Psych Congress Presents

MDD BOOTCAMP

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Beyond Partial Response: Augmentation, Persistence, and Novel Adjuncts

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Faculty Disclosures

- **Michael Asbach, DMSc, PA-C**: Consultant – Axsome, Biogen, Bristol Myers Squibb, Intra-Cellular Therapies Inc, Janssen Pharmaceuticals, Neurocrine Biosciences; Speakers Bureau – AbbVie, Avanir Pharmaceuticals (ended) Axsome, Bristol Myers Squibb, Intra-Cellular Therapies Inc, Janssen Pharmaceuticals, Neurocrine Biosciences, Otsuka Pharmaceuticals
- **C. Brendan Montano, MD**: Advisory Board – AbbVie Inc, Axsome, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Eisai, Eli Lilly Pharmaceuticals, Johnson & Johnson, Otsuka Pharmaceutical Inc, Tris Pharma; Contracted Research – AbbVie Inc, Axsome, Boehringer Ingelheim Pharmaceuticals Inc, Eli Lilly Pharmaceuticals, Intra-Cellular Therapeutics, Kallyope, Neurocrine Biosciences Inc, Otsuka Pharmaceutical Inc, Pfizer, Seaport, Supernus Pharmaceuticals, Vistagen, Xenon; Speakers Bureau – AbbVie Inc, Axsome, Corium, Evoke, Intra-Cellular Therapeutics, Otsuka Pharmaceutical Inc, Vanda Pharmaceuticals Inc.

Disclosures

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Learning Objectives

- Evaluate evidence-based augmentation approaches for patients with partial response, including pharmacologic and non-pharmacologic options
- Implement practical methods to enhance adherence, tolerability, and persistence through real-world strategies and lifestyle integration
- Use evidence-driven approaches for treatment sequencing and maintenance to achieve remission and sustain long-term functional recovery

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Making an Appropriate Diagnosis

Making an Appropriate Diagnosis: MDD Is a Diagnosis of Exclusion

- In order to treat for unipolar depression, one must rule out bipolar I or II disorder

- Approximately 25% of patients who present with major depressive disorder are on the bipolar spectrum

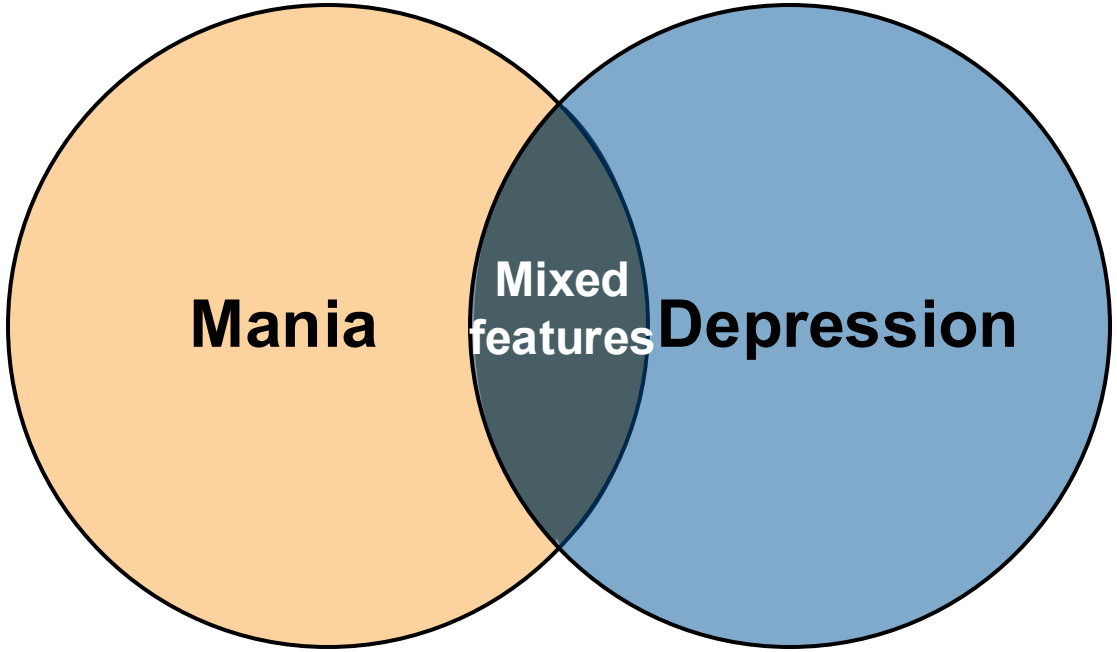
Angst J, Azorin J, Bowden CL, et al. Prevalence and Characteristics of Undiagnosed Bipolar Disorders in Patients with a Major Depressive Episode: The BRIDGE Study. Arch Gen Psychiatry. 2011;68(8):791–799. doi:10.1001/archgenpsychiatry.2011.87

Bipolar I Disorder Episodes Can Span a Spectrum of Overlapping Mood Symptoms

***DSM-5* defines bipolar I disorder as a disorder in which criteria have been reached for ≥1 manic episode, but many patients also experience depressive mood episodes and/or mixed features.[1,2]**

At least 3 of the following symptoms or **4** if mood is only irritable[1]

- Inflated self-esteem or grandiosity
- Decreased need for sleep
- More talkative or pressured speech
- Flight of ideas or racing thoughts
- Distractibility
- Increase in goal-directed activity or psychomotor agitation
- Excessive involvement in activities that have high potential for painful consequences



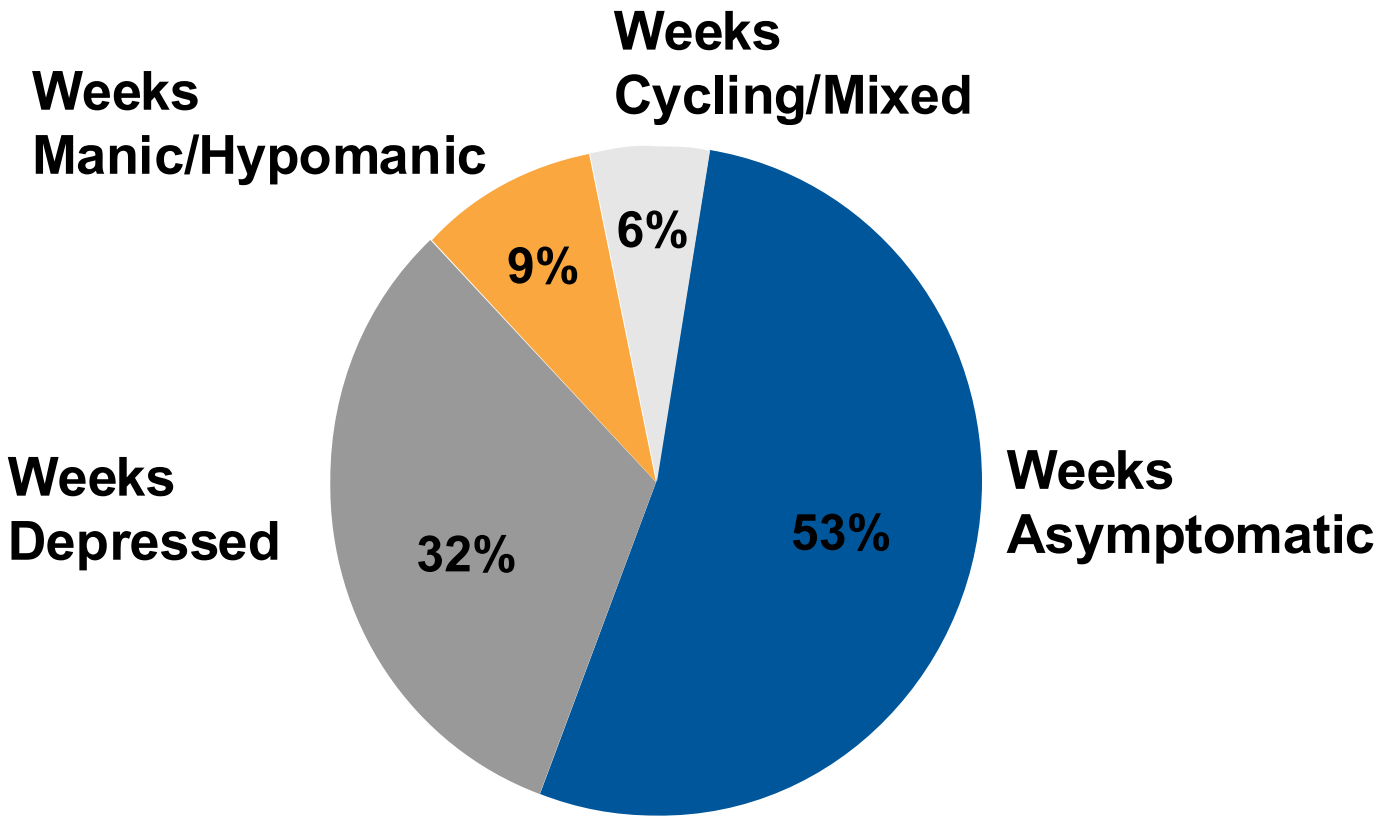
DSM-IV-TR: ~ 6% with a mixed episode[3]
DSM-5: ~20% with mixed features (majority manic/hypomanic)[3]

DSM-5, Diagnostic and Statistical Manual of Mental Disorders **(5th ed.);** ***DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders*** **(4th ed., text revision).**

1. American Psychiatric Association. 5th ed. American Psychiatric Association; 2013. 2. Stahl SM. 5th ed. Cambridge University Press; 2021. 3. Shim IH, et al. ***J Affect Disord.*** **2015;173:120-125.**

Patients with BD-I Are Symptomatic Almost Half Their Lives

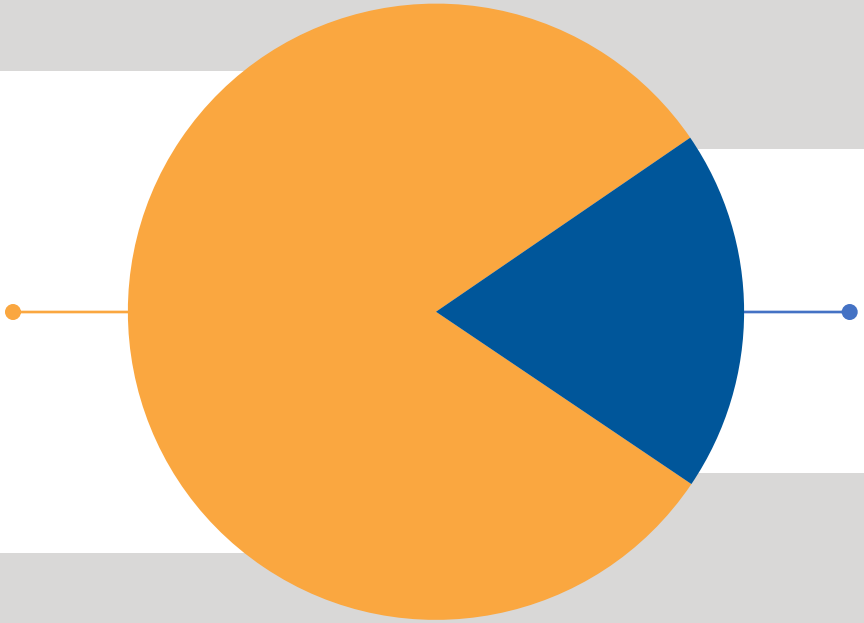
NIMH Collaborative Depression Study



N=146 patients followed every 6 months over 2–20 years; Mean follow-up = 12.8 years; Judd LL et al. (2002), Arch Gen Psychiatry 59(6):530-537

When Symptomatic, Most Patients with Bipolar II Disorder Spend More Time in Depression Than Hypomania[1]

81%
Time ill due to depressive morbidity[1]



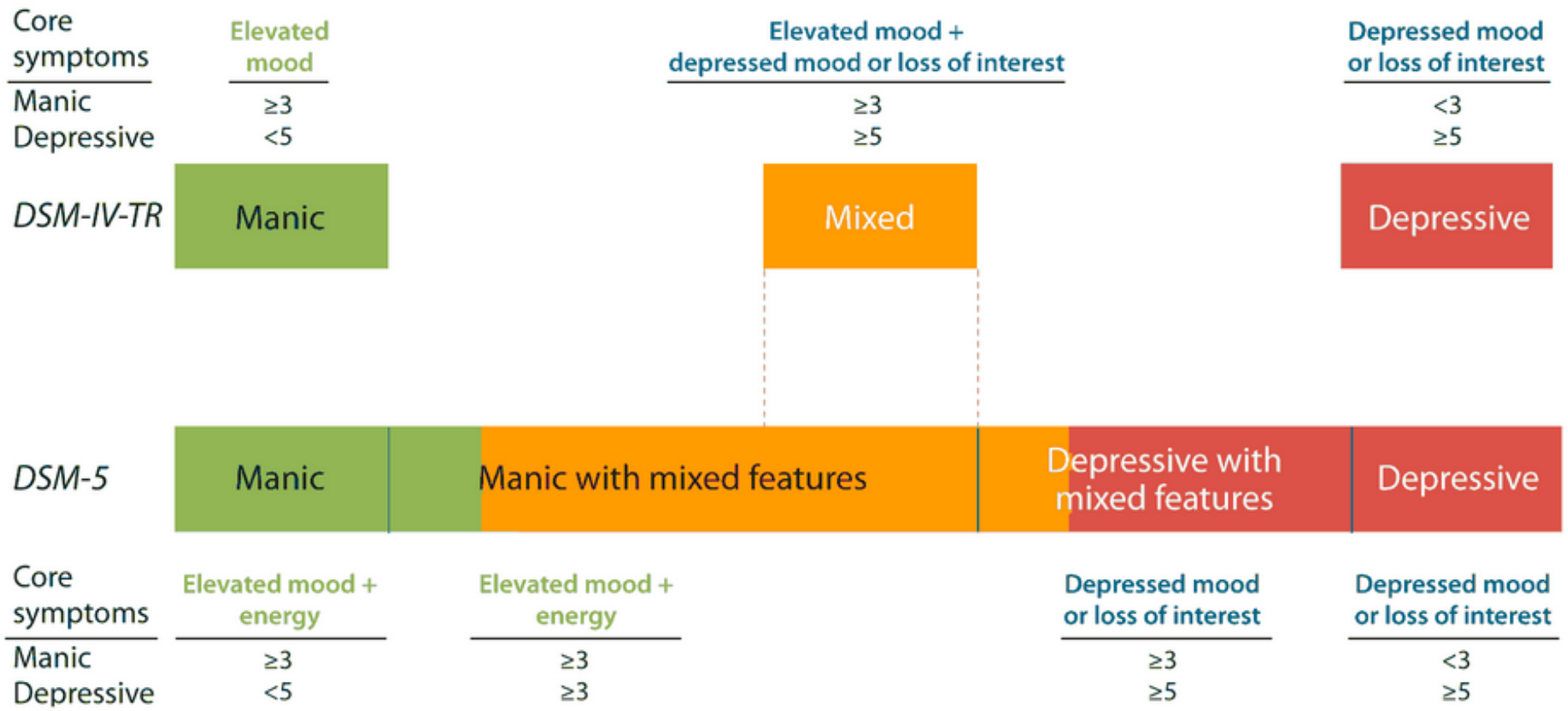
19%
Time ill due to hypomania or other[1,*]

While the prevalence of bipolar disorder is thought to be <u>similar</u> between men and women, <u>women are more likely to be diagnosed with bipolar II</u> disorder compared with men[2-4]

*Other includes mixed states and anxiety.

1. Forte A et al. *J Affect Disord*. 2015;178:71-78. 2. Dell'Osso B et al. *Int J Bipolar Disord.* 2021;9(1):3. 3. Swartz HA, Suppes T, eds. *Bipolar II Disorder: Recognition, Understanding, and Treatment*. Washington, DC: American Psychiatric Association Publishing; 2019. 4. Karanti A et al. *Bipolar Disord*. 2020;22(4):392-400.

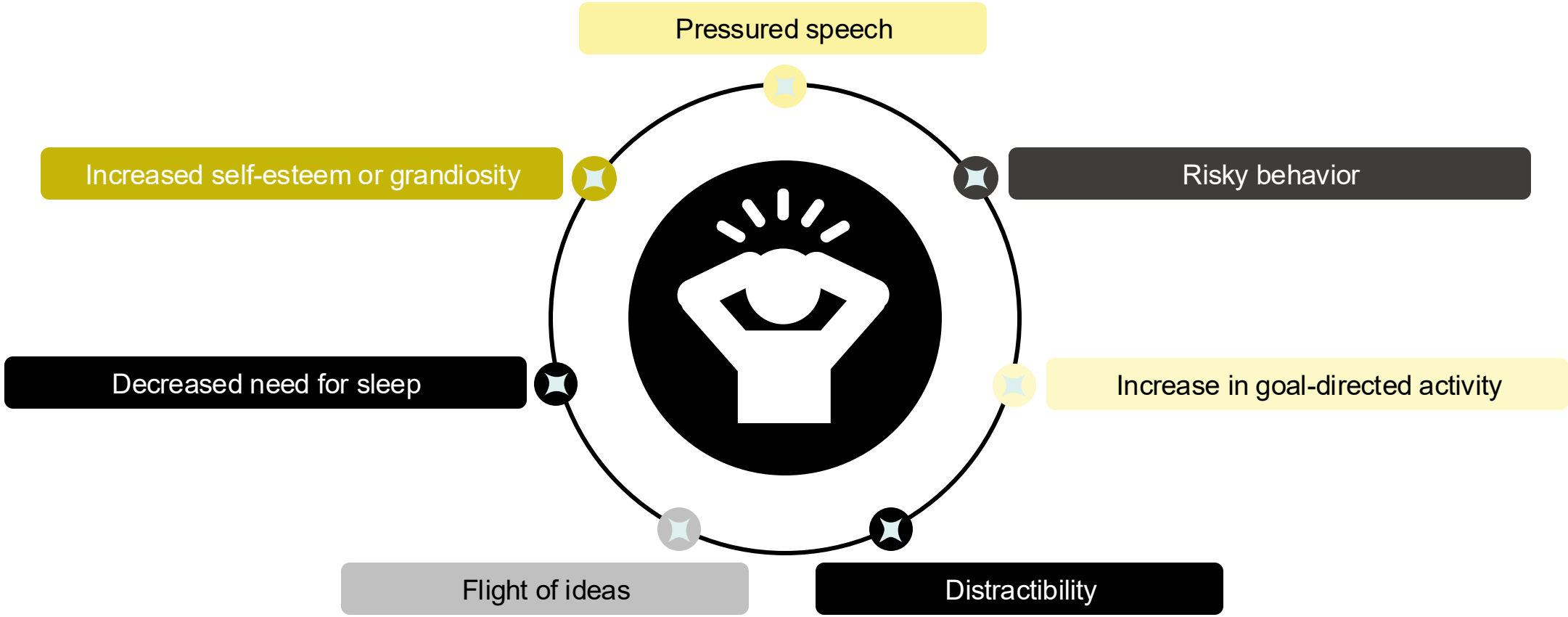
A Spectrum of Symptoms



Softer presentations of hypomania and mixed features are often seen in primary care, but are not properly diagnosed or treated.

Hu J, et al. *Prim Care Companion CNS Disord*. 2014;16(2).

Hypomania Is Characterized by Abnormally Increased Energy and Elevated or Irritable Mood



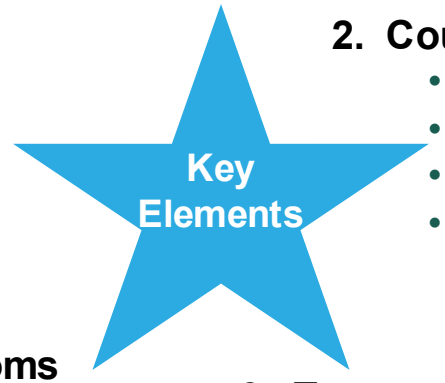
The DSM-5-TR diagnostic criteria specify that at least 3 of these symptoms must be present for ≥4 days to diagnose bipolar II disorder, and that the hypomanic symptoms or mood episode(s) be observable by others.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed, Text Revision. Washington, DC: American Psychiatric Association; 2022.

Differential Diagnosis: Bipolar Disorder

21.4% to 54% of women with PPD have a diagnosis of bipolar disorder.

Women with PPD in particular should be routinely screened for mania and hypomania.



1. **Family History**
   - Higher rates of psychiatric illness
   - Positive for bipolar disorder
2. **Course of Illness**
   - Age of first mania/depression
   - Duration of episodes
   - Frequency of episodes
   - Seasonality
3. **Treatment Response**
   - Multiple treatment failures
   - Nonresponse or erratic response to antidepressants
4. **Mania Symptoms**
   - Distractibility
   - Insomnia
   - Grandiosity
   - Flight of ideas
   - Activities
   - Pressured speech
   - Thoughtlessness
5. **Associated Features**
   - Unevenness in intimate relationships
   - Frequent career changes
   - Substance use disorders

PPD = postpartum depression

Sharma V, et al. *J Affect Disord*. 2017;219:105-111.

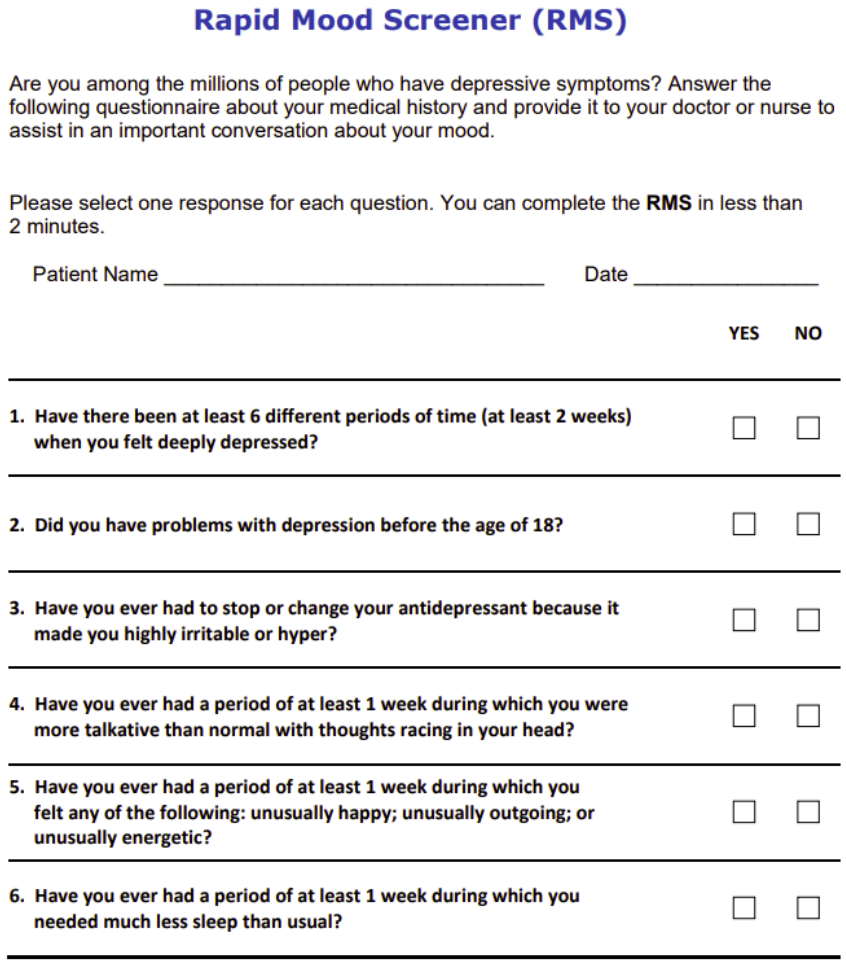
Rapid Mood Screener

RMS is a short self-report screener for BP-I.

Scoring: “YES” to 4 or more items is considered “positive” for high confidence for BP-I and should be followed up with clinical interview.

Validity: 88% sensitivity, 80% specificity, and 84% accuracy.

It has subsequently been validated for BP-II disorder, as well.



Rapid Mood Screener (RMS)

Are you among the millions of people who have depressive symptoms? Answer the following questionnaire about your medical history and provide it to your doctor or nurse to assist in an important conversation about your mood.

Please select one response for each question. You can complete the **RMS** in less than 2 minutes.

Patient Name _____ Date _____

	YES	NO
1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?	☐	☐
2. Did you have problems with depression before the age of 18?	☐	☐
3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	☐	☐
4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?	☐	☐
5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?	☐	☐
6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?	☐	☐

BP-1 = bipolar 1 disorder; BP-II = bipolar 2 disorder; RMS = Rapid Mood Screener

McIntyre RS, et al. *Curr Med Res Opin*. 2021;37(1):135-144. Liao Y, et al. *J Affect Disord*. 2024;348:54-61.

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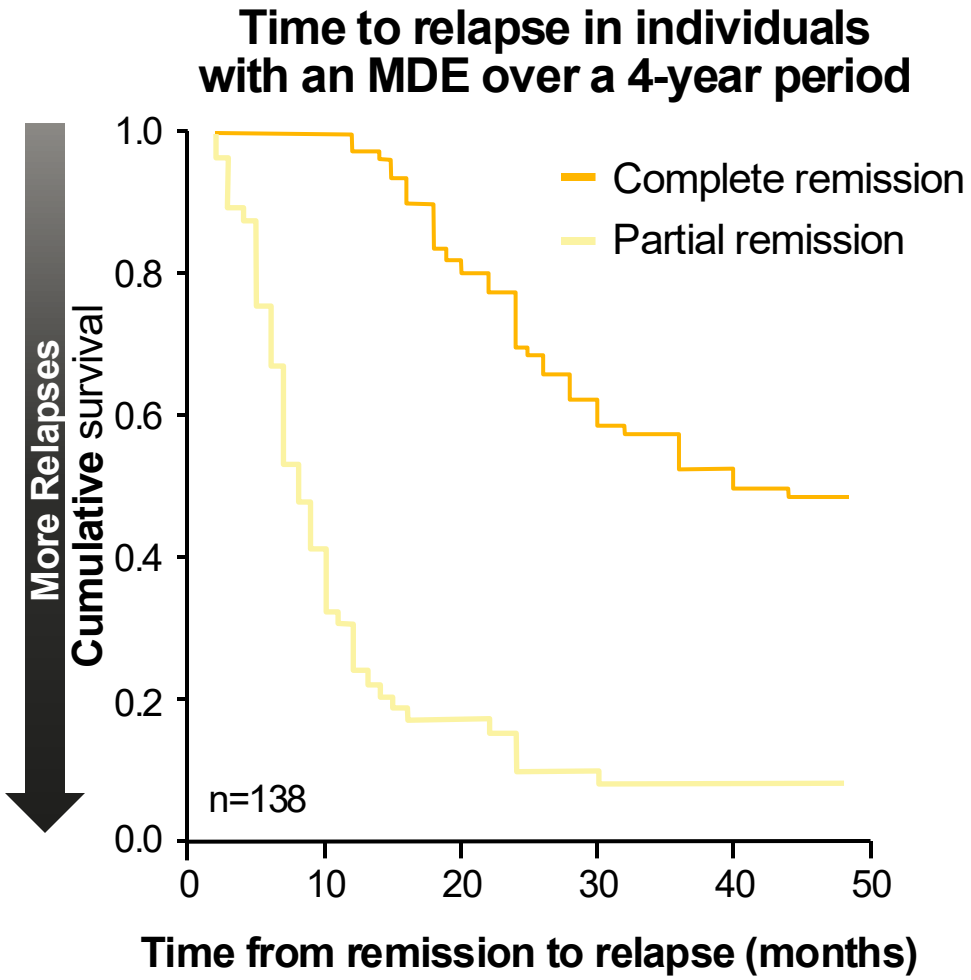
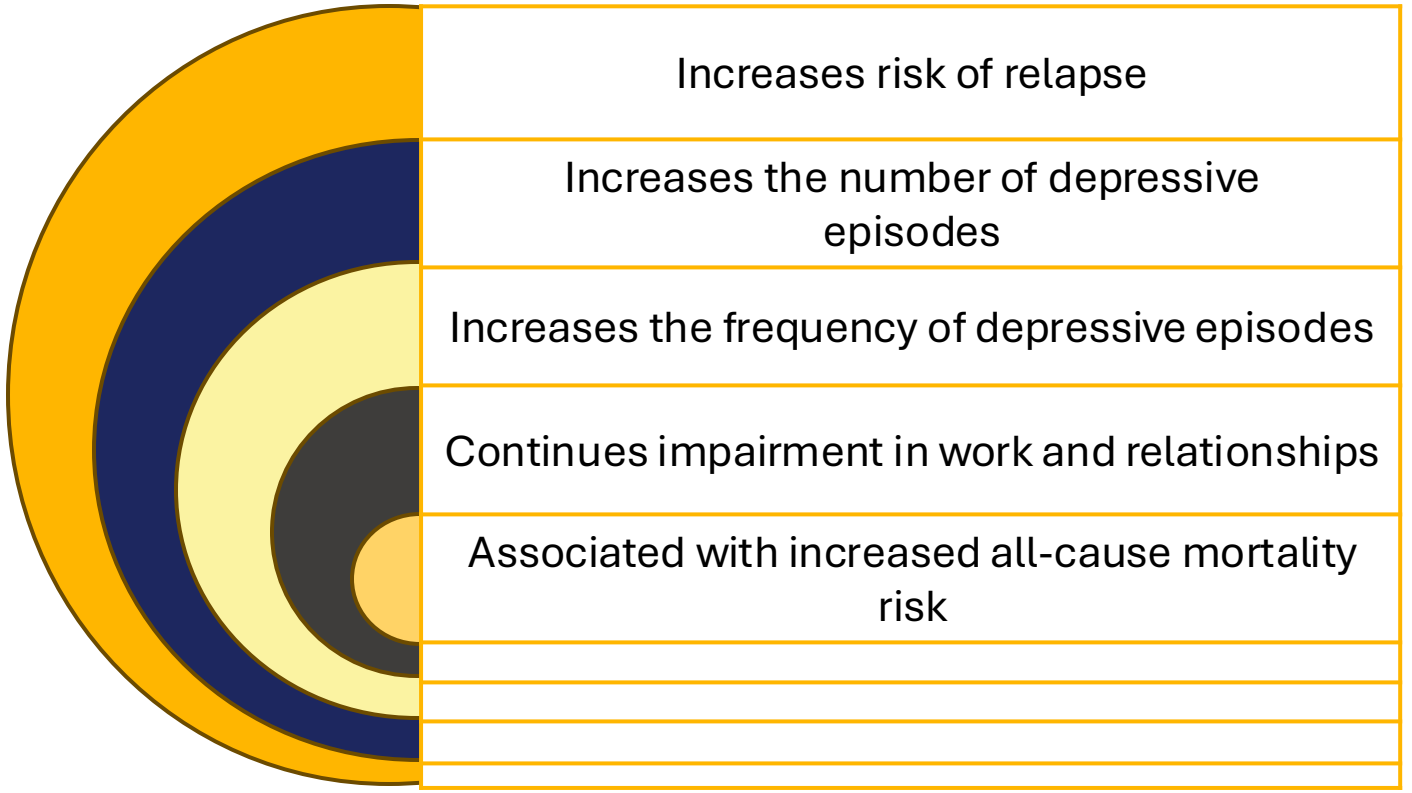
Why Response Isn't Enough

Settling for Partial Response Worsens Outcomes



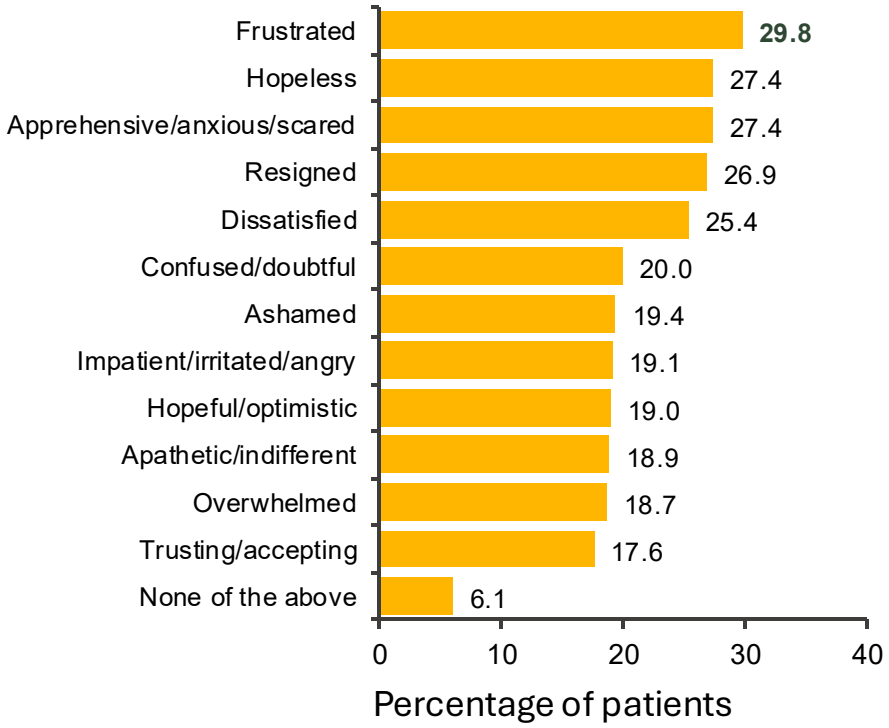


MDE = major depressive episode

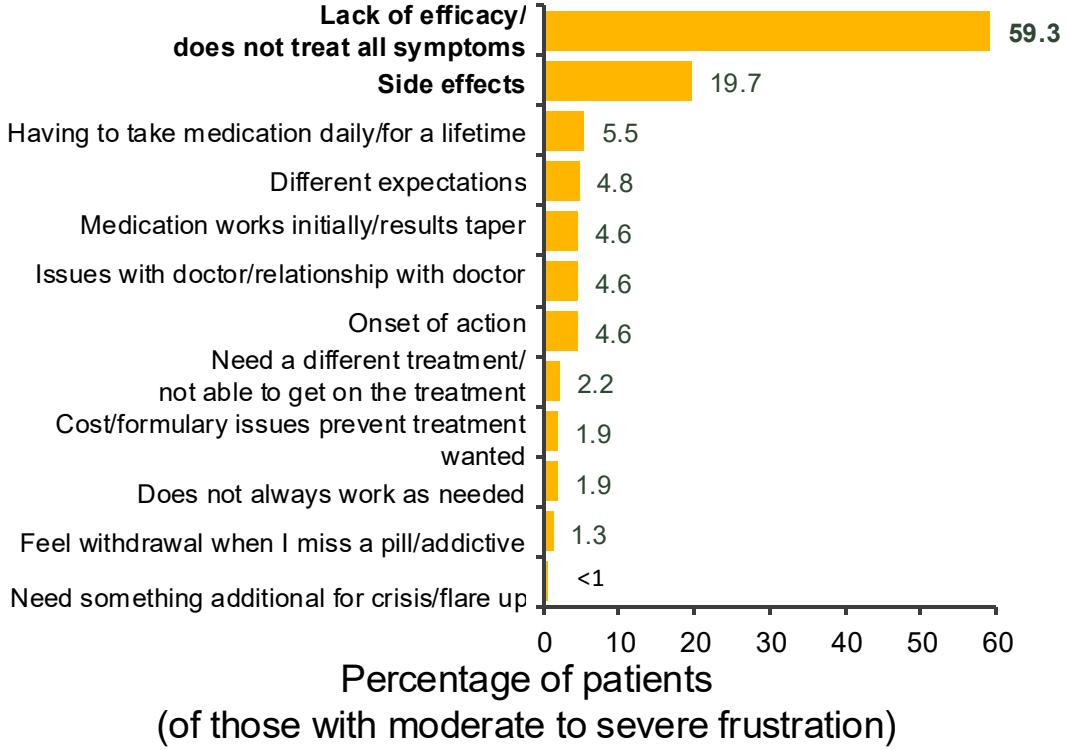
Judd LL, et al. *Am J Psychiatry*. 2000;157(9):1501-1504. McLaughlin KA. *Prev Sci*. 2011;12(4):361-371. Hare DL, et al. *Eur Heart J*. 2014;35(21):1365-1372. Murphy JM, et al. *Arch Gen Psychiatry*. 1987;44(5):473-480. Miloyan B, Fried E. *World Psychiatry*. 2017;16(2):219-220. van Dooren FE, et al. *PLoS One*. 2013;8(3):e57058. de Groot M, et al. *Psychosom Med*. 2001;63(4):619-630. Kubo K, et al. *J Affect Disord*. 2023;320:710-715. Pintor L, et al. *J Affect Disord*. 2004;82(2):291-296.

Patients with Inadequate Response to Antidepressant Treatment Often Feel Frustrated by Their Medication

Patients' emotions regarding their medication (n=2,096)*



Patients' reasons for frustration with their medication (n=536)

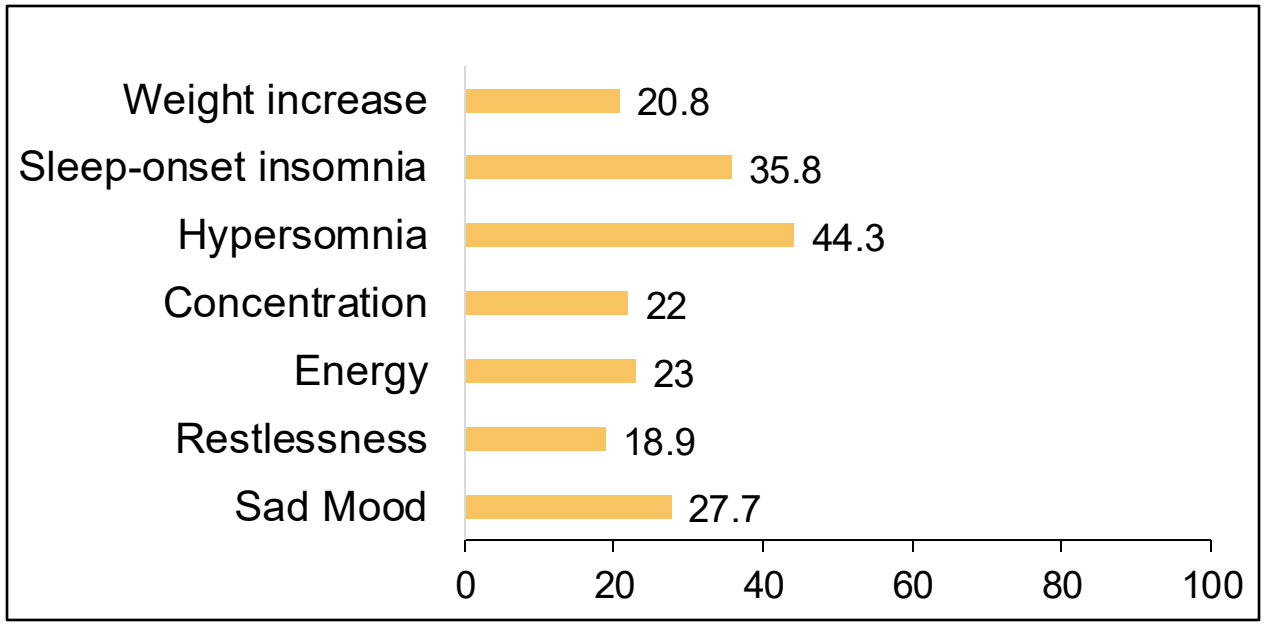


***Patients could select all emotions that applied.**

Mago R, et al. *BMC Psychiatry*. 2018;18(1):33.

Persistent Symptoms* in MDD Remitters Are Common and Negatively Affect Outcomes

Proportion of Remitters with Persistent Baseline Symptoms at the End of Step 1 (STAR*D Study)

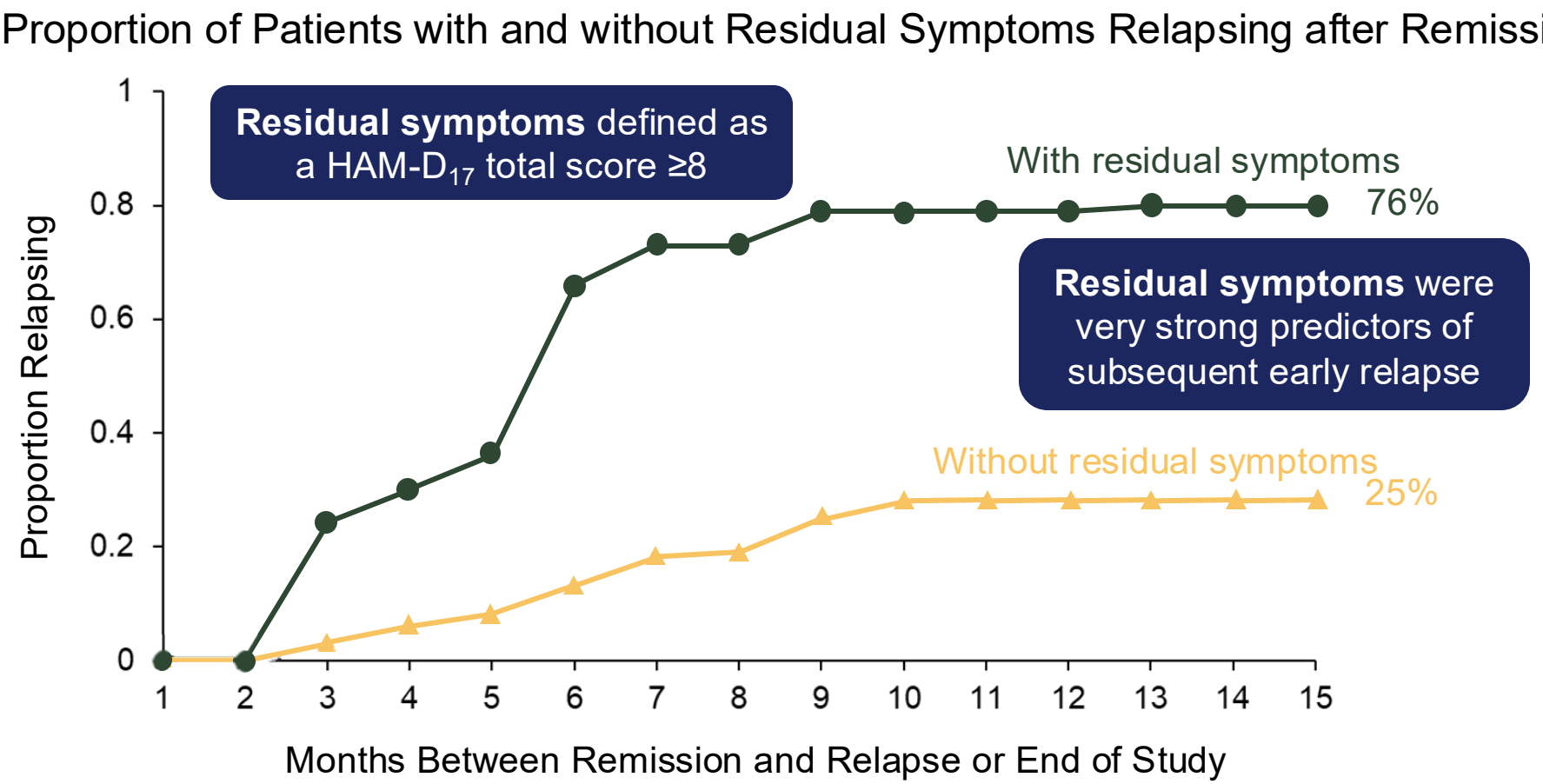


- Residual symptoms increase the risk for suicide and relapse.
- Residual symptoms have an adverse impact on psychosocial and occupational functioning.

***Persistent symptoms defined as QIDS-SR16 item score ≥1.**

Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50. Blier P. *J Clin Psychiatry*. 2013;74(Suppl 2):19-24. Romera I, et al. *BMC Psychiatry*. 2013;13:51.

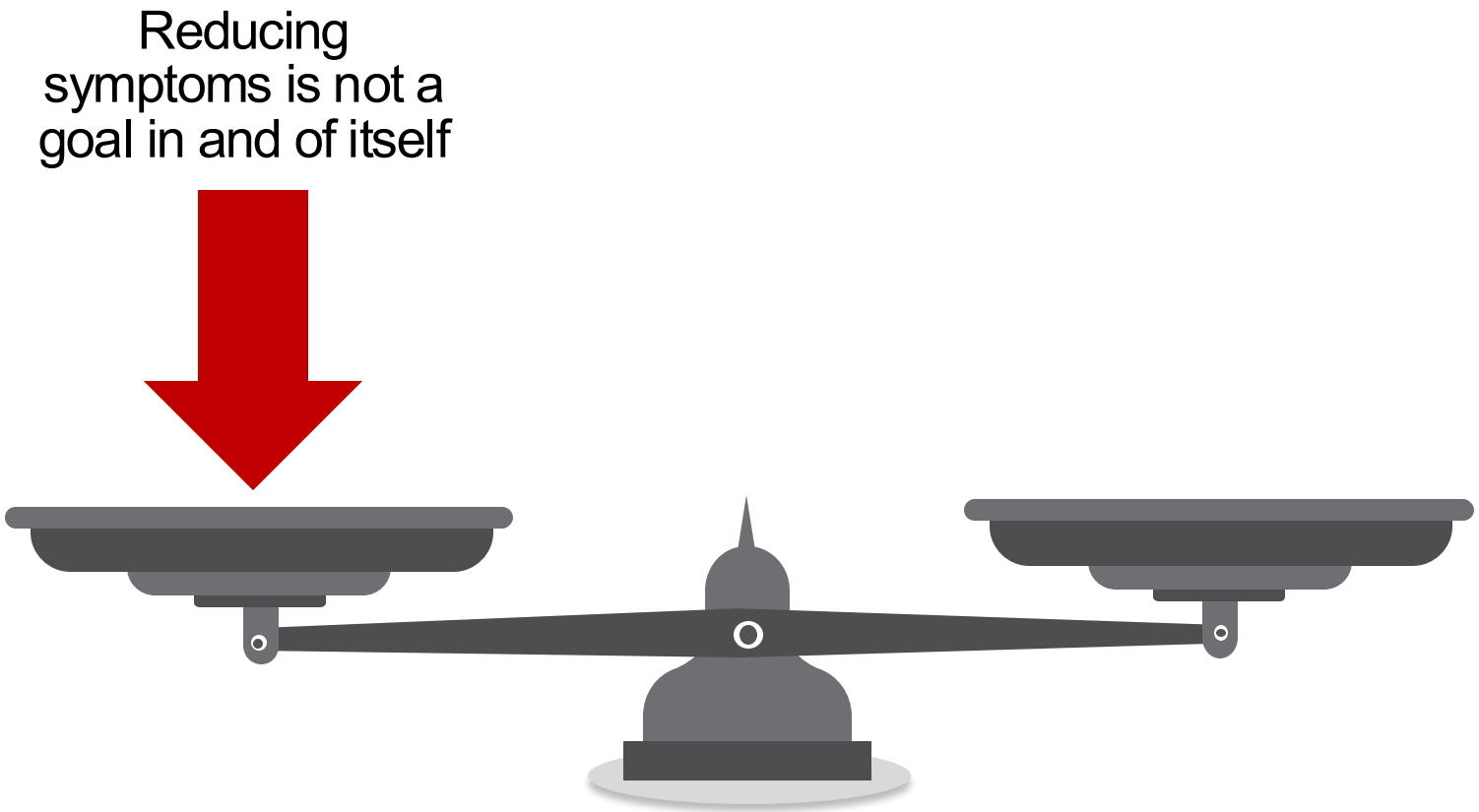
Patients with Residual Symptoms Relapse Faster Than Do Patients without Residual Symptoms



HAM-D = Hamilton Depression Rating Scale

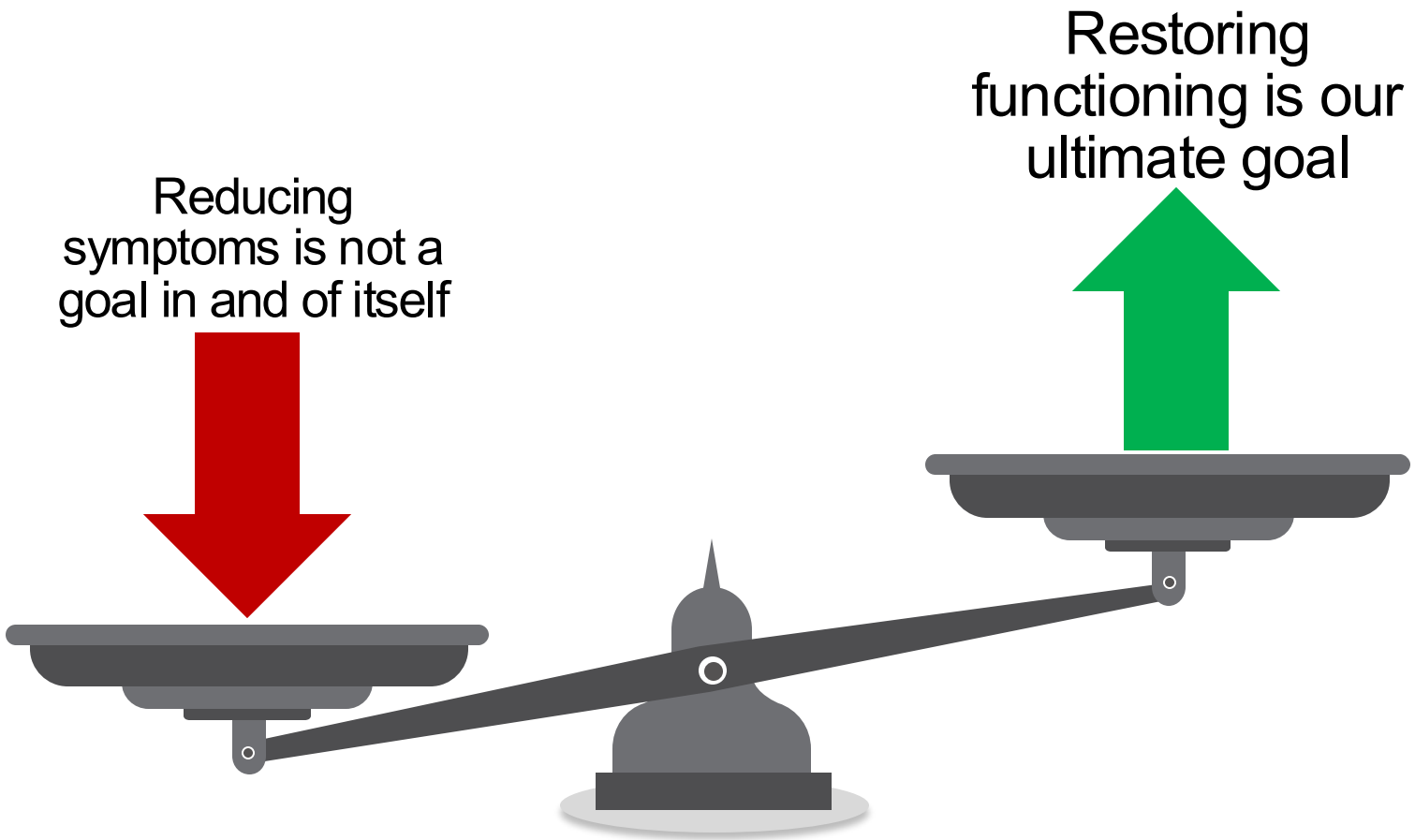
Paykel ES, et al. *Psychol Med*. 1995;25(6):1171-1180.

The Goal of Treating Major Depressive Disorder Is Not Simply to Reduce Symptoms



Papakostas GI. *J Clin Psychiatry*. 2016;77(8):e1009. Trivedi MH, et al. *Int Clin Psychopharmacol*. 2009;24(3):133-138. American Psychiatric Association. *Am J Psychiatry*. 2000;157(4 Suppl):1-45.

The Goal of Treating MDD Is to Restore Function



Papakostas GI. *J Clin Psychiatry*. 2016;77(8):e1009. Trivedi MH, et al. *Int Clin Psychopharmacol*. 2009;24(3):133-138. American Psychiatric Association. *Am J Psychiatry*. 2000;157(4 Suppl):1-45.

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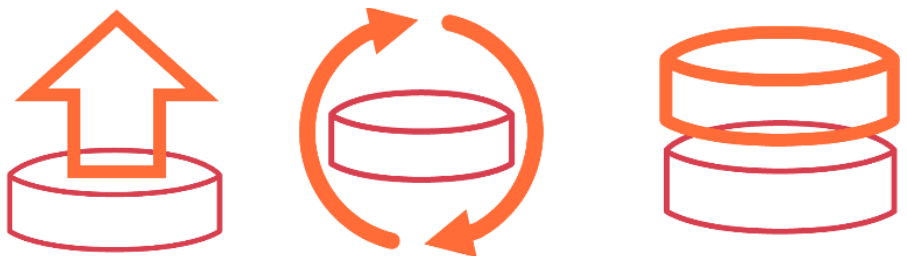
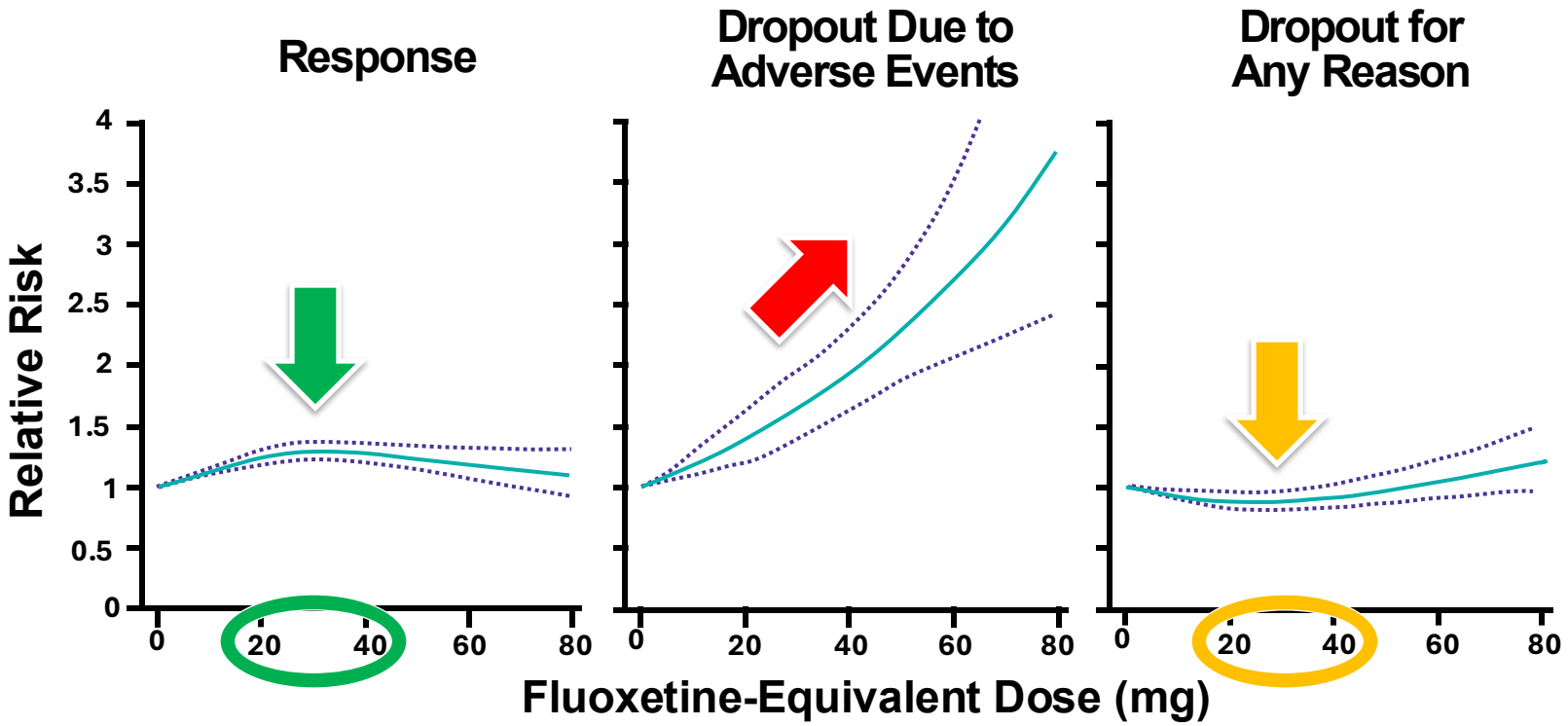
Evidence-Based Augmentation

To Switch or Add? …That Is the Question



The Optimal Dose of SSRIs Is Not Always the Maximum Dose



Approximate Optimal Doses	
Citalopram	20-40 mg
Escitalopram	10-20 mg
Fluoxetine	20-40 mg
Paroxetine	17-34 mg
Sertraline	50-100 mg

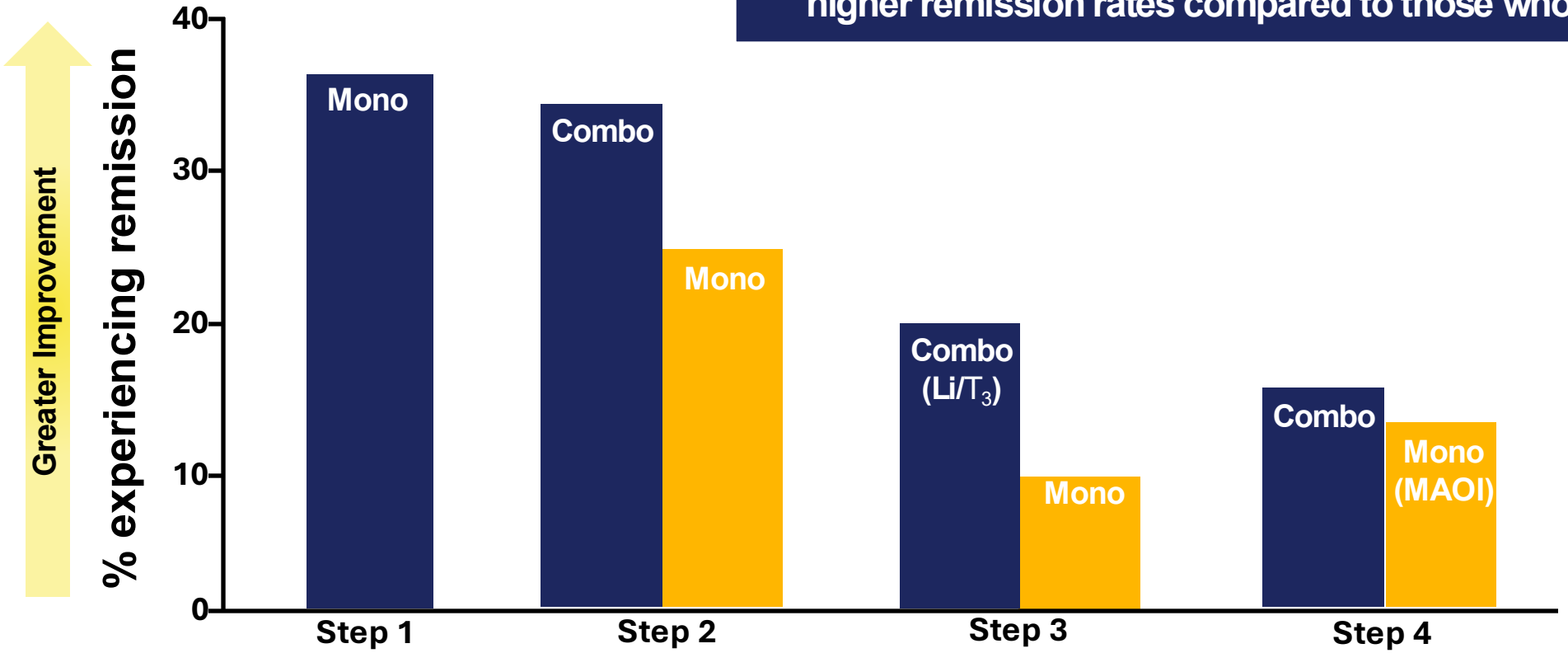
Doses equivalent to 20-40 mg fluoxetine achieve the optimal balance between efficacy, tolerability, and acceptability.

SSRI = selective serotonin reuptake inhibitor

Furukawa TA, et al. *Lancet Psychiatry*. 2019;6(7):601-609. Hayasaka Y, et al. *J Affect Dis*. 2015;180:179-184.

Adding a Treatment May Be Better Than Switching

Although STAR*D was not powered to compare options against one another, people who added a treatment had numerically higher remission rates compared to those who switched.



Mono = monotherapy; Combo = combination; Li = lithium; T_3 = triiodothyronine; MAOI = monoamine oxidase inhibitor

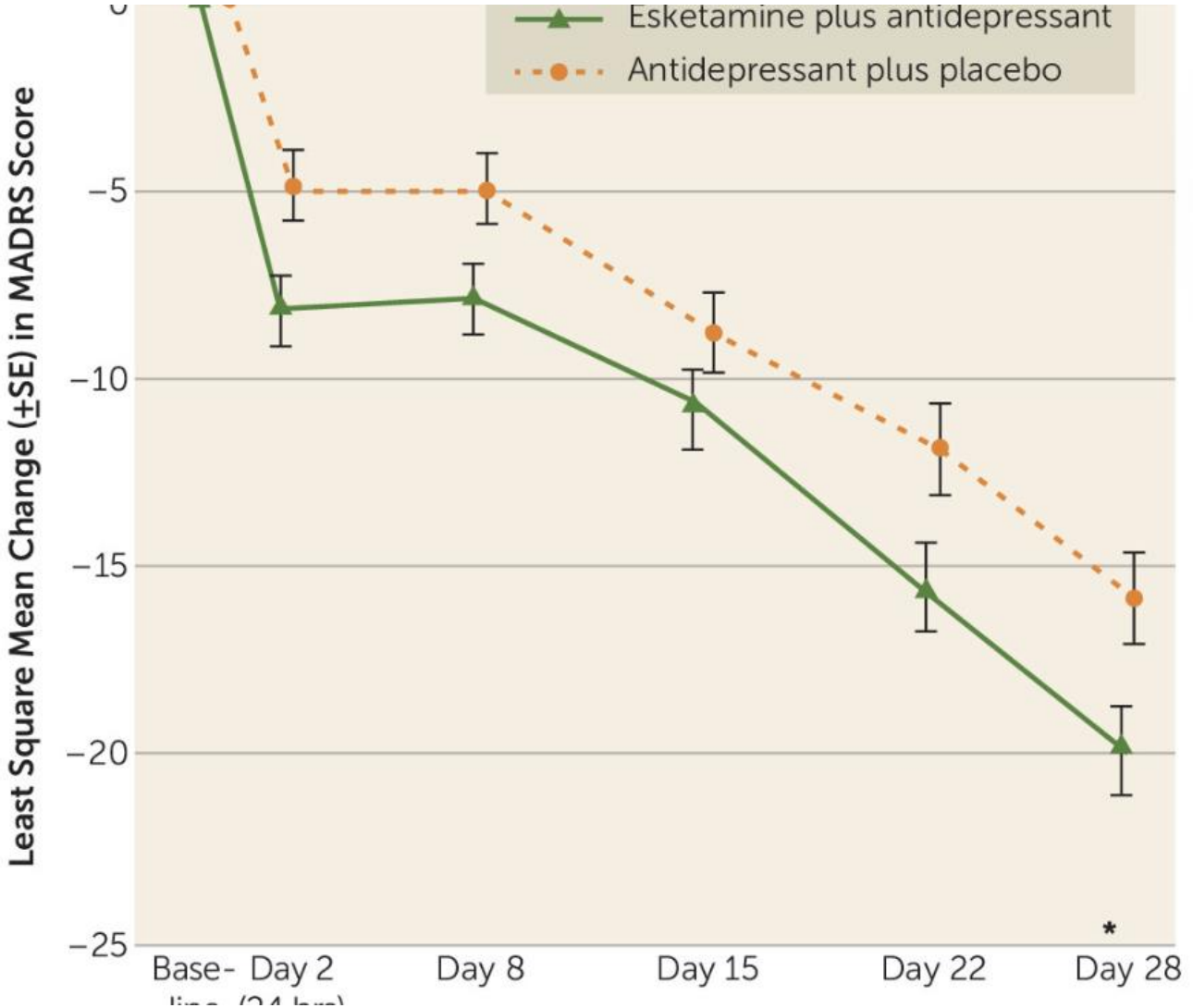
Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40. Trivedi MH, et al. *N Engl J Med*. 2006;354(12):1243-1252. Rush AJ, et al. *N Engl J Med*. 2006;354(12):1231-1242. Nierenberg AA, et al. *Am J Psychiatry*. 2006;163(9):1519-1530. Fava M, et al. *Am J Psychiatry*. 2006;163(7):1161-1172. McGrath PJ, et al. *Am J Psychiatry*. 2006;163(9):1531-1541.

Esketamine Nasal Spray: Pivotal Acute Study

Clinical Highlights

- Shows fast symptom relief in treatment-resistant depression
- Works by blocking NMDA receptors
- Used with oral antidepressants; monitor dissociation and blood pressure
- NNT of 5–6 is comparable to atypical antipsychotic augmentation

Esketamine Adjunctive to Antidepressant

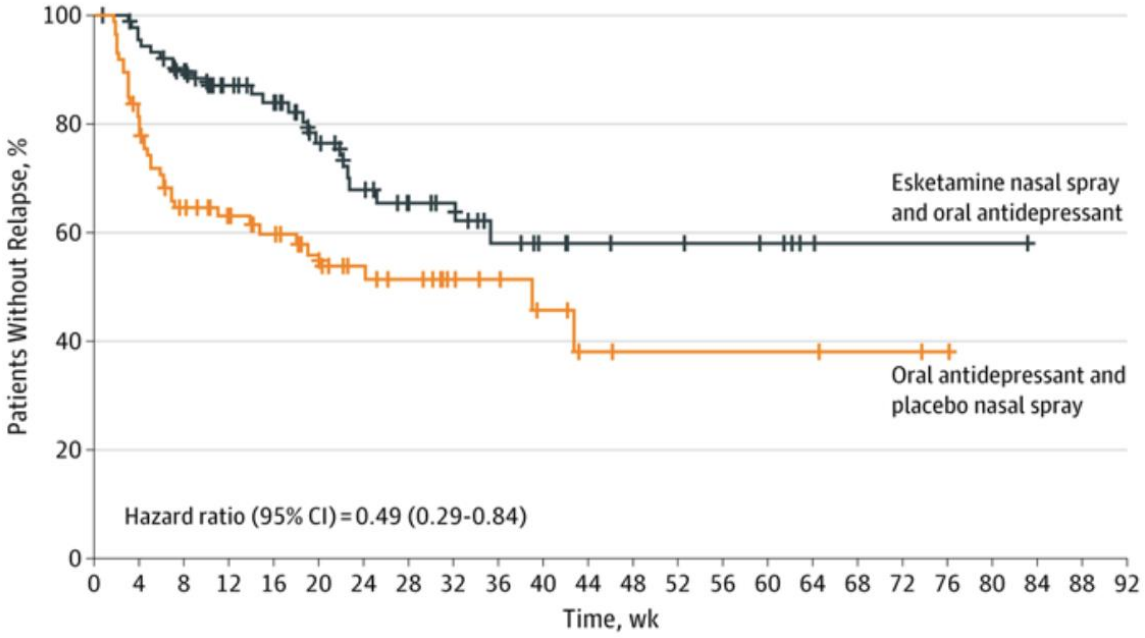


NNT = number needed to treat; SE = standard error; MADRS = Montgomery-Åsberg Depression Rating Scale

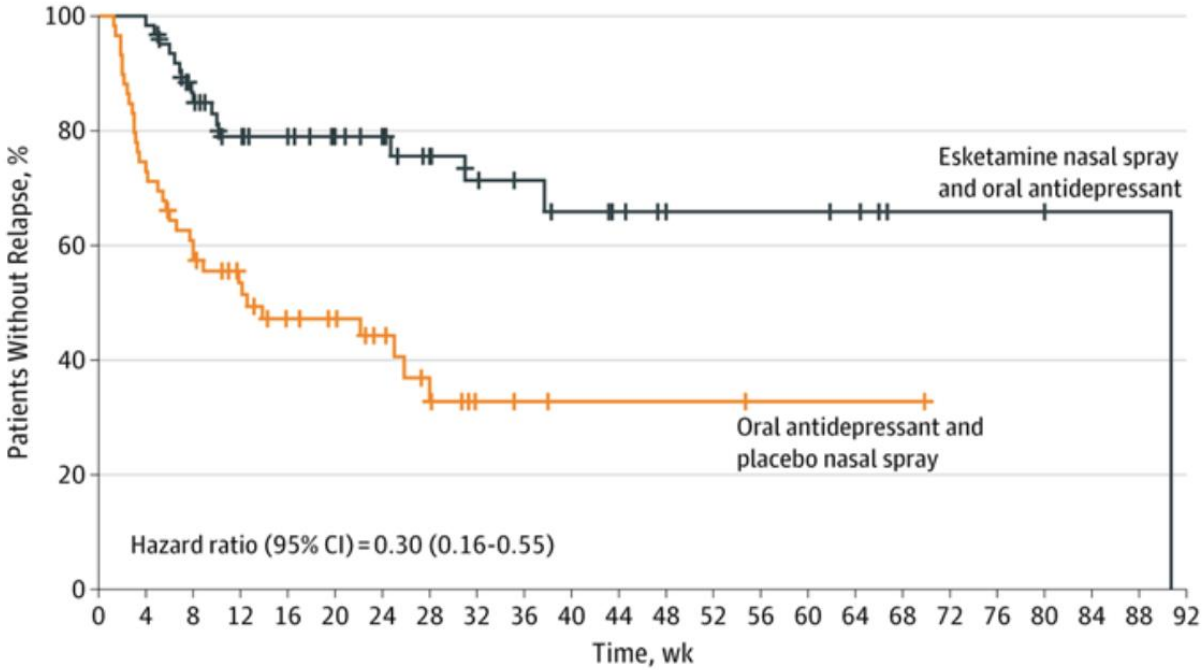
Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438.

Esketamine Nasal Spray: Pivotal Maintenance Study

Patients with Stable Remission



Patients with Stable Response



Clinical Implications

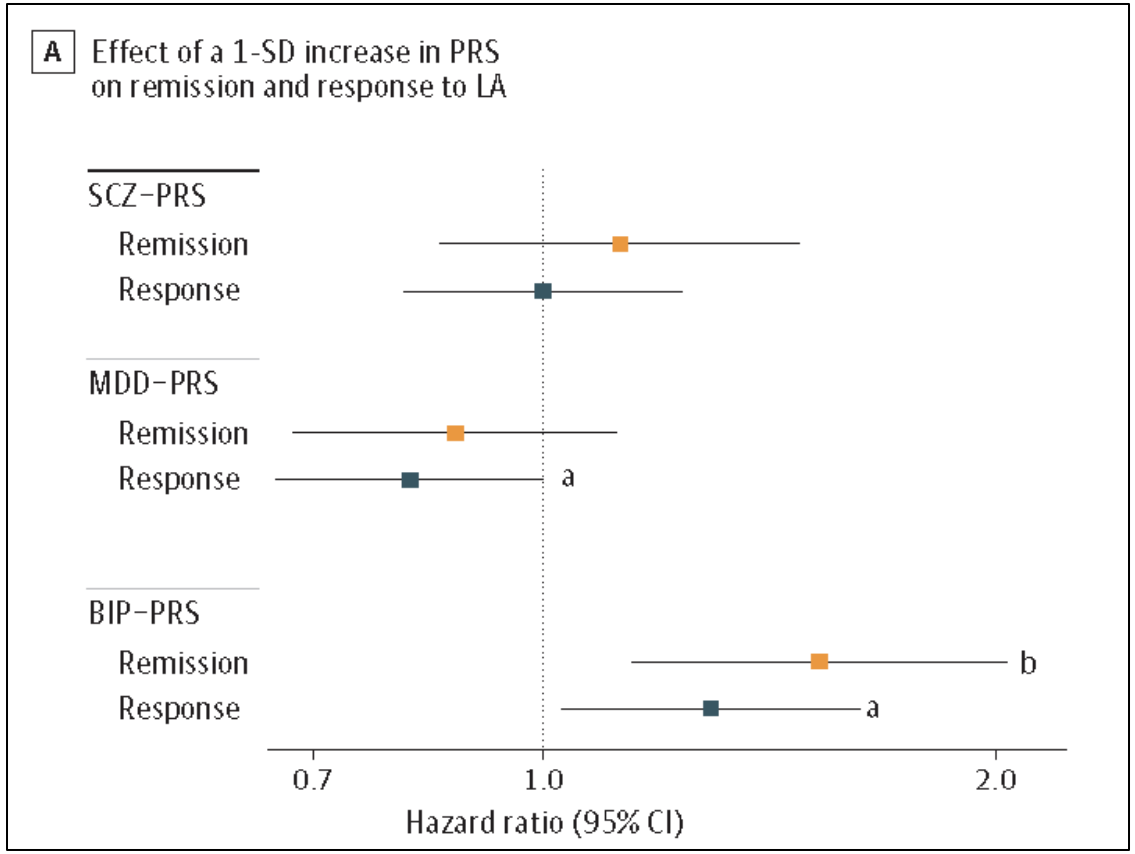
- Continuation of esketamine sustains antidepressant benefit and **reduces relapse risk by 50%–70%**
- Supports **maintenance-phase use** for ongoing TRD management
- Highlights the importance of **long-term relapse prevention strategies** beyond acute response

TRD = treatment-resistant depression

Daly EJ, et al. *JAMA Psychiatry*. 2019;76(9):893-903.

Lithium Augmentation for Unipolar MDD

1. Commonly used as augmentation, with response rates around 41%.
2. Recent research indicates that response to adjunctive lithium in unipolar depression may be associated with the polygenic risk score (PRS) for bipolar disorder (see blue box below).
3. **Clinical consideration:** Consider even more so in patients who present with unipolar MDD with mixed features (ie, nonoverlapping features of bipolar disorder) or in those with a family history of bipolar disorder in 1st degree relatives.



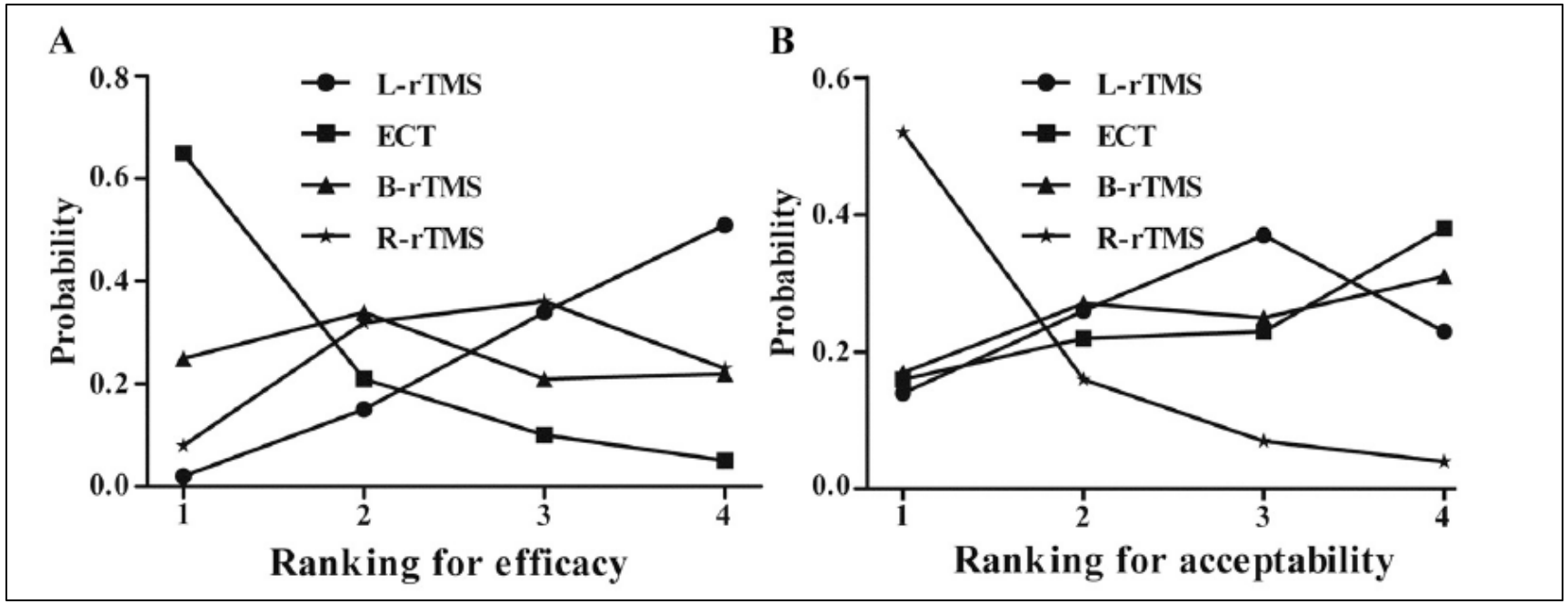
1. Prospective open-label trial of lithium augmentation in 193 participants, mean age 49.45, 61.1% female. Baseline antidep therapy: SSRI/SNRI – 79%; TCA – 11%; Other – 10%. Choice of lithium augmentation was made by treating clinician prior to study enrollment.
2. Response (≥ 50% reduction in HAMD-17): **47%**
3. Remission (HAMD-17 score ≤ 7): **32%**

PRS = polygenic risk score; SD = standard deviation; LA = lithium augmentation; CI = confidence interval; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant

Kraft J, et al. JAMA *Psych*. 2025;82(11):1137-1141.

TMS vs ECT for Unipolar MDD

1. Meta-analysis of 25 studies comprising 1288 participants.
2. **ECT was more effective but less well tolerated.**
3. Newer TMS protocols may have narrowed that efficacy difference, but no recent comparative data.



The distribution of probabilities of each treatment modality ranked at each of four possible positions.

(A) ECT was the most efficacious treatment, with the cumulative probabilities of being the most efficacious treatment being: ECT (65%), B-rTMS (25%), R-rTMS (8%), and L-rTMS (2%).

(B) R-rTMS was the best-tolerated treatment, with the cumulative probabilities of being the best-tolerated treatment being: R-rTMS (52%), B-rTMS (17%), L-rTMS (16%), and ECT (14%).

TMS = transcranial magnetic stimulation; ECT = electroconvulsive therapy
Chen JJ, et al. *Behav Brain Res*. 2017;320:30-36.

TMS Effectiveness – Newer Data

Real-World Results: Empirical success in TRD (treatment-resistant depression)

- **Response: 50%–60%; Remission: ~25%–30%**
- Even after ≥ 2 med failures, TMS > med switch/augmentation
- Durable, well-tolerated, minimal cognitive effects
- Expanding approvals: MDD, OCD; trials ongoing in PTSD, anxiety, SUDs, cognitive disorders

SAINT: 10 sessions/day × 5 days (≈ 10 weeks' dose)

- **Response: 70% response; Remission 50% remission within 1 week**
- Mechanism: dose-intensity drives plasticity engagement
- Especially valuable in acute suicidality or severe TRD

JC Brown. *Psychiatry Online*. October 31, 2025. Accessed November 2025. https://psychiatryonline.org/doi/10.1176/appi.pn.2025.11.11.4.

Antipsychotics in Depression: New Idea or Tale as Old as Time?

Atypical Antipsychotics Approved for Augmentation of MDD in Adults

- Aripiprazole (2007)
- Quetiapine XR (2009)
- Brexpiprazole (2015)
- Cariprazine (2022)
- Lumateperone (2025)

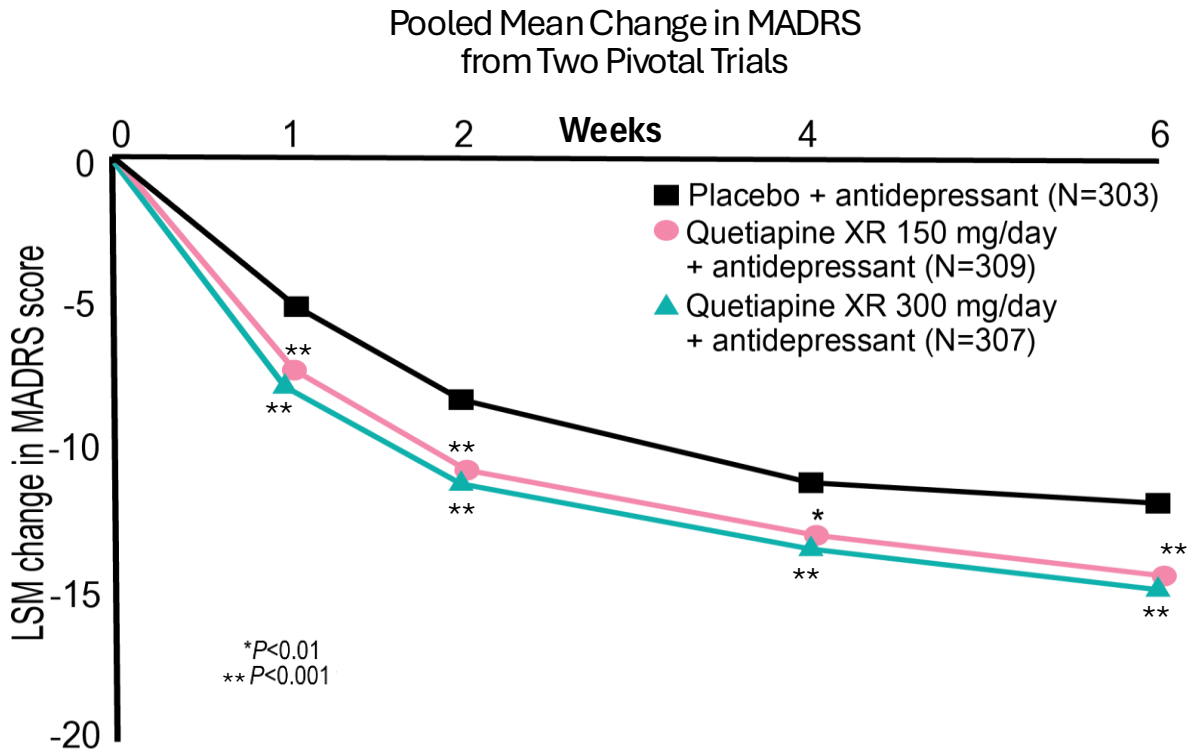
The combination of amitriptyline and perphenazine was approved in 1965 for the treatment of depression comorbid with anxiety and/or agitation.

The description of this combination in its PI:
"a broad-spectrum psychotherapeutic agent"

PI = prescribing information

Perphenazine and amitriptyline hydrochloride tablets Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed February 28, 2025. www.accessdata.fda.gov/scripts/cder/daf/. Nelson JC, et al. *Am J Psychiatry*. 2009;166(9):980-991.

Pivotal Trials of Quetiapine XR for Adjunctive MDD Treatment



Adverse events in pivotal trials	150 mg	300 mg	Placebo
Somnolence	37%	43%	9%
Dry mouth	27%	40%	8%
Fatigue	11%	14%	4%
Dizziness	11%	12%	7%
Weight gain	2 lb	2.9 lb	0.4 lb
Weight ≥7%	3.2%	7.2%	1.7%
D/C due to AE	8%	15%	2%

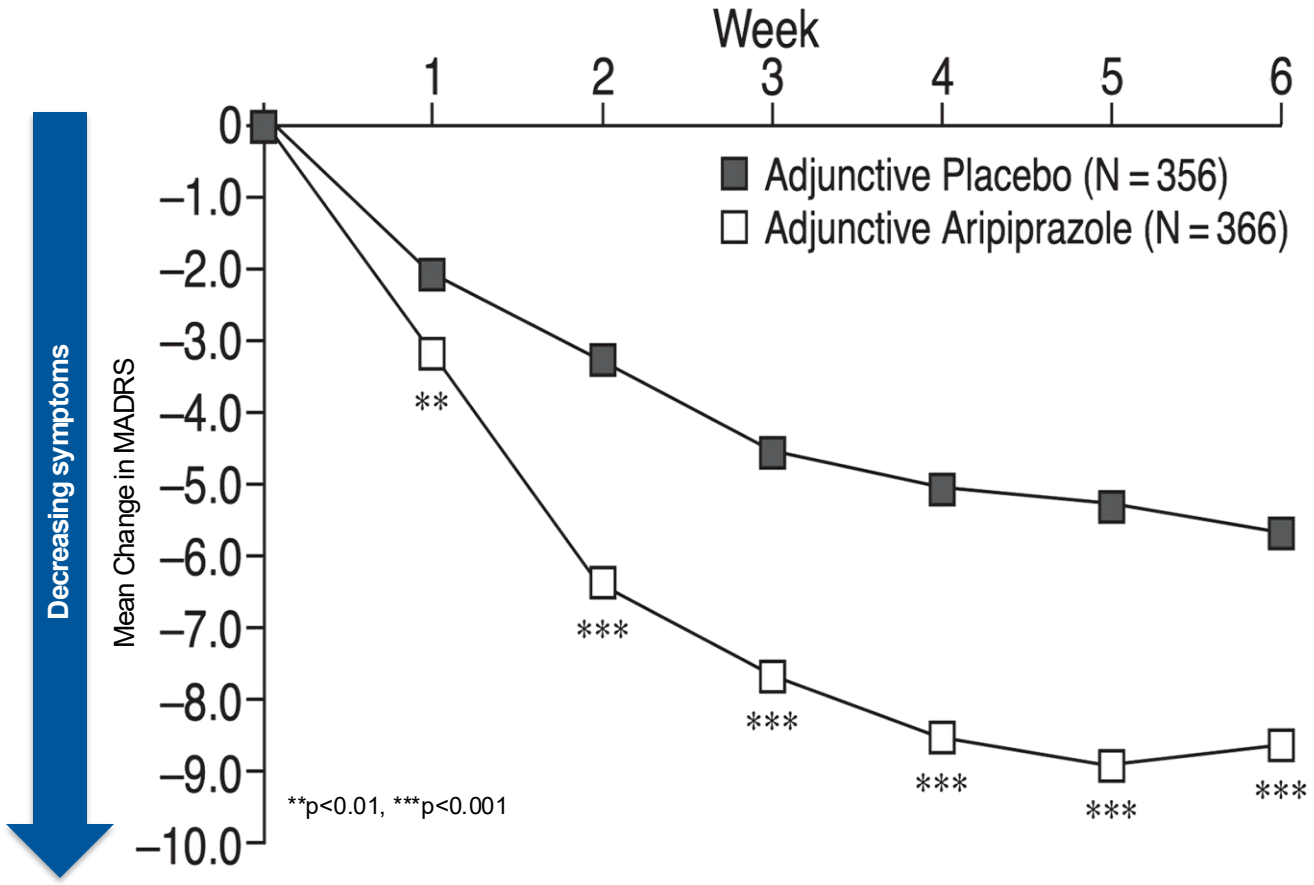
Long-term adverse event data unavailable for quetiapine XR

At week 6, Quetiapine XR does separate on 4 of 6 "core" MADRS items at 150 mg and 5 of 6 at 300 mg, but much of the overall separation is still driven by sleep.

LSM = least squares mean; D/C = discontinuation; AE = adverse event

Quetiapine Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed February 28, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022047s048lbl.pdf. Bauer M, et al. *J Affect Disord*. 2010;127(1-3):19-30.

Pivotal Trials of Adjunctive Aripiprazole for MDD



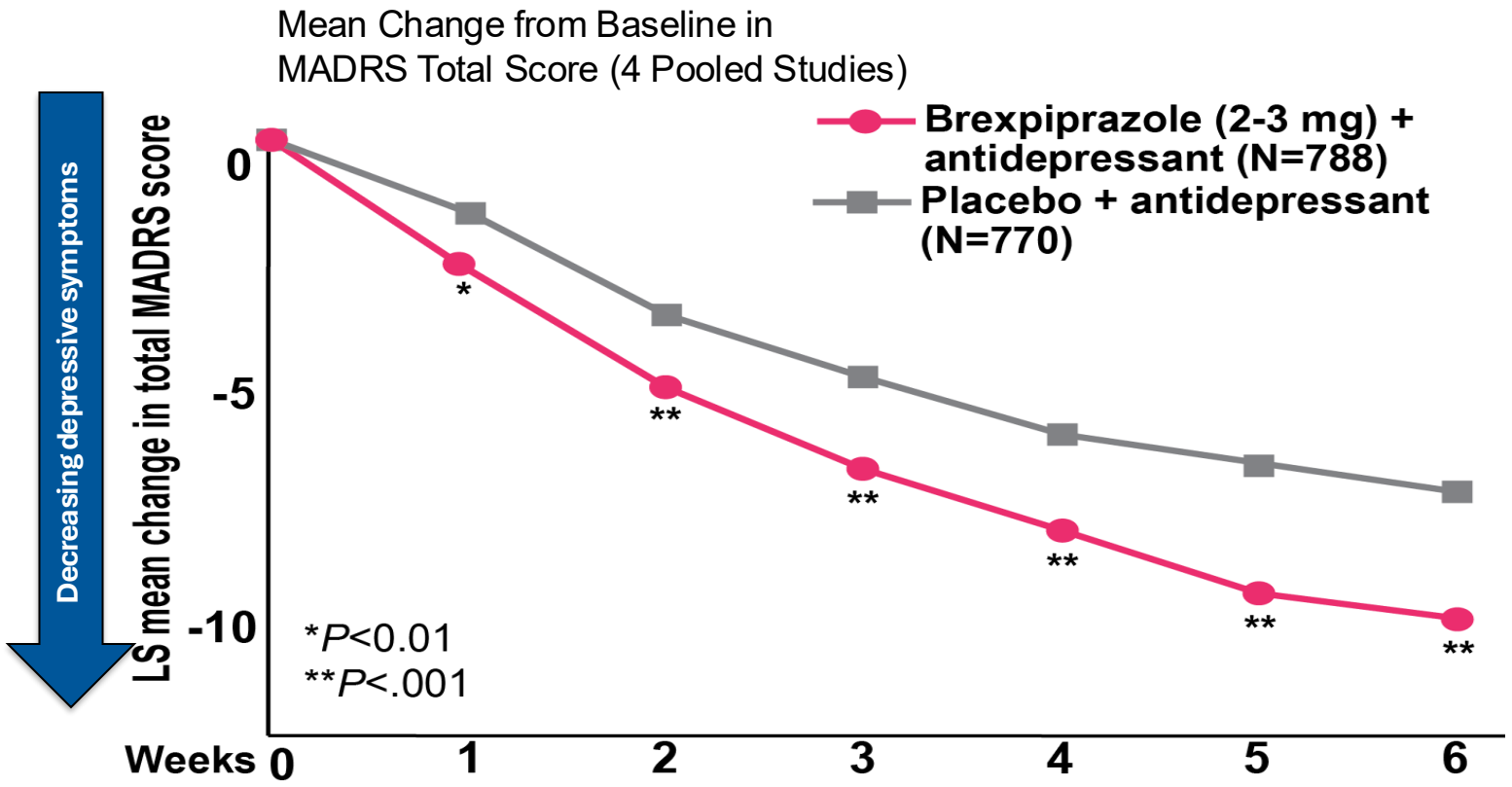
Starting dose: 2–5 mg once daily
Recommended dose: 5–10 mg/day;
Max dose in MDD: 15 mg/day

Adverse Events in Pivotal Trials

	All doses pooled	Placebo
Akathisia	25%	4%
Restlessness	12%	2%
Insomnia	8%	2%
Blurred vision	6%	1%
Weight gain	3.8 lb	0.9 lb
Weight ≥7%	5.2%	0.6%
D/C due to AE	6%	2%

Aripiprazole Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021436s046s050lbl.pdf. Berman RM, et al. *Neuropsychiatry Dis Treat*. 2011;7:303-312. Pae CU, et al. *CNS Drugs*. 2011;25(2):109-127. Thase ME, et al. *Prim Care Companion J Clin Psychiatry*. 2008;10(6):440-447.

Pivotal Trials of Adjunctive Brexpiprazole for MDD

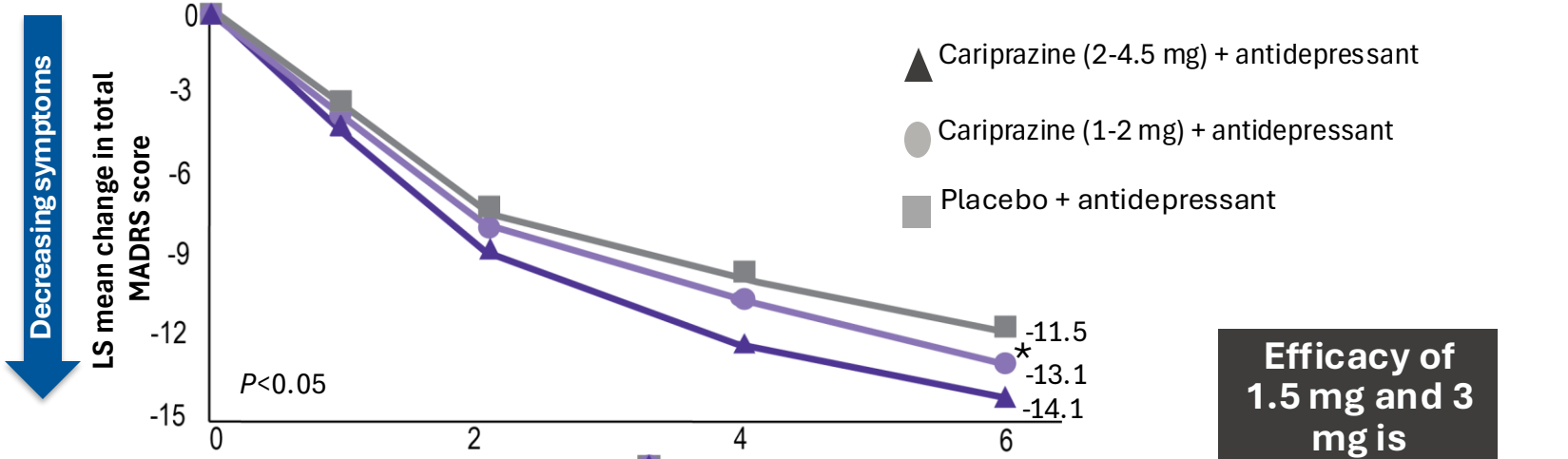


Approved doses: 2 or 3 mg/day
Titrate from 0.5 mg to 1 mg to 2 mg in weekly increments

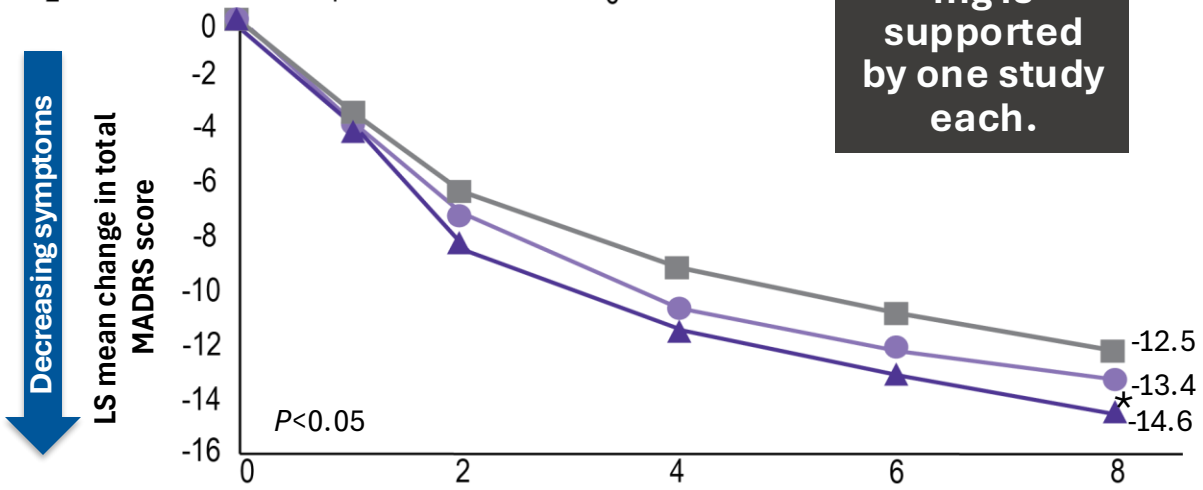
Adverse Events in Pivotal Trials			
	2 mg	3 mg	Placebo
Akathisia	7%	14%	2%
Weight gain	8%	6%	2%
Somnolence	4%	6%	2%
Restlessness	3%	4%	0%
Weight gain	3.3lb	3.3lb	0.7lb
Weight ≥7%	5%	2%	2%
D/C due to AE	3% pooled		1%

Brexpiprazole Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/205422s014lbl.pdf. Hobart M, et al. *J Clin Psychopharmacol*. 2019;39(3):203-209. Thase ME, et al. *Expert Opinion on Pharmacotherapy*. 2019;20(15):1907-1916.

Pivotal Trials of Adjunctive Cariprazine for MDD



Approved doses: 1.5 or 3 mg/day. PI recommends waiting two weeks if titrating to 3 mg.



Efficacy of 1.5 mg and 3 mg is supported by one study each.

Adverse Events in Pivotal Trials

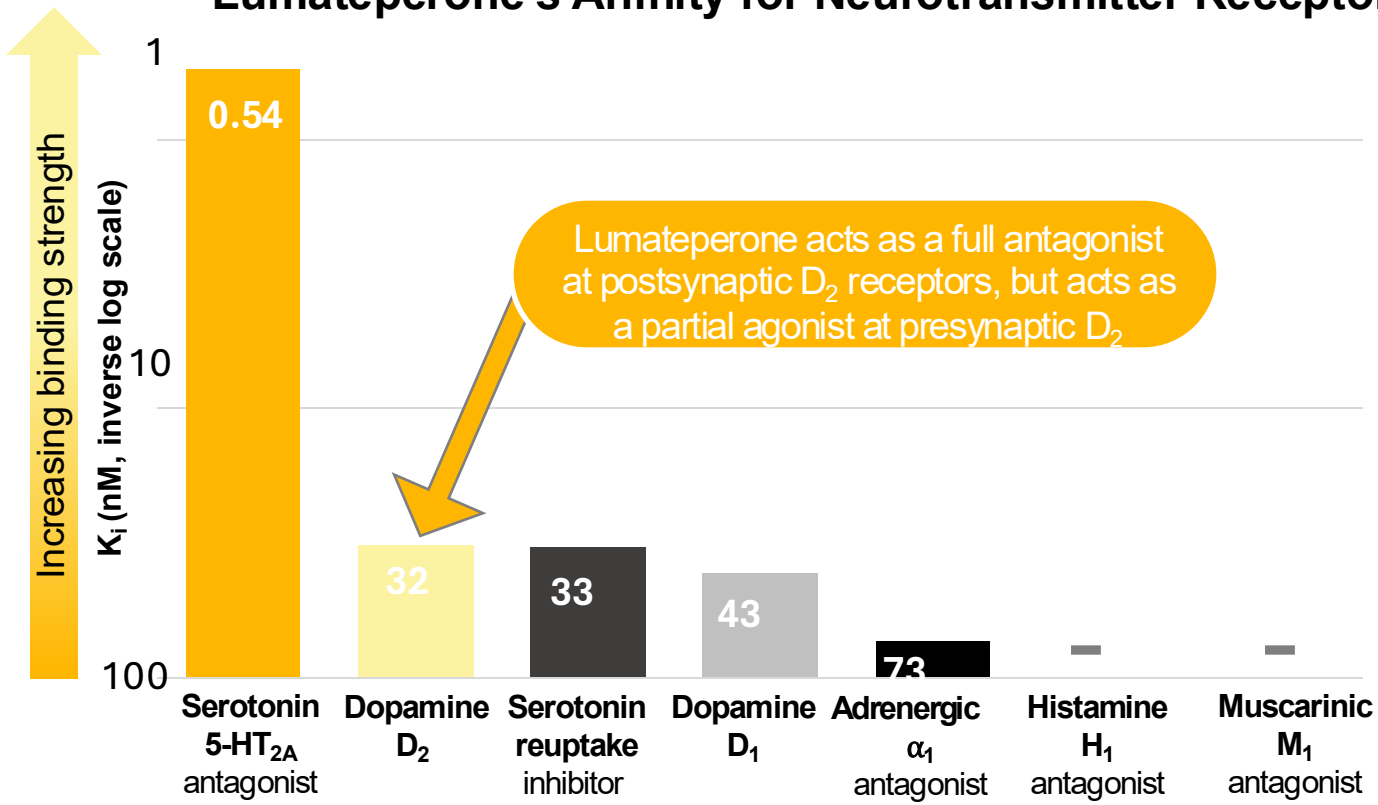
	1.5 mg	3 mg	Placebo
Insomnia	9%	10%	5%
Akathisia	7%	10%	2%
Nausea	7%	6%	3%
Somnolence	5%	7%	4%
Weight gain	1.5lb	1.5lb	0.4lb
Weight ≥7%	2%	2%	1%
D/C due to AE	6% pooled		3%

Cariprazine Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/204370s012lbl.pdf. Durgam S, et al. *J Clin Psychiatry.* 2016;77(3):371-378. Sachs, GS, et al. *Am J Psychiatry.* 2023;180(3):241-251. Earley WR, et al. *Psychopharmacol Bull.* 2018;48(4):62-80. Vieta E, et al. *Int J Clin Psychopharmacol.* 2019;34(2):76-83. National Library of Medicine. Accessed August 2025. https://clinicaltrials.gov/study/NCT03739203.

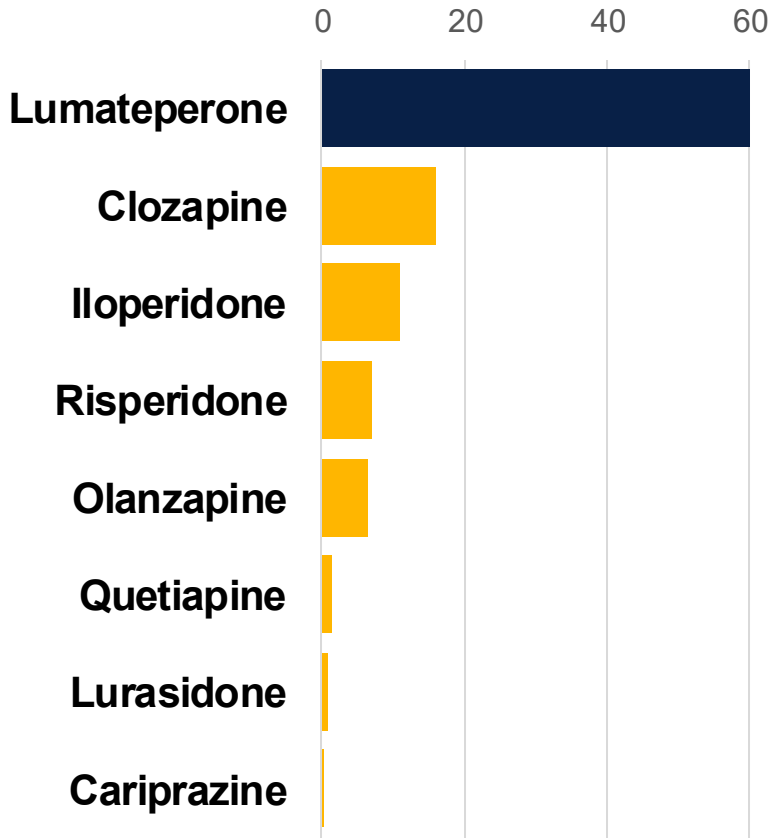
Lumateperone Pharmacology

Lumateperone's 60x greater selectivity for 5-HT_{2A} to D_2 receptor affinity is higher than that of any other antipsychotic.

Lumateperone's Affinity for Neurotransmitter Receptors



5-HT_{2A} to D_2 ratios

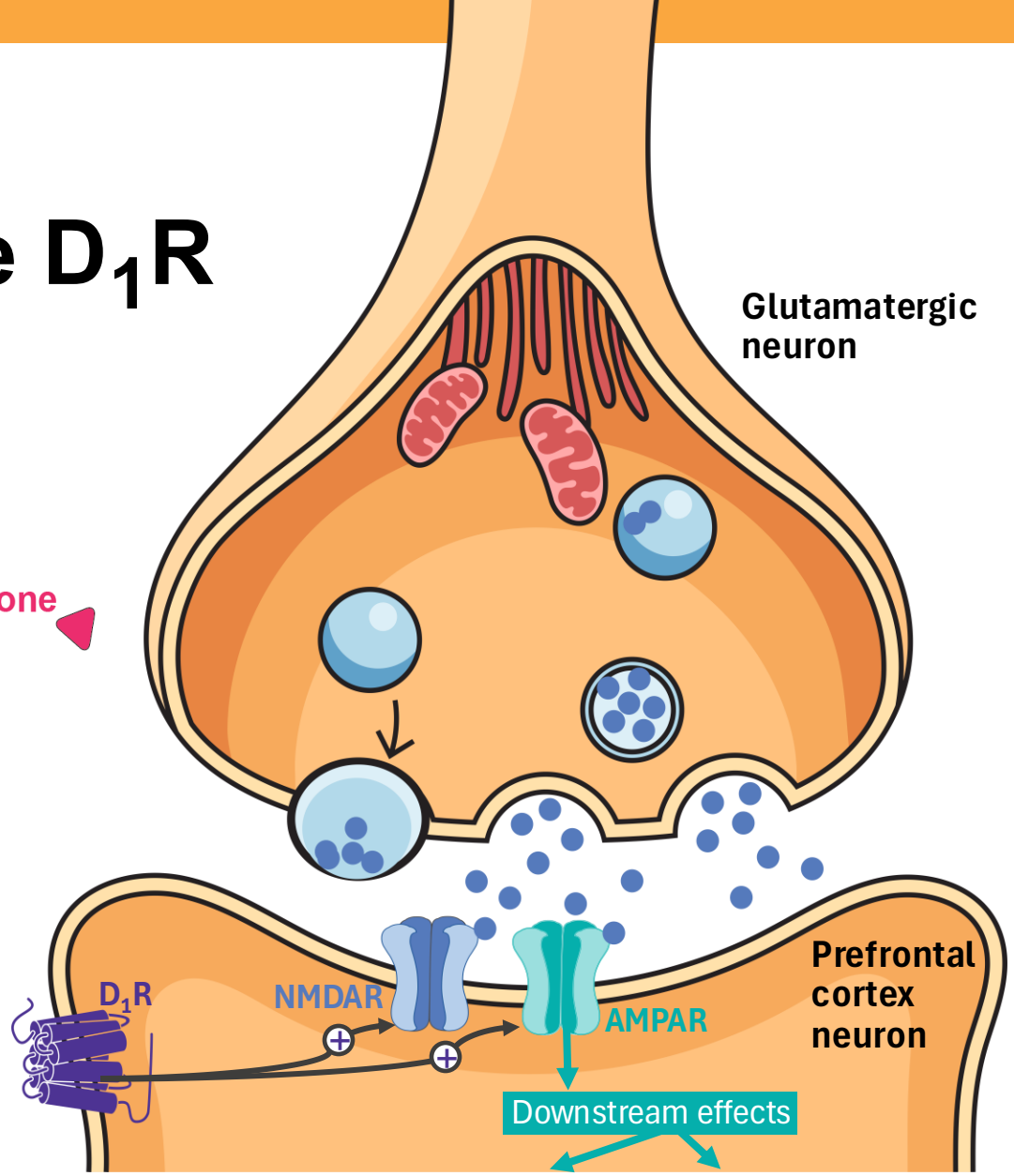


Lumateperone Prescribing information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209500s011lbl.pdf. Li P, et al. *J Med Chem.* 2014;57(6):2670-2682. Kantrowitz JT. *CNS Drugs. 2020;*34(9):947-959.

Lumateperone Modulates Glutamate Indirectly via the D_1R

In preclinical studies, lumateperone indirectly activates both NMDA and AMPA glutamate receptors in the prefrontal cortex.

1. Lumateperone binds the D_1R receptor.
2. Activation of the D_1R receptor strengthens AMPA and NMDA glutamate signaling.
3. The AMPA receptor activates multiple downstream processes that are important for learning, memory, and mood.

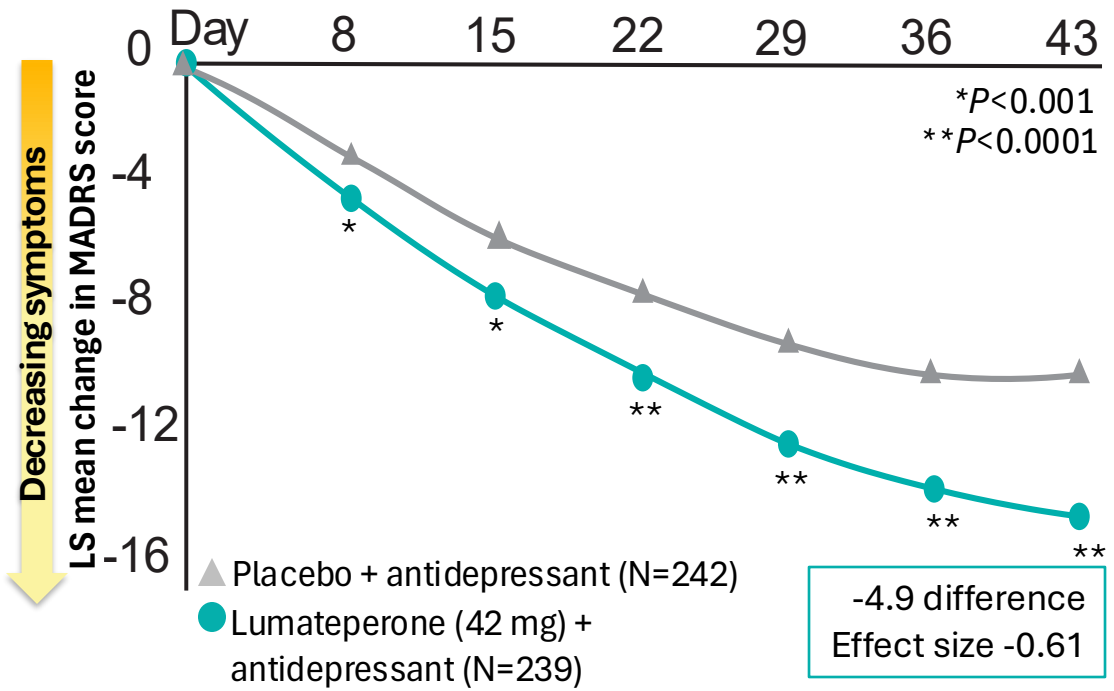


AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor; D1R = D1 dopamine receptor; NMDAR = N-methyl-D-aspartate glutamate receptor

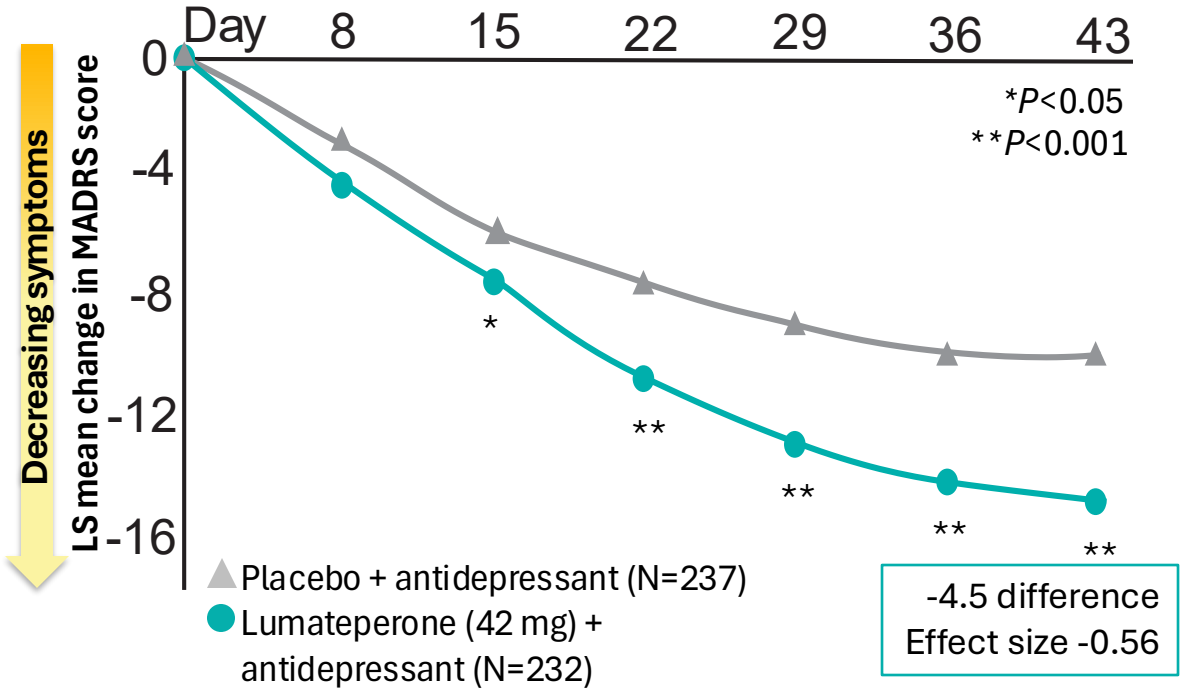
Harvey J, et al. *J Neurosci*. 1997;17(14):5271-5280. Vanover, KE, et al. *European Neuropsychopharmacol.* 2017;27:S660-S661.

Lumateperone Efficacy for Adjunctive MDD Treatment in Phase 3 Studies

Study 1 of Lumateperone Plus Antidepressant for MDD



Study 2 of Lumateperone Plus Antidepressant for MDD



In two placebo-controlled studies, adjunctive lumateperone vs placebo reduced MADRS score by 4–5 points more than placebo at week 6.

Durgam S, et al. *J Clin Psychiatry*. 2025;86(4):25m15848.

Phase 3 Studies of Lumateperone for Adjunctive MDD Treatment

Adverse Events in Study 501		
	Lumateperone 42 mg (N=241)	Placebo (N=243)
Dry Mouth	26 (11%)	5 (2%)
Nausea	12 (5%)	10 (4%)
Fatigue	23 (10%)	5 (2%)
Tremor	12 (5%)	1 (0.4%)
Dizziness	25 (10%)	15 (6%)
Headache	38 (16%)	37 (15%)
D/C due to AE	14 (6%)	2 (0.08%)

Adverse Events in Study 502		
	Lumateperone 42 mg (N=242)	Placebo (N=243)
Dry Mouth	35 (14%)	11 (5%)
Nausea	29 (12%)	9 (4%)
Diarrhea	13 (5%)	2 (0.8%)
Fatigue	12 (5%)	1 (0.4%)
Dizziness	54 (22%)	9 (4%)
Somnolence	39 (16%)	7 (3%)
Headache	49 (20%)	35 (15%)
D/C due to AE	29 (12%)	1 (0.4%)

In both studies, weight and body mass index remained stable in both groups, and no clinically relevant increases in prolactin or cardiometabolic parameters occurred.

Durgam S, et al. *J Clin Psychiatry*. 2025;86(4):25m15848. National Library of Medicine. Accessed August 2025. https://clinicaltrials.gov/study/NCT05061706. National Library of Medicine. Accessed August 2025. https://clinicaltrials.gov/study/NCT04985942.

Integrating Lifestyle Interventions with Pharmacologic Care

Small, structured lifestyle goals in the first 2–4 weeks can accelerate improvement, improve medication adherence, and reinforce agency and self-efficacy.
Exercise: Regular aerobic or resistance activity (≥150 min/week) improves mood, increases BDNF, and complements medication effects.
Sleep Hygiene: Prioritize consistent sleep-wake cycles, limit caffeine after noon, and use behavioral strategies to reduce insomnia.
Nutrition: Encourage Mediterranean or anti-inflammatory dietary patterns; address deficiencies (vitamin D, omega-3s, folate).
Behavioral Activation: Frame physical and nutritional goals as *treatment steps*, not extras—emphasize measurable targets.
Pharmacologic Integration: Pair lifestyle strategies with early pharmacologic intervention in moderate MDD to enhance energy and motivation for behavior change.

BDNF = brain-derived neurotrophic factor

Adherence and Persistence – Practical Pearls

Treatment adherence is built through trust, structure, and symptom tracking.

Common Barriers

- Early side effects or delayed response
- Medication skepticism or stigma
- Forgetfulness, low motivation, or chaotic schedules
- Poor communication or lack of follow-up

Teaching Pearl

- Adherence improves when patients *see and feel* progress.
- Measurement, feedback, and empathy are the most effective tools clinicians have.

Strategies to Improve Adherence

- **Measurement-Based Care:** Use rating scales to show objective progress.
- **Set Expectations:** Normalize transient side effects and clarify efficacy timeline.
- **Follow-Up Frequency:** Schedule contact within 2 weeks of initiation or dose change.
- **Shared Decision-Making:** Discuss side effect profiles, cost, and lifestyle fit before prescribing.
- **Simplify Regimens:** Once-daily dosing and aligning medication with daily routines improves persistence.
- **Reinforce Success:** Acknowledge small improvements in sleep, focus, or energy to strengthen engagement.

Case Discussion: The Partial Responder

- 42-year-old woman, single parent with 9-year-old daughter. Patient has recurrent MDD, previously treated with several SSRI's.
- Presently on sertraline 200 mg x 6 weeks → ~40% improvement, and still many symptoms of residual anhedonia with low mood, and impaired functioning both at home and at work.
- She has had good tolerability and adherence to her sertraline.
- Clinical question: Switch vs. Augment?

Management Decision & Recommendation

- Guidelines: partial response = 25–49%
- If tolerating medication → optimize dose first.
- Switch mainly for minimal response or intolerability.
- Options: increase dose; augment (bupropion, AAPs, CBT); switch antidepressant
- Recommendation: augmentation with atypical antipsychotic

Psych Congress Presents

Q&A

Psych Congress