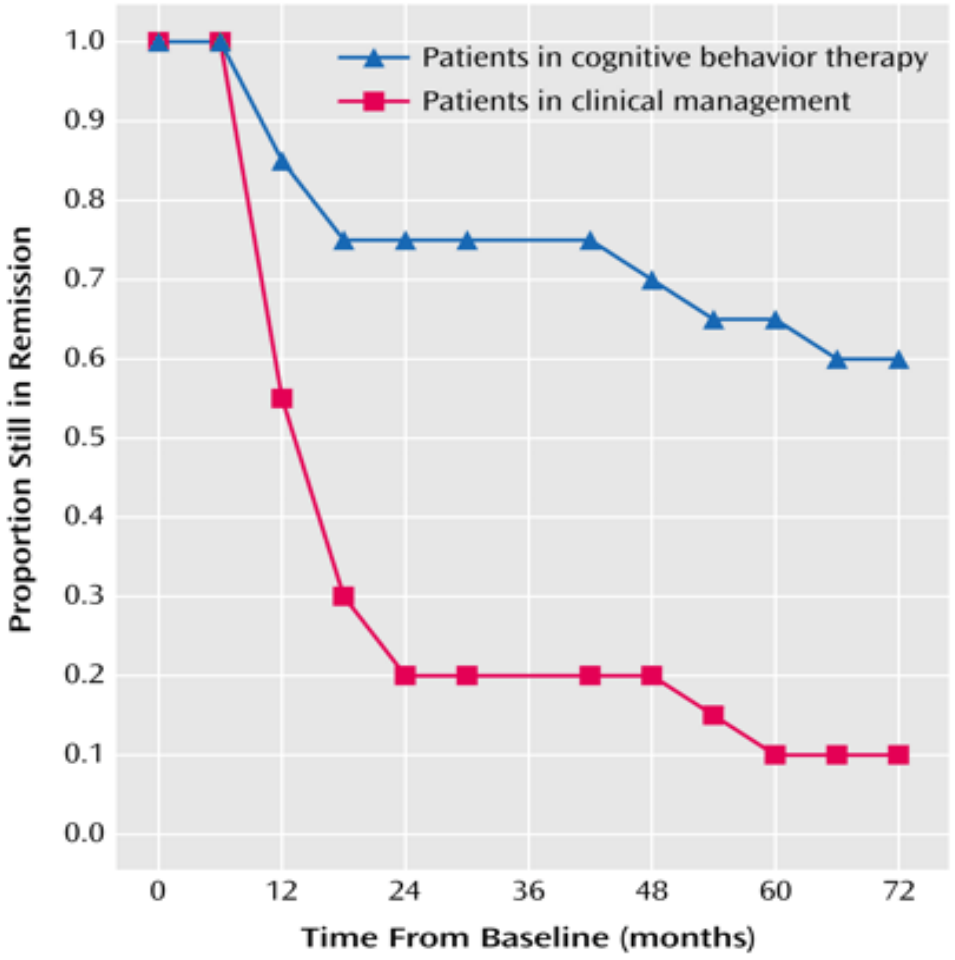
HAM-D_{17} LSMD: -22 (95% CI = -4.35 to 0.05), $P < 0.05$

Recourt K, et al. *Transl Psychiatry.* 2019;9(1):216.

Psychotherapy for Depression

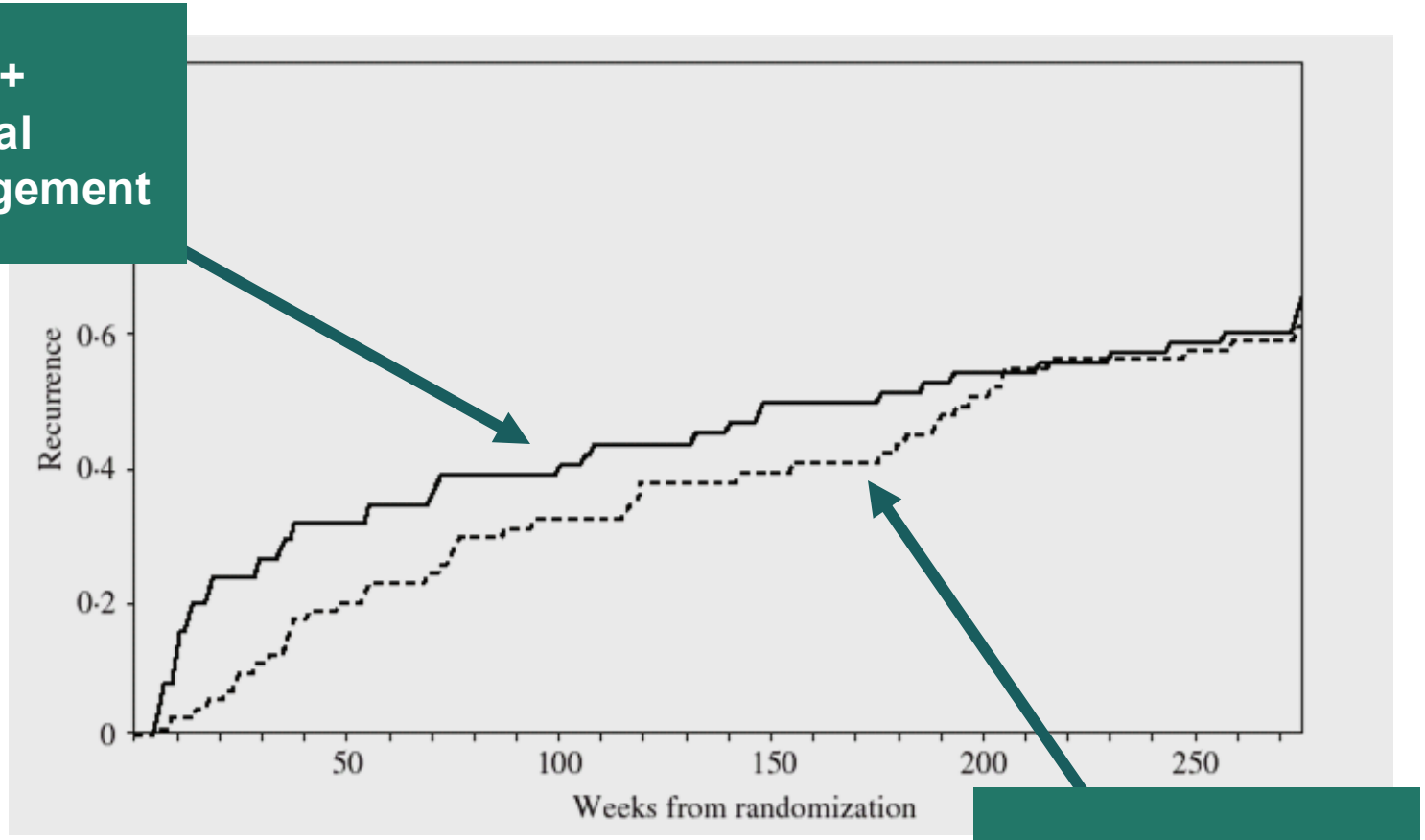
- Evidence-based therapies include:
  - Cognitive Behavioral Therapy (CBT)
  - Interpersonal Therapy (IPT)
  - Psychodynamic Psychotherapy
  - Problem-Solving Therapy
  - Acceptance and Commitment Therapy
- Can be done individually or in groups
- Sessions can be limited (12–20 in CBT) or open-ended (psychodynamic psychotherapy)

Adding Therapy After Successful Treatment: Cognitive Behavior Therapy With "Well-Being Therapy" Prevented Relapse



Fava GA, et al. *Arch Gen Psychiatry*. 1998;55(9):816-820. Fava GA, et al. *Am J Psychiatry*. 2004;161(10):1872-1876.

CBT for Residual Symptoms Prevents Recurrence for Up to 3 ½ Years



Paykel ES, et al. *Psychol Med.* 2005;35(1):59-68.

Other Avenues for Depression Treatment

- Es/ketamine – rapidly acting, antisuicidal effects, duration of benefit, optimal dosing/route of administration currently being investigated
- Bright light therapy – works for seasonal depression more than nonseasonal depression
- St. John's wort – avoid using with SSRIs
- SAMe, methylfolate – suggested efficacy
- Omega 3 fatty acids – anecdotal evidence to support augmentation of antidepressants
- Vitamin D – insufficient evidence to support benefit in depression

Aan Het Rot M, et al. *Biol Psychiatry*. 2012;72(7):537-547. Maeng S, Zarate CA Jr. *Curr Psychiatry Rep*. 2007;9(6):467-474.
Diazgranados N, et al. *Arch Gen Psychiatry*. 2010;67(8):793-802. Ibrahim L, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(4):1155-1159.
Puri BK, et al. *Int J Clin Pract*. 2001;55(8):560-563. Eastman CI, et al. *Arch Gen Psychiatry*. 1998;55(10)883-889. Linde K, et al. *BMJ*. 1996;313(7052):253-258.
Galizia I, et al. *Cochrane Database Syst Rev*. 2016;10(10):CD011286. Papakostas GI, et al. *Am J Psychiatry*. 2012;169(12):1267-1274.
Anglin RE, et al. *Br J Psychiatry*. 2013;202:100-107. Gowda U, et al. *Nutrition*. 2015;31(3):421-429.

Electroconvulsive Therapy

- ECT: *the* most rapid, effective treatment for major depression (60%-90% response rates)
- Developed in 1930s, FDA-approved 1979
- Usually 6-12 treatments, 2-3x per week
- Associated with increases in BP, heart rate, heart attack, heart arrhythmias, memory loss
- Done under general anesthesia, very safe
- Utilize continuation ECT/meds to remain well

Janicak PG, et al. *Am J Psychiatry.* 1985;142(3):297-302.
Kellner CH, et al. *Arch Gen Psychiatry.* 2006;63(12):1337-1344.
Sackeim HA, et al. *Arch Gen Psychiatry.* 2009;66(7):729-737.

Other “Somatic” Therapies

- Repetitive Transcranial Magnetic Stimulation
  - 30-45 min/day for 4-6 weeks, no anesthesia needed
  - New 'theta burst' and SAINT protocols greatly accelerate treatment
  - 1/2 respond, 1/3 remit (~same as antidepressant trial)
- Vagal Nerve Stimulation
  - Pulse generator in the chest, attaches via wire lead to left vagal nerve
  - FDA approved for treatment-resistant depression in 2005, but results mixed
- Deep Brain Stimulation
  - Used successfully to treat tremor, OCD
  - Investigational in treatment-resistant depression, small numbers

Summary

- A majority of patients with MDD experience incomplete remissions with standard antidepressant pharmacotherapies
- Ensure accurate diagnoses, appropriate pharmacotherapies, adequate adherence, adequate trials, and address comorbidities
- Favor the augmentation of partial responses and switch strategies after failure to achieve even partial response (≤25% improvement from baseline)
- Use measurement-based care to quantify outcomes
- Emerging role for multimodal treatment pathways and novel neurotransmitter systems to address incomplete response and residual symptoms of major depression
- Don’t forget psychotherapy
- Consider referral to psychiatry for advanced psychopharmacology or neuromodulation

Post-Assessment Questions

Your mobile device can be used to participate in polling, Q&A, and to download today's presentation.
Join in by using the QR code!

A 35-year-old patient with major depressive disorder (MDD) has been on an SSRI for 8 weeks. The patient reports mild improvement but continues to experience persistent depressive symptoms that impair daily functioning. As their clinician, which measurement-based care tool would be most appropriate to guide the next treatment decision?

A. Patient Health Questionnaire-9 (PHQ-9) to quantify symptom severity and response
B. Mini-Mental State Examination (MMSE) to assess cognitive impairment
C. Glasgow Coma Scale (GCS) to evaluate consciousness levels
D. CAGE questionnaire to assess alcohol use disorder

TOTAL CME

A 28-year-old patient presents with depressive symptoms, including fatigue, low mood, and difficulty concentrating. Their history reveals episodes of increased energy, decreased need for sleep, and impulsive spending that lasted for several days. Which diagnosis should be considered before initiating antidepressant treatment?

A. Generalized anxiety disorder, due to overlapping symptoms with depression
B. Treatment-resistant MDD, requiring immediate antidepressant augmentation
C. Bipolar disorder if the patient meets DSM-5 syndromal criteria
D. Persistent depressive disorder, given the chronic nature of symptoms

TOTAL CME

A 47-year-old patient with MDD has been on 20 mg escitalopram (SSRI) for 12 weeks with partial improvement but continues to struggle with anhedonia and fatigue. The patient denies severe side effects and has no history of previous treatment failures. What is the most appropriate next step in managing this patient's depression?

A. Discontinue escitalopram and switch to a TCA
B. Add an atypical antipsychotic with antidepressant properties
C. Increase escitalopram beyond the maximum FDA-approved dose
D. Discontinue antidepressant therapy and reassess in 3 months

TOTAL CME

A 38-year-old patient with treatment-resistant MDD has failed 2 SSRI trials and continues to experience severe anhedonia. The clinician is considering a medication that targets multiple neurotransmitter pathways to optimize efficacy. Which of the following treatments would be the most appropriate choice?

A. Continue the SSRI and wait for additional response
B. Switch to desvenlafaxine
C. Augment with intranasal esketamine
D. Prescribe a benzodiazepine to help with anhedonia

TOTAL CME

Lumateperone, which is being studied as an adjunctive treatment for major depressive disorder (MDD), acts on several neurotransmitter systems relevant to mood regulation. Which of the following is not directly modulated by lumateperone?

A. Dopaminergic transmission via D1 receptor phosphorylation pathways

B. Histaminergic modulation through H1 receptor inverse agonism

C. Glutamatergic signaling through indirect NMDA receptor facilitation

D. Serotonergic balance through 5-HT2A antagonism and serotonin reuptake inhibition

TOTAL CME

Question and Answer Session

TOTAL CME

Thank you!