Augmentation Expectations:

Finding the Right Treatment for Partial Response in MDD

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Scott Burke

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Disclosure

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Learning Objectives

1. Recognize and assess inadequate responses to antidepressants in patients with MDD and determine when adjunctive treatment is warranted

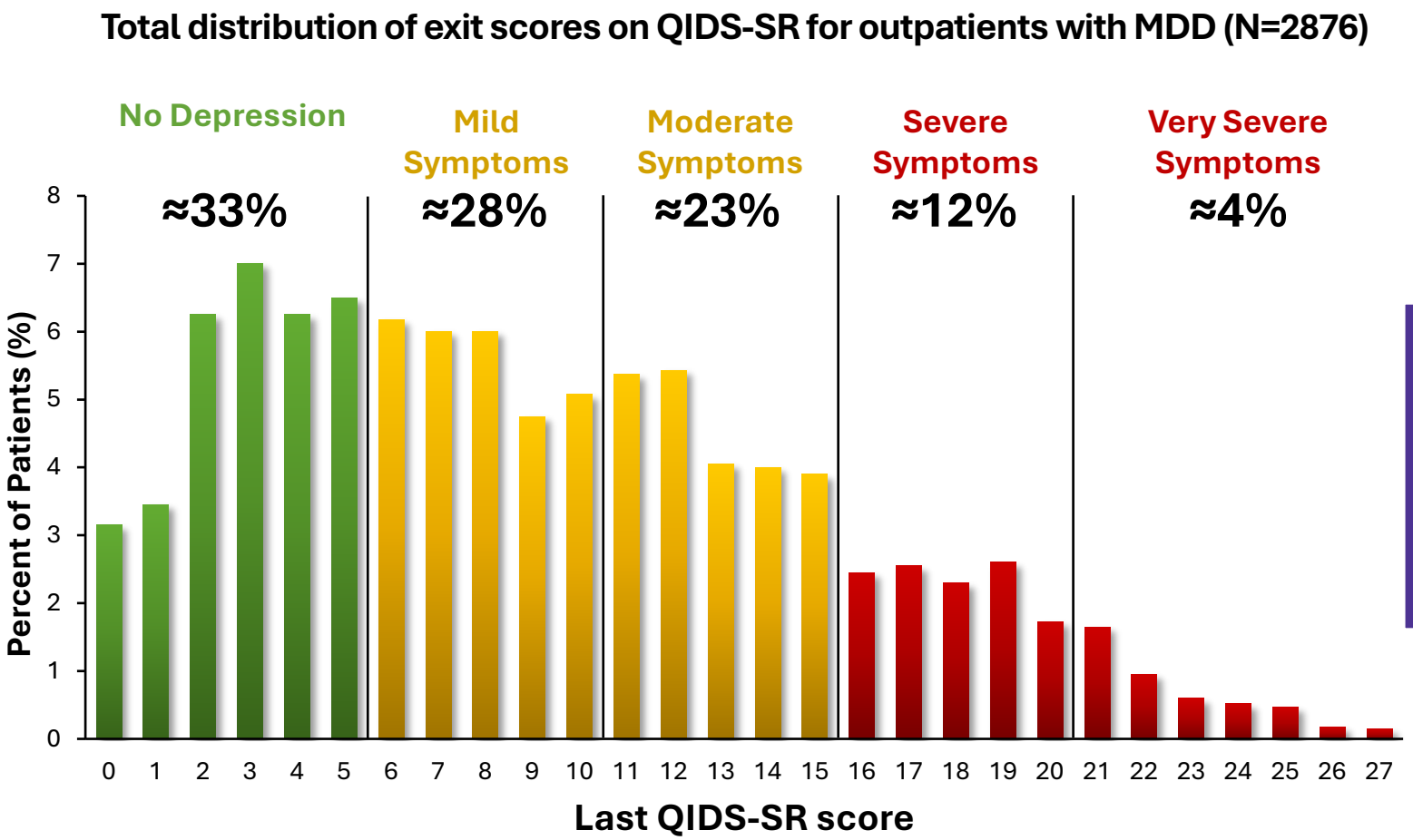
2. Evaluate the mechanisms of action and latest clinical data associated with FDA-approved and emerging atypical antipsychotics for adjunctive treatment of MDD

3. Implement strategies for selecting among adjunctive atypical antipsychotics and overcoming barriers to their optimal use in MDD

FDA = US Food and Drug Administration; MDD = major depressive disorder.

Understanding Inadequate Treatment Response In MDD

Partial Response Is Extremely Common in MDD

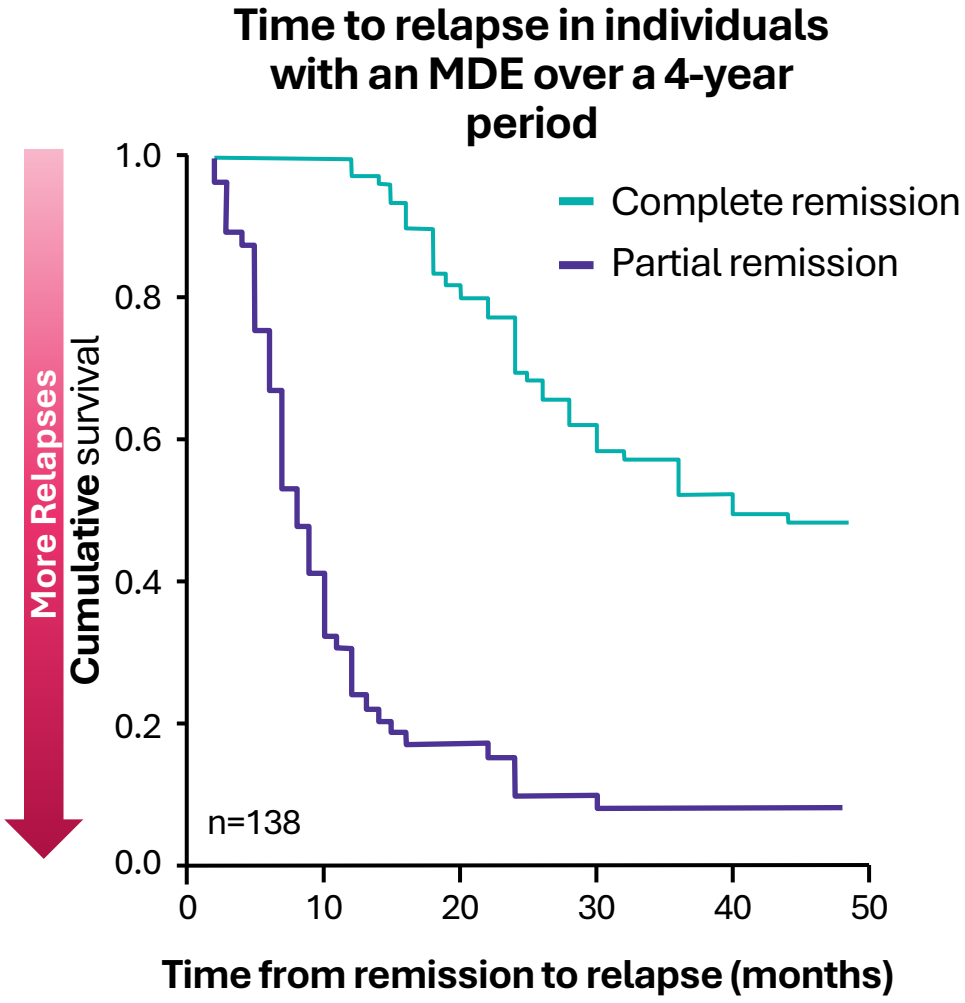


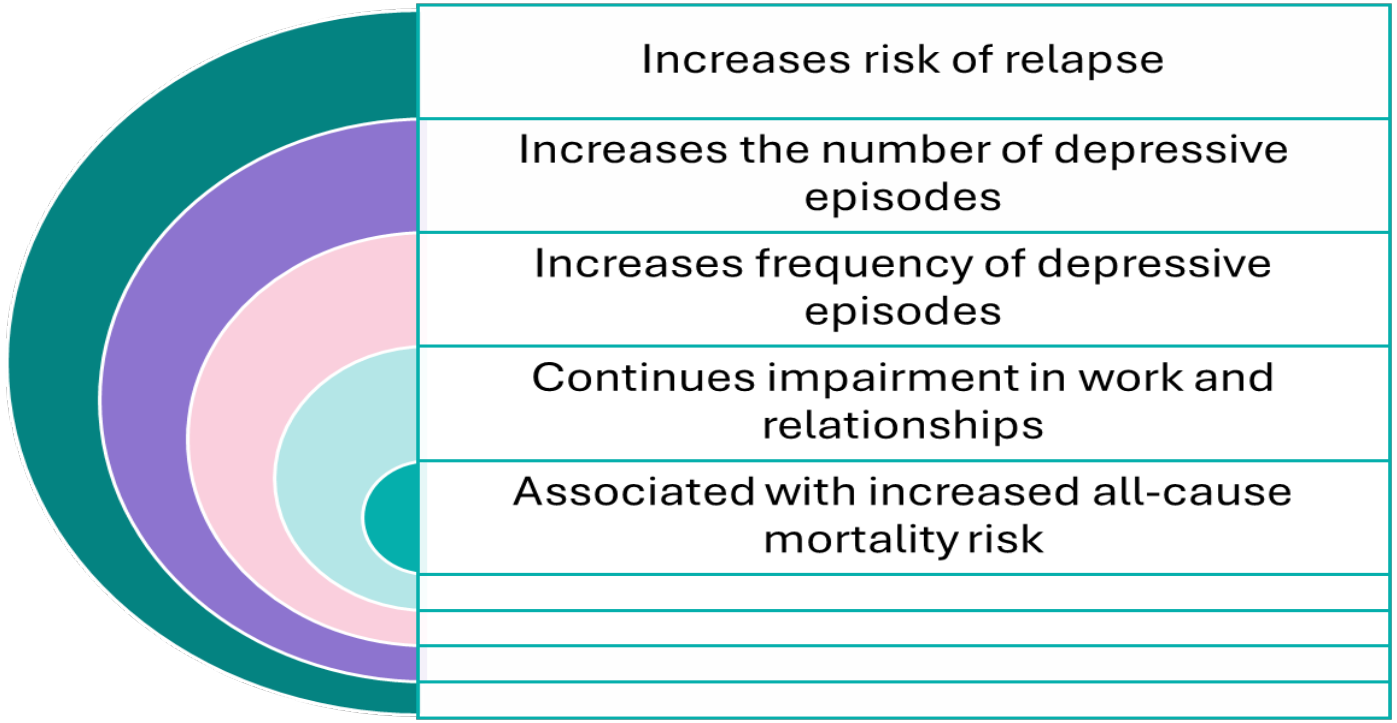
The majority of participants in STAR*D remained symptomatic after receiving a first-line antidepressant as monotherapy for up to 14 weeks.

QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40. Gülpen J, et al. *BMJ Ment Health*. 2023;26(1):1-9.

Settling for Partial Response Worsens Outcomes

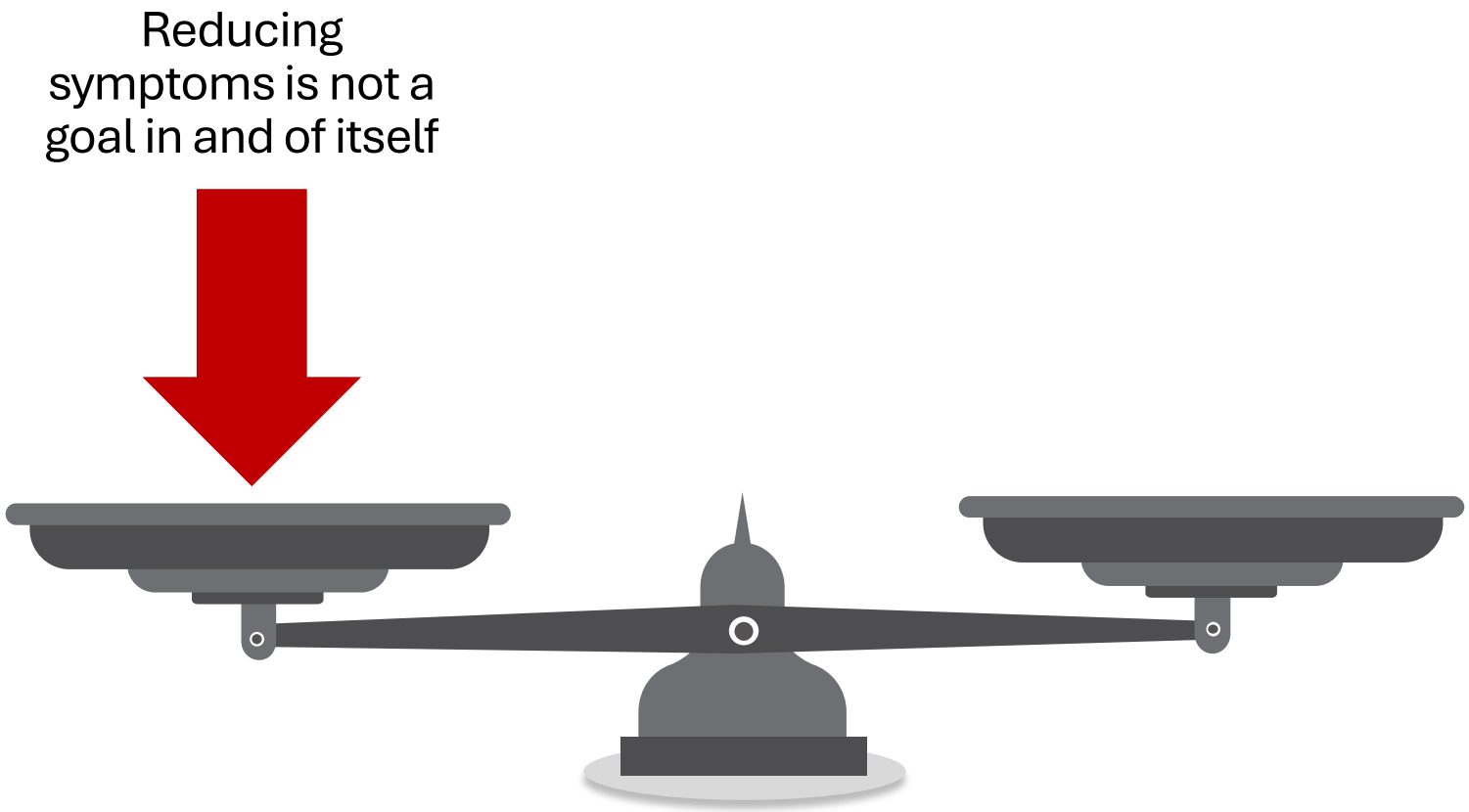




MDE = major depressive episode.

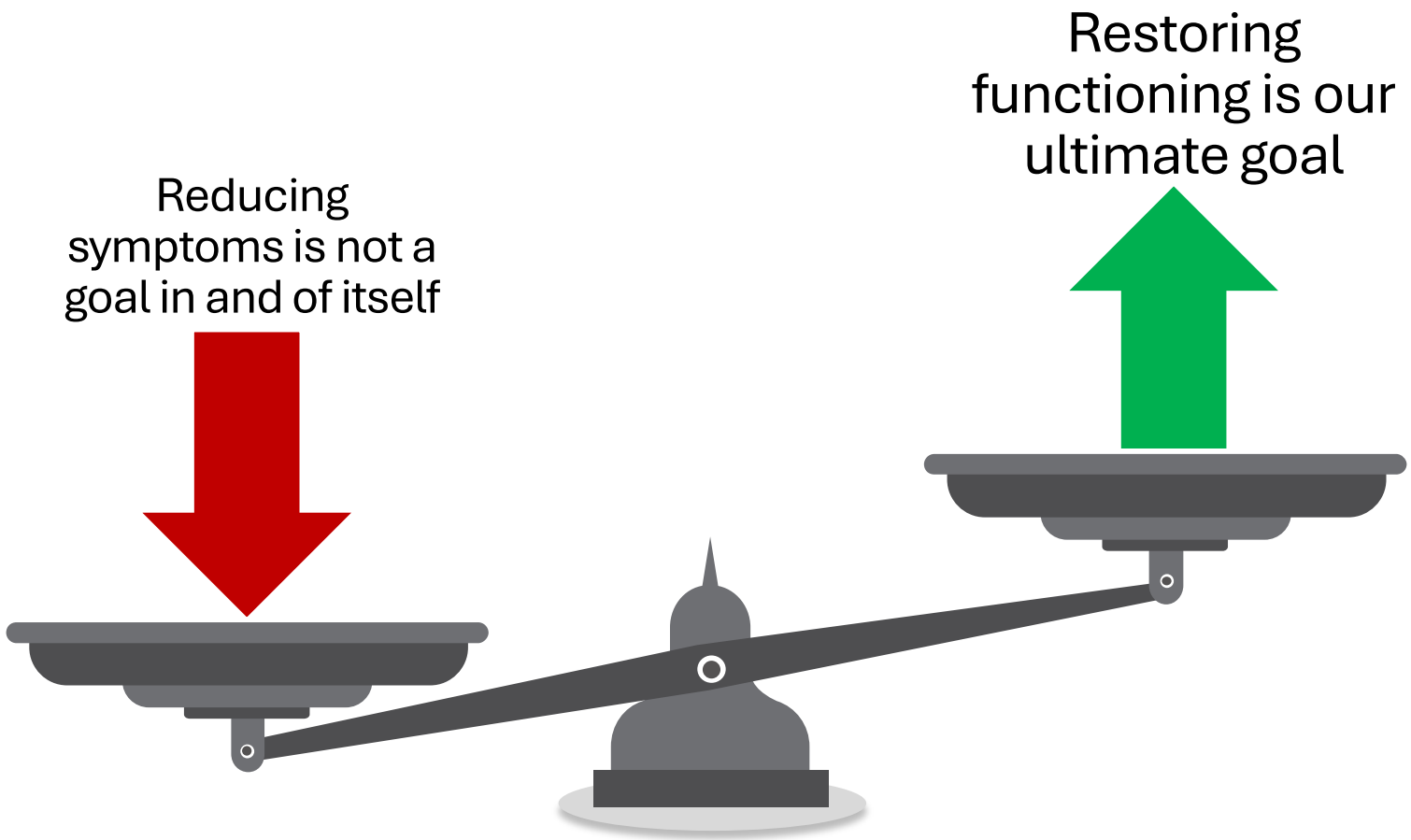
Judd LL, et al. *Am J Psychiatry*. 2000;157(9):1501-1504. McLaughlin KA. *Prev Sci*. 2011;12(4):361-371. Hare DL, et al. *Eur Heart J*. 2014;35(21):1365-1372. Murphy JM, et al. *Arch Gen Psychiatry*. 1987;44(5):473-480. Miloyan B, Fried E. *World Psychiatry*. 2017;16(2):219-220. van Dooren FE, et al. *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.

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.

Key Learning Points

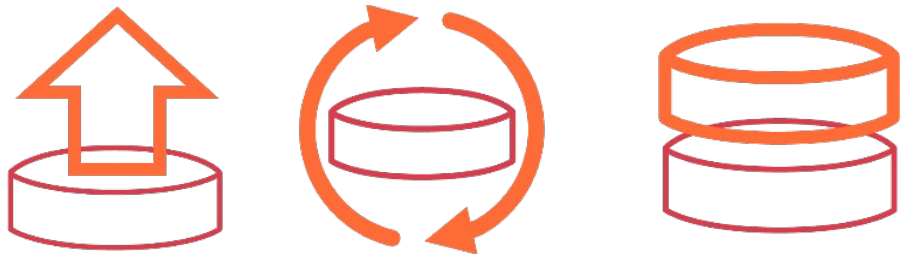
- Results of the STAR*D trial indicated that **the majority** of patients with MDD **remained symptomatic after** first-line **antidepressant monotherapy** for up to 14 weeks
- **Partial response** leaves patients at **higher risk of relapse** and **recurrence** and may increase **all-cause mortality**
- The **goal of treatment** is to **restore function** and quality of life; symptom reduction is not enough

Meet Scott

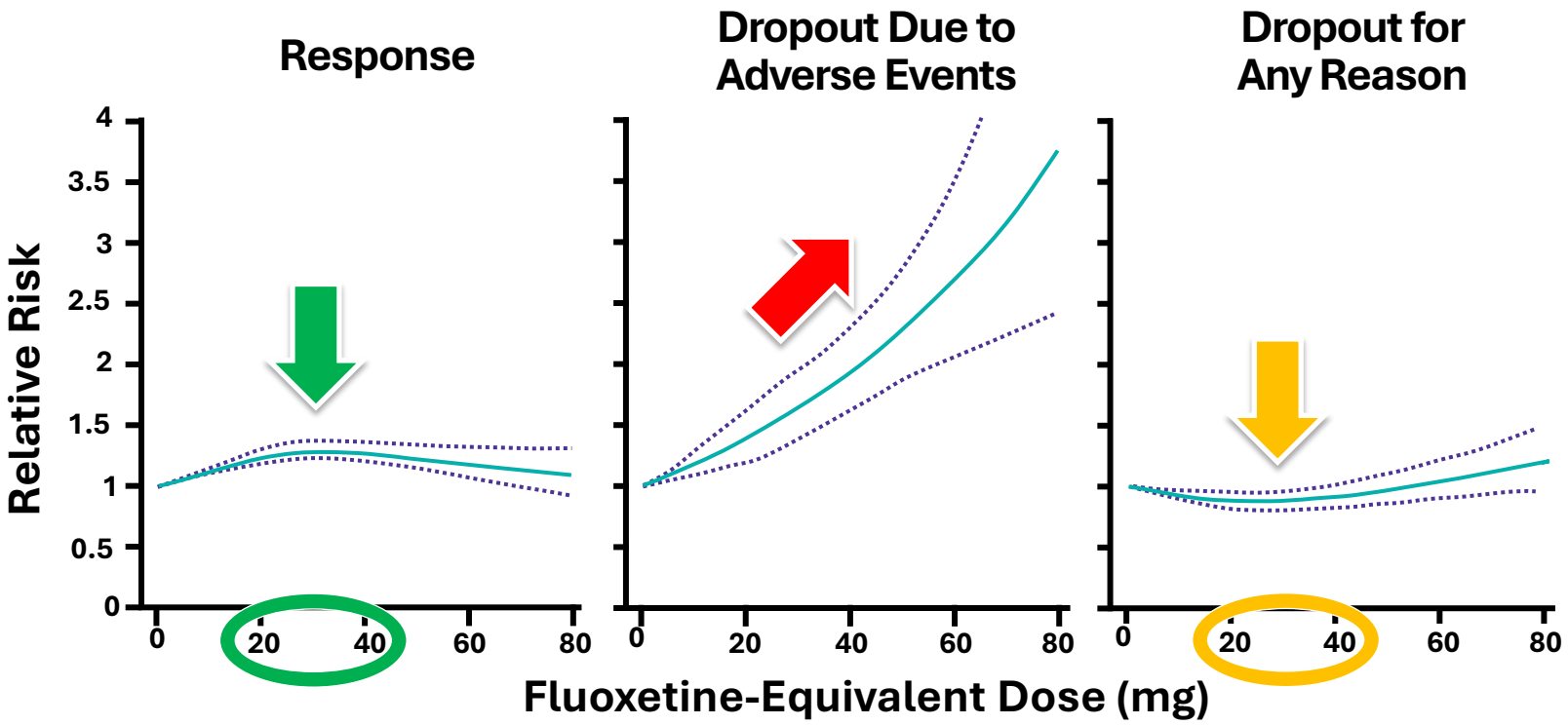
Patient Advocate

Strategies to Improve Treatment Response in MDD

To Switch or Add? ...That Is the Question



The Optimal Dose of SSRIs Is Not Always the Maximum Dose



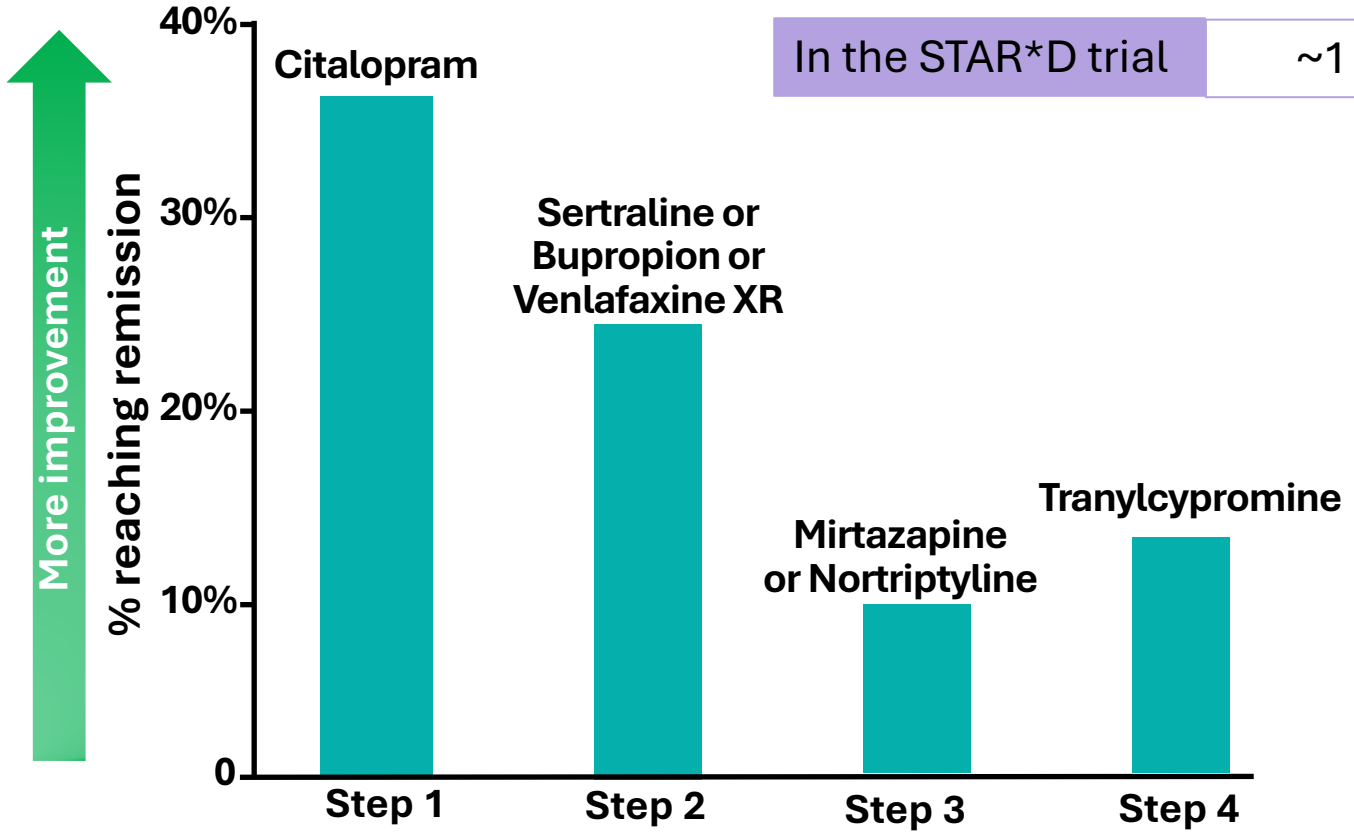
Approximate Optimal Doses	
Citalopram	20-40 mg
Escitalopram	10-20 mg
Fluoxetine	20-40 mg
Paroxetine	17-34 mg
Sertraline	50-100 mg

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.

Switching Antidepressants Produces Diminishing Returns



In the STAR*D trial ~1 in 3 reached remission with first study drug

Among those who switched treatments, remission rates either decreased or did not significantly improve

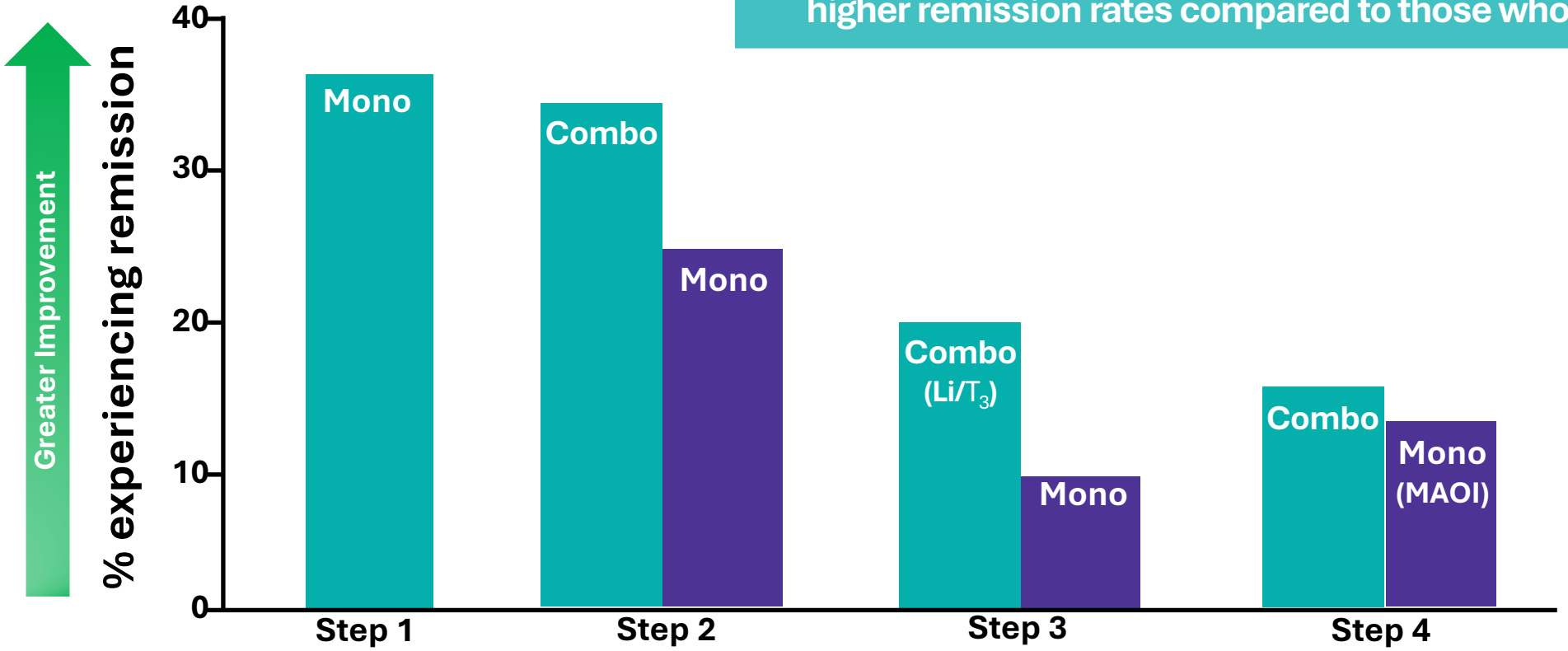
Out-of-class switches **did not improve** outcomes vs within-class switches

XR = extended release.

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.

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.

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)

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 was:
"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.

Potential Neurobiological Rationales for Use of Atypical Antipsychotics in MDD

Receptor Activity	Potential Effects
5-HT_{1A} partial agonism	Increases dopamine in medial PFC; anxiolytic & antidepressant effects
5-HT_{2A} antagonism	Increases DA in PFC, increases NE release; antidepressant effect
5-HT_{2C} antagonism	Increases dopamine and norepinephrine in cortex; antidepressant effect
5-HT_{7} antagonism	Enhances serotonin and glutamate release; antidepressant & procognitive effects
α1 antagonism	Similar to (and can be synergistic with) 5-HT_{2A} antagonism
α2 antagonism	May enhance underactive noradrenergic tone (eg, low energy, cognition)
D_1 Modulation	May indirectly increase glutamate signaling; ↑ learning, reward, neuroplasticity
D_2 partial agonism	May play a role in affect and cognition
D_3 partial agonism	May increase signaling in reward pathway and impact mood, cognition

…and many, many others likely play a role!

The non-dopamine receptor binding effects of antipsychotics may be the most important for MDD

Hot Take!

PFC = prefrontal cortex; DA = dopamine; NE = norepinephrine.

Goldberg JF, et al. *Practical Psychopharmacology.* Cambridge University Press; 2021:17-19. Gross G, et al. *Handb Exp Pharmacol.* 2012;(213):167-210. Leggio GM, et al. *Eur J Pharmacol.* 2013;719(1-3):25-33. Yamamoto K, et al. *Psychiatry Clin Neurosci.* 2014;68(1):1-20. Uys MM, et al. *Frontiers in Psychiatry.* 2017;8:144. Arnsten AFT, et al. *Neurobiology of Stress.* 2015;1: 89-99. Vanover KE, et al. *Nature and Science of Sleep.* 2010:139-150.

Key Learning Points

- **STAR*D trial shows** only **1 in 3** patients **reach remission** with first SSRI and suggests that **partial response** may be **better improved** by **adding** a second therapy **rather than switching** to another

- The **maximum dose** for an SSRI **may not be the optimal dose** for a particular patient; **consider tolerability** and **customize** treatment **to the individual**

- **Atypical antipsychotics act at serotonin receptors** as well as dopamine receptors, and this may contribute to their utility for MDD

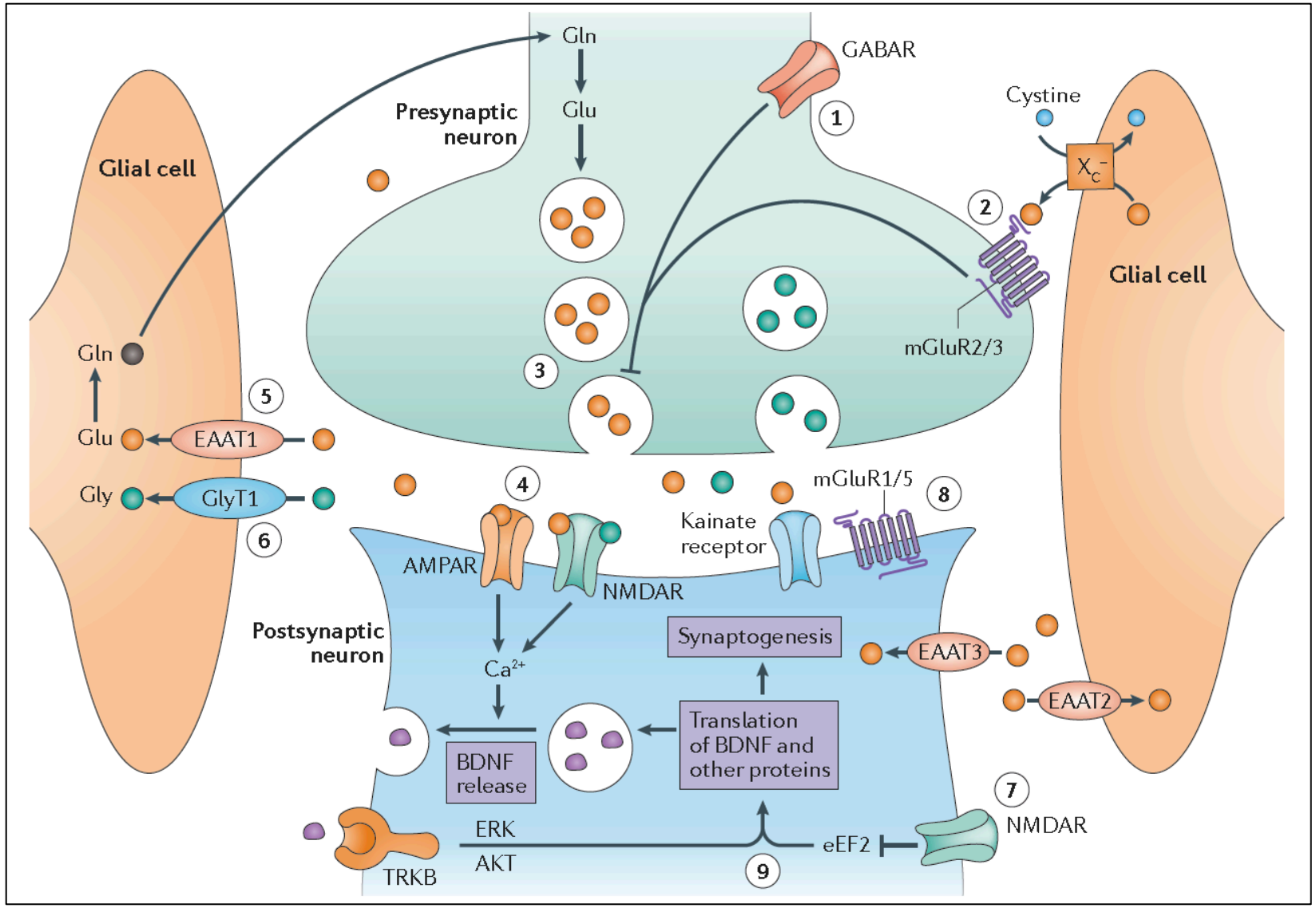
Novel Adjunctive Mechanisms Which We Hope Might Work!

Agents in Phase 2b or 3 Studies for Adjunctive MDD

Molecule	MOA	Comments
CYB003 (deuterated psilocin)	5HT2A agonist	Positive Phase 2b data. Phase 3 planned
JNJ-42847922 (MIN-202) (seltorexant)	Orexin receptor 2 antagonist	Positive Phase 2b data. Phase 3 planned targeting depression and insomnia (and the combination)
ABX-002	Thyroid receptor β agonist	Phase 2 planned
REL-1017 (esmethadone)	NMDA antagonist	Two Phase 3 failures. No active studies, but perhaps in the future
BI-1569912	NMDA NR2B subunit NAM	Phase 2b planned
NBI-1070770	NMDA NR2B subunit NAM	Phase 2b ongoing
NBI-1065845 (TAK-653) (osavampator)	AMPA PAM	Positive Phase 2 data. Phase 3 planned
SEP-363856 (ulotaront)	TAAR1 agonist	Two Phase 3 schizophrenia trial failures, but being pursued for MDD and possibly for schizophrenia
JNJ-67953964 (aticaprant)	Kappa opioid receptor antagonist	Phase 3 failure. Program terminated
NMRA-335140 (navacaprant)	Kappa opioid receptor antagonist	Phase 3 failure (KOASTAL-1). Awaiting data from KOASTAL-2 and -3
ALTO-300	Melatonin agonist and 5HT2C antagonist	Positive Phase 2b data. Phase 3 planned

MOA = mechanism of action; NAM = negative allosteric modulator; PAM = positive allosteric modulator.
National Library of Medicine. Accessed July 31, 2025. https://clinicaltrials.gov/.

Targeting AMPA for MDD



- NMDAR and AMPAR activation leads to synaptogenesis partly through release of BDNF, which stimulates TRKB receptors and activates the AKT and ERK signaling pathways
- NMDAR blockade further stimulates this process by blocking NMDARs on inhibitory GABAergic interneurons, inducing more glutamate release, and greater stimulation of postsynaptic NMDARs and AMPARs
- Animal models indicate that blocking AMPA blocks the antidepressant effects of NMDA antagonists
- **Issues**
  - NMDAR antagonists tend to have relatively short duration of action (ketamine or esketamine), and some do not respond to or tolerate dextromethorphan/bupropion
  - AMPAR agonists and AMPAR PAMs have some limitations, such as insufficient potency, risk of seizure, and bell-shaped dose–response

NMDAR = N-methyl-d-aspartate receptors; AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors; TRKB = tropomyosin-related kinase B receptor; ERK = extracellular signal-regulated kinase.

Murrough JW, et al. *Nat Rev Drug Discov*. 2017;16(7):472-486. Hara H, et al. *Pharmacol Biochem Behav*. 2021;211:173289.

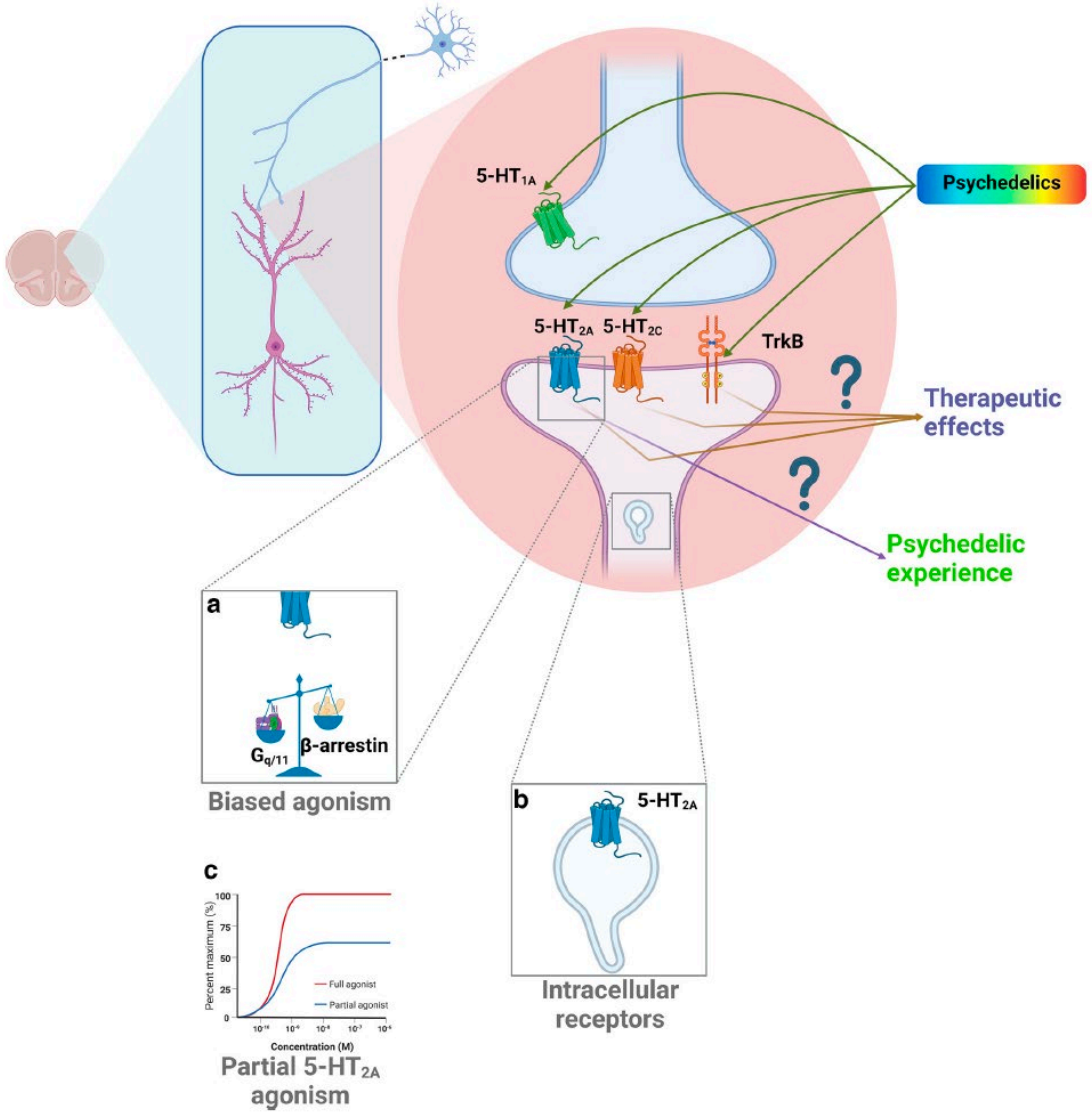
NBI-1065845 (TAK-653): An AMPA PAM for MDD

- **NBI-1065845 (TAK-653):** By identifying an AMPAR PAM with minimal agonist activity, scientists avoided issues of seizure induction and bell-shaped response curves seen with AMPAR agonists, and without any of the dissociative effects of ketamine
- **The Savitri Phase 2b Trial:** Enrolled 183 adults with a primary diagnosis of MDD and inadequate response to current antidepressant treatment
- **Results:** The study met its endpoints—a statistically significant change from baseline in MADRS total score at day 28, the primary endpoint, and day 56, the secondary endpoint
  - The least squares mean differences from baseline in MADRS total score for NBI-1065845 was an improvement over placebo of -4.3 (*P*=0.0159) and -7.5 (*P*=0.0016) at day 28 and day 56, respectively, for one of the doses; and a trend toward improvement over placebo of -3.0 (*P*=0.0873) and -3.6 (*P*=0.1082) at day 28 and day 56, respectively, for another dose
- **Tolerability:** NBI-1065845 was generally well tolerated, with the most common adverse event being headache. The adverse event profile for both doses of NBI-1065845 was comparable to placebo. There were no deaths or serious adverse events. The discontinuation rates were low throughout the study
- **Phase 3 study initiated in January 2025:** Adults with primary Dx of recurrent MDD (moderate or severe) or persistent depressive disorder & inadequate response to oral antidep in the current episode for at least 8 weeks

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; MADRS = Montgomery-Åsberg Depression Rating Scale.

Hara H, et al. *Pharmacol Biochem Behav*. 2021;211:173289. PR Newswire. April 23, 2024. Accessed August 2025. https://www.prnewswire.com/news-releases/neurocrine-biosciences-reports-positive-phase-2-data-for-nbi-1065845-in-adults-with-major-depressive-disorder-302123889.html.

How Psychedelics Work



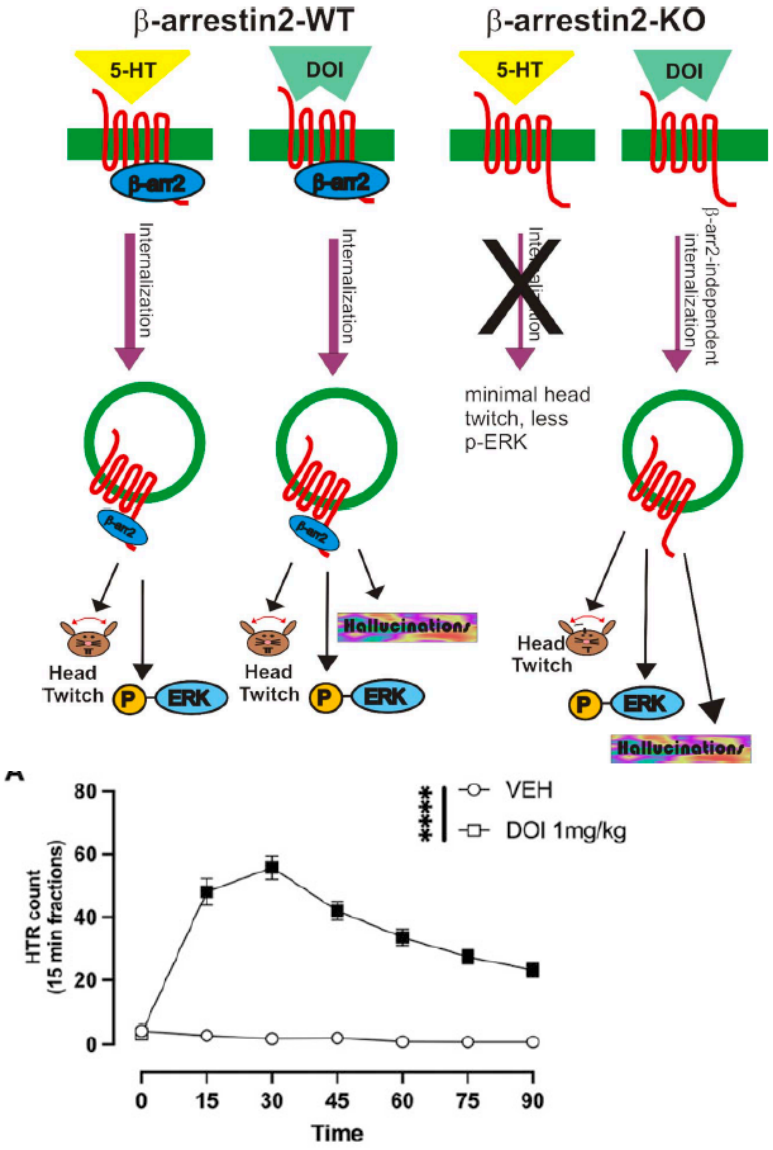
1. LSD and psilocybin bind to multiple 5-HT receptors, and are agonists of varying potency at all of these receptors
   - 5-HT_{2A} receptor activation leads to changes in neuronal growth and is not well defined, but appears to involve TrkB, mechanistic target of rapamycin (mTOR), and AMPA receptor signaling
2. The psychedelic, antidepressant, and neuroplasticity effects in animal models are blocked by 5-HT_{2A} antagonists (eg, ketanserin), leading to the conclusion that 5-HT_{2A} receptor stimulation must be a core aspect of the MOA
3. Issue: Why don't certain 5-HT_{2A} agonists (eg, lisuride) induce psychedelic effects or exhibit antidepressant properties?
   - Answer: The actions of psychedelics occur at intracellular 5HT_{2A} receptors, not those on the cell surface, so lipophilicity correlates with plastogenicity
   - Question: Psychedelics exhibit effects on G-protein-dependent and independent intracellular pathways, but are both necessary for antidepressant actions? (Does one need to trip?)

LSD = lysergic acid diethylamide.

Cameron LP, et al. *J Neurosci*. 2023;43(45):7472-7482. Vargas MV, et al. *Science*. 2023;379(6633):700-706.

Psychotropic Actions at G-Protein Coupled Receptors:
Example of agonist actions at $5HT_{2A}$ receptors

1. $5HT_{2A}$ Receptor Activation: Agonists stimulate the G-protein pathway but also induce recruitment of the scaffolding protein Beta arrestin2 (βArr2) that results in internalization of the ligand-receptor complex.
2. The role of βArr2: The absence of βArr2 greatly attenuates many 5-HT induced downstream events at $5\text{-}HT_{2A}$ receptors, including internalization, head twitch response.
3. Animal correlate of hallucinations
   - βArr2 knockout (KO) mice: Assays indicate that it is recruitment of the βArr2 pathway that is involved with the psychedelic properties of traditional $5HT_{2A}$ agonists (e.g. LSD, psilocybin). The animal analog of the psychedelic property is the head-twitch response (HTR): βArr2 KO mice have minimal HTR from $5HT_{2A}$ agonists
   - DOI: The experimental ligand DOI (2,5-Dimethoxy-4-iodoamphetamine) is able to induce HTRs by βArr2 independent methods and is often used as a comparative model



KO = knockout; HTR = head-twitch response.

Abbas A, Roth BL. *Proc Natl Acad Sci U S A*. 2008;105(3):831-832. Jaster AM, González-Maeso J. *Methods Mol Biol*. 2023;2687:65-76.

CYB003: MDD Adjunctive Data

1. **Method:** Phase 1/2 randomized, double-blind study of adults with moderate to severe MDD (≥ 21 on the MADRS) with inadequate response to current antidepressant. Patients were randomized across three cohorts with 12 patients per cohort. N=36 were randomized to placebo or CYB003 at a 1:2 ratio for the first dose (Days 1-21), with all patients receiving CYB003 as the second dose on Day 22.
2. **Efficacy**
   - **Day 21 MADRS:** CYB003 12 mg: difference of 14 points vs PBO, **effect size of 2.15 (*P*=0.0005)** at the end of the double-blind phase

     CYB003 16 mg: difference of 13 points vs PBO, **effect size of 2.54 (*P*=0.008)** at the end of the double-blind phase
   - **Day 21 Response and Remission:** Response rates (≥ 50% decrease in MADRS) were 53.3% and 44.4% for the 12 mg and 16 mg groups, respectively. The remission rates (MADRS ≤ 10) were 20% and 22.2% for the 12 mg and 16 mg groups, respectively, compared to 0% response and remission in the placebo group
   - **Day 42 Response and Remission:** A second dose of CYB003 on Day 22 led to further improvement of the response and remission rates for the 12 mg (78.6% and 78.6%) and 16 mg (75% and 50%) groups, respectively
3. **Tolerability:** Adverse effects were mild or moderate and mostly self-limiting, and no severe or serious AEs occurred.
4. **12 Month OLE:** Of the 36 eligible participants, 21 provided informed consent and were followed up to 12 months from the time of initial dosing. Response rates were 60% and 100% at 12 months and remission rates were 50% and 71% for those receiving 2 doses of 12 mg and 16 mg, respectively. There were no AEs reported, nor any instances of suicidal ideation or behavior.

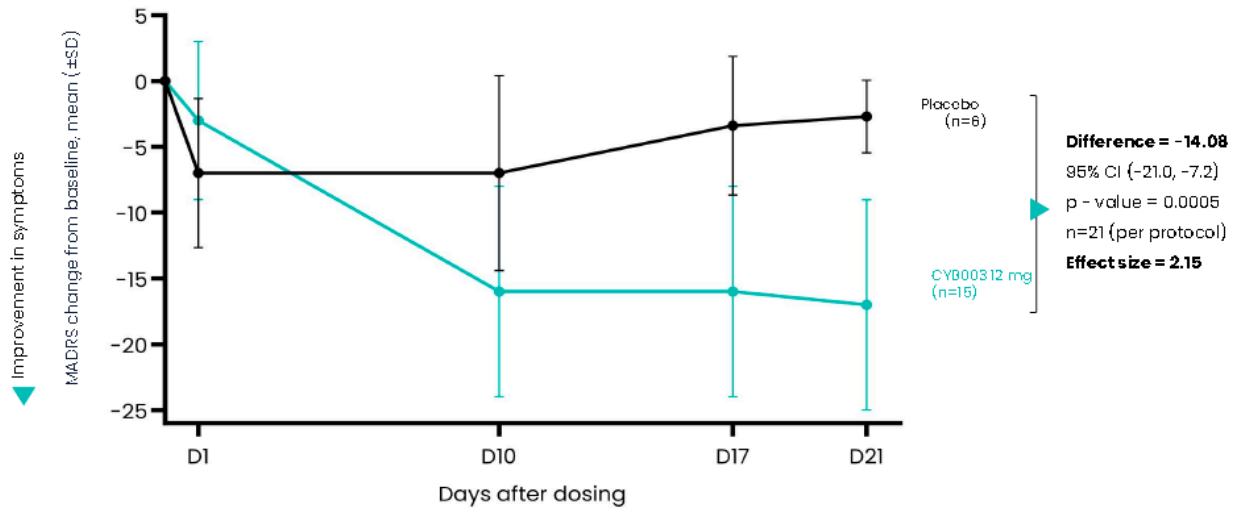
Comments: The reported data are very terse regarding the extent of psychedelic experiences seen in the trial. The presence of such experiences raises the specter of functional unblinding, an issue for interpretation of studies with psychedelics.

PBO = placebo; AE = adverse event.

Inamdar A. Development of deuterated analogues of psychedelics for the treatment of mental health conditions. Presented at: ASCP 2025 Annual Meeting, Abstracts; May 27-30, 2025; Scottsdale, AZ. Poster T24, p. 250.

CYB003: MDD Adjunctive Data

improvement after a single dose of 12 mg



improvement after a single dose of 16 mg

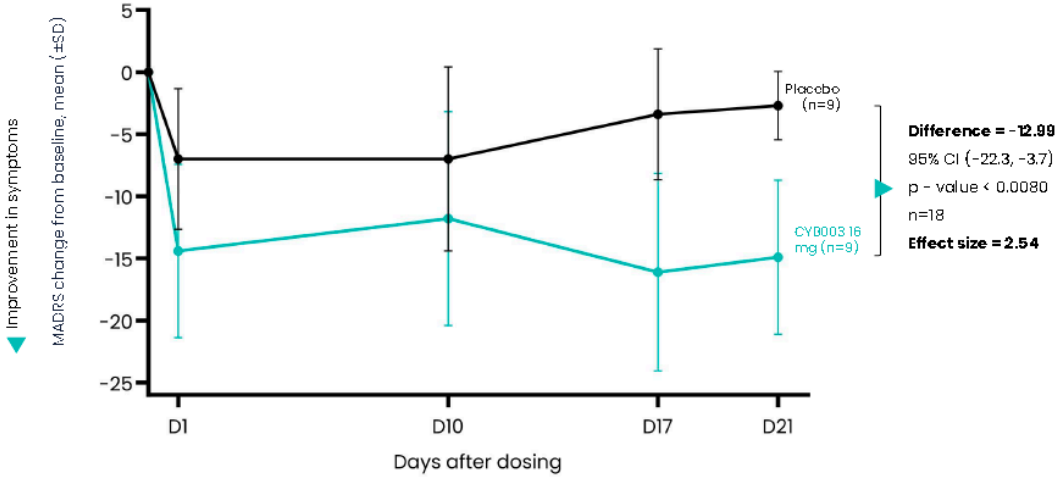


Table 1: Drug-related, treatment-emergent adverse events*

Drug-related, treatment-emergent adverse events*		
	CYB003 n (%)	Placebo n (%)
At least one AE	21 (60.0)	8 (61.5)
Nausea	6 (17.1)	3 (23.1)
Blood pressure increased	5 (14.3)	3 (23.1)
Headache	3 (8.6)	0
Vomiting	2 (5.7)	1 (7.7)
Eructation	1 (2.9)	0
Dizziness	1 (2.9)	0
Affect lability	1 (2.9)	0
Anxiety	2 (5.7)	1 (7.7)
Panic Attack	1 (2.9)	0
Confusional state	1 (2.9)	0
Nasal congestion	1 (2.9)	0
Tachycardia	1 (2.9)	0

*includes participants from all cohorts (CYB003 n=35, Placebo n=13)

Comments on AEs

- Most common AEs were nausea, elevated BP, and headache
- All AEs were mild or moderate in intensity and resolved without intervention
- Increases in BP and HR were transient and resolved without intervention
- No clinically relevant changes in chemistry, hematology markers, or ECG parameters

BP = blood pressure; HR = heart rate; ECG = electrocardiogram.

Inamdar A. Development of deuterated analogues of psychedelics for the treatment of mental health conditions. Presented at: ASCP 2025 Annual Meeting Abstracts; May 27-30, 2025; Scottsdale, AZ; Poster T24, p. 250.

Key Learning Points

- There are many interesting new mechanisms for adjunctive MDD use, but which of these will end up in our hands as clinicians is not clear. We hope several!

  —**Hope is the thing with feathers (Emily Dickinson)**

- **In the meantime, clinicians must become adept at using our currently available agents,** as well as understand their differences and limitations

Approved & Emerging Treatments for Adjunctive Treatment of MDD

Atypical Antipsychotics Approved for MDD Treatment

	Dose	
	Initial	Recommended
Aripiprazole	2-5 mg	5-15 mg
Quetiapine / Quetiapine XR	50 mg	150-300 mg
Olanzapine/fluoxetine	6/25 mg	6/25-12/50 mg
Brexpiprazole	0.5-1 mg	2-3 mg
Cariprazine	1.5 mg	1.5-3 mg

There are no head-to-head clinical studies comparing the safety and efficacy of these products. This chart is descriptive of the FDA-approved indications.

Prescribing Information: Aripiprazole, quetiapine, quetiapine XR, olanzapine/fluoxetine, brexpiprazole, and cariprazine. Drugs@FDA: FDA-Approved Drugs. Accessed March 10, 2024. www.accessdata.fda.gov/scripts/cder/daf/.

Pharmacology of Quetiapine XR

Receptor Affinity, in vitro (k_i, nM)	D_1	D_2	5-HT_{1A}	5-HT_{2A}	α_1	α_2	H_1	M_1	NET
Quetiapine	428	626	1040	38	14.6	617	4.4	1086	927
Norquetiapine	*99.8*	*489*	***45***	***2.9***	*46.4*	*1290*	*1.1*	*38.3*	***12***

Quetiapine XR's half-life is 7 hr while quetiapine's is 6 hr

However, its T_{max} is 6 hr vs quetiapine's 1.5 hr

The active metabolite norquetiapine is believed to contribute to quetiapine's antidepressant effects via antagonism of 5-HT_{1A} and 5-HT_{2A} and norepinephrine reuptake inhibition; but is also quite anticholinergic and antihistaminic

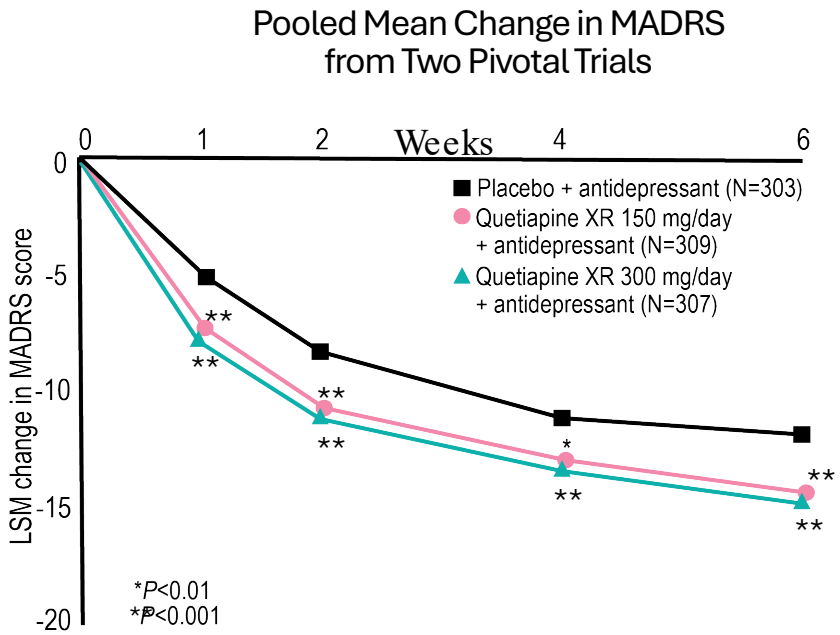
Pro Tip!

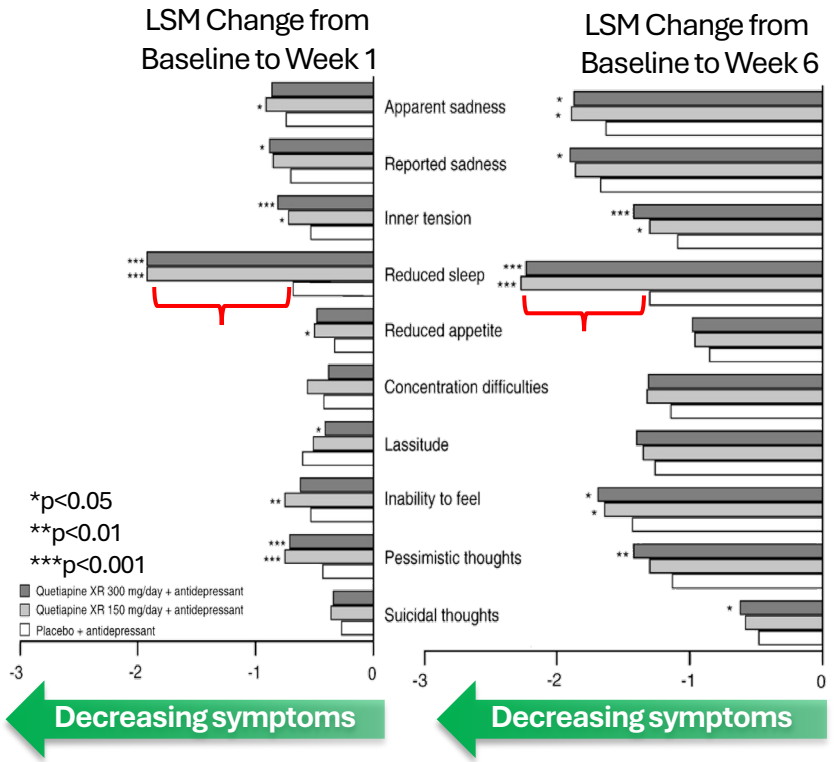
To help with sleep, as well as reduce next-day sedation, patients may need to take it before dinner

NET = Norepinephrine Transporter.

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. *Journal of Affective Disorders*. 2010;127(1-3):19-30. Jensen NH, et al. *Neuropsychopharmacology*. 2008;33(10):2303-2312.

Pivotal Trials of Quetiapine XR for Adjunctive MDD Treatment





Approved doses: 150 and 300 mg in the evening, *without* food (<300 cal)

Recommended to start 50 mg/d for 2 days, then increase to 150 mg

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%

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

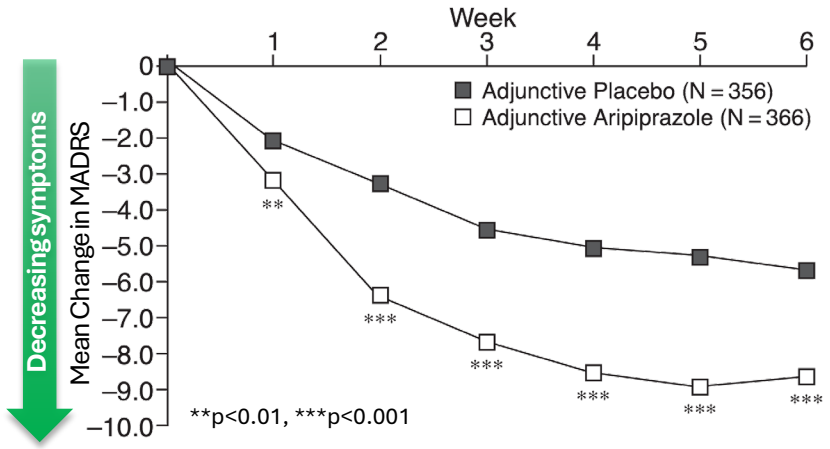
Long-term adverse event data unavailable for quetiapine XR

LSM = least squares mean.

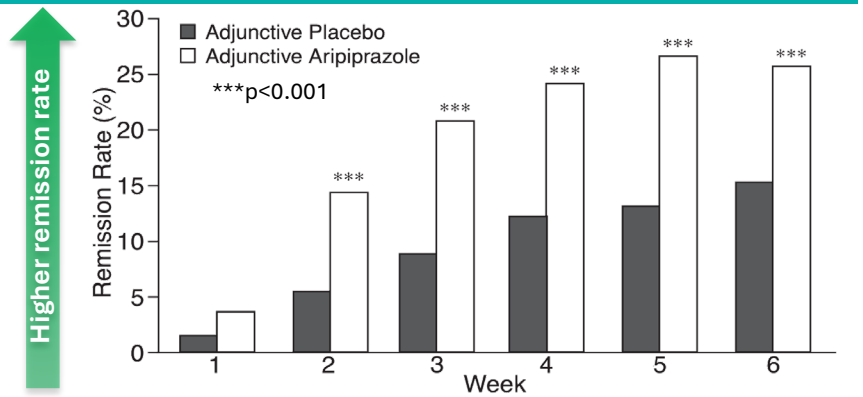
Quetiapine Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed February 28, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022047s048lbl.pdf. Bauer M, et al. *J Affect Disord*. 2010;127(1-3):19-30.

Pivotal Trials of Adjunctive Aripiprazole for MDD

Adjunctive aripiprazole reduced depressive symptoms significantly more than placebo



AND improved remission rates



First medication with monoamine receptor partial agonism and antagonism found effective for adjunctive MDD treatment

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

75-hour half-life; metabolized by 2D6 + 3A4

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%

Adverse events in Open-Label Extension (52 weeks, N=994)	
Akathisia	26%
Fatigue	18%
Weight increase	17%
Restlessness	14%
Somnolence	14%
Insomnia	12%
URI	11%
Nausea	9%
Dizziness	9%
D/C due to AE	23%

Weight gain ≥7% reported in 26%

D/C = discontinuation; URI = upper respiratory infection.

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.

Augmenting with Aripiprazole Is Superior to Switching to or Adding Bupropion

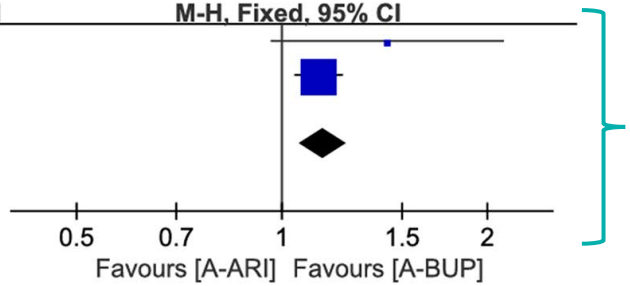
Meta analysis of 5 RCTs of patients (N=4,480) with MDD or TRD

Randomized to:

1. Switch to bupropion
2. Augment antidepressant with **bupropion (A-BUP)**
3. Augment antidepressant with **aripiprazole (A-ARI)**

Study or Subgroup	A-ARI Events	A-ARI Total	A-BUP Events	A-BUP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cheon 2017	34	56	20	47	6.2%	1.43 [0.96, 2.11]
Mohamed 2017	375	505	332	506	93.8%	1.13 [1.04, 1.23]
Total (95% CI)		**561**		**553**	**100.0%**	**1.15 [1.06, 1.25]**
Total events	409		352			

Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 3.41 (P = 0.0007)



Consistent effect of **aripiprazole augmentation** on response rate for 2 RCTs

Key findings from recent meta-analysis

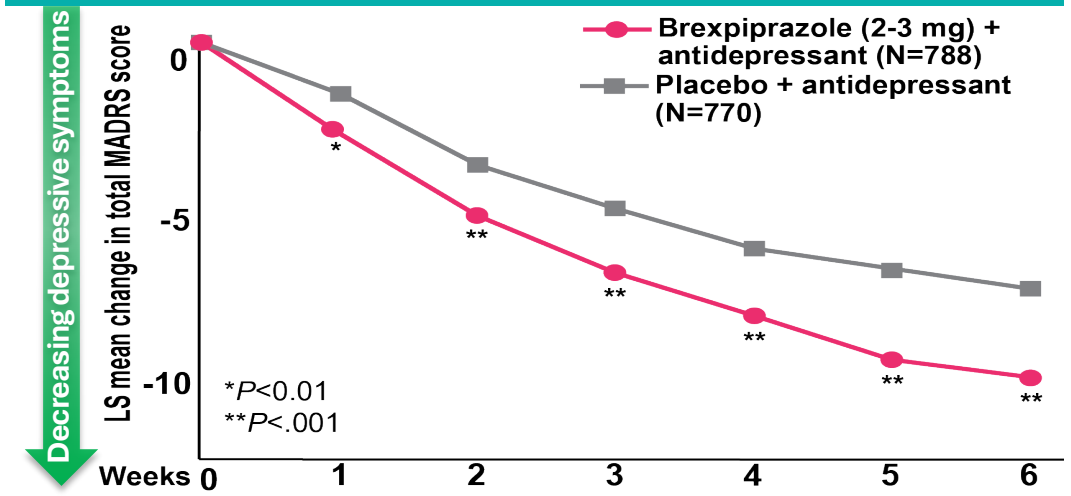
- ☑ **Aripiprazole augmentation** was associated with
  - ⟶ a significantly higher response rate compared to bupropion augmentation
  - ⟶ a significantly higher remission rate compared to switching to bupropion
- ☑ No significant difference in AEs or serious AEs across randomized groups

RCT = randomized controlled trial; TRD = treatment-resistant depression; A-BUP = augment antidepressant with bupropion; A-ARI = augment antidepressant with aripiprazole; CI = confidence interval.

Ji M, et al. *PLoS ONE*. 2024;19(4):e0299020.

Pivotal Trials of Adjunctive Brexpiprazole for MDD

Adjunctive brexpiprazole reduced depressive symptoms significantly more than placebo



	Pooled 2-3 mg	Pooled 2 mg
Response	38% greater than PBO	33% greater than PBO
Remission	30% greater than PBO	35% greater than PBO

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

91-hour half-life; metabolized by 2D6 + 3A4

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%

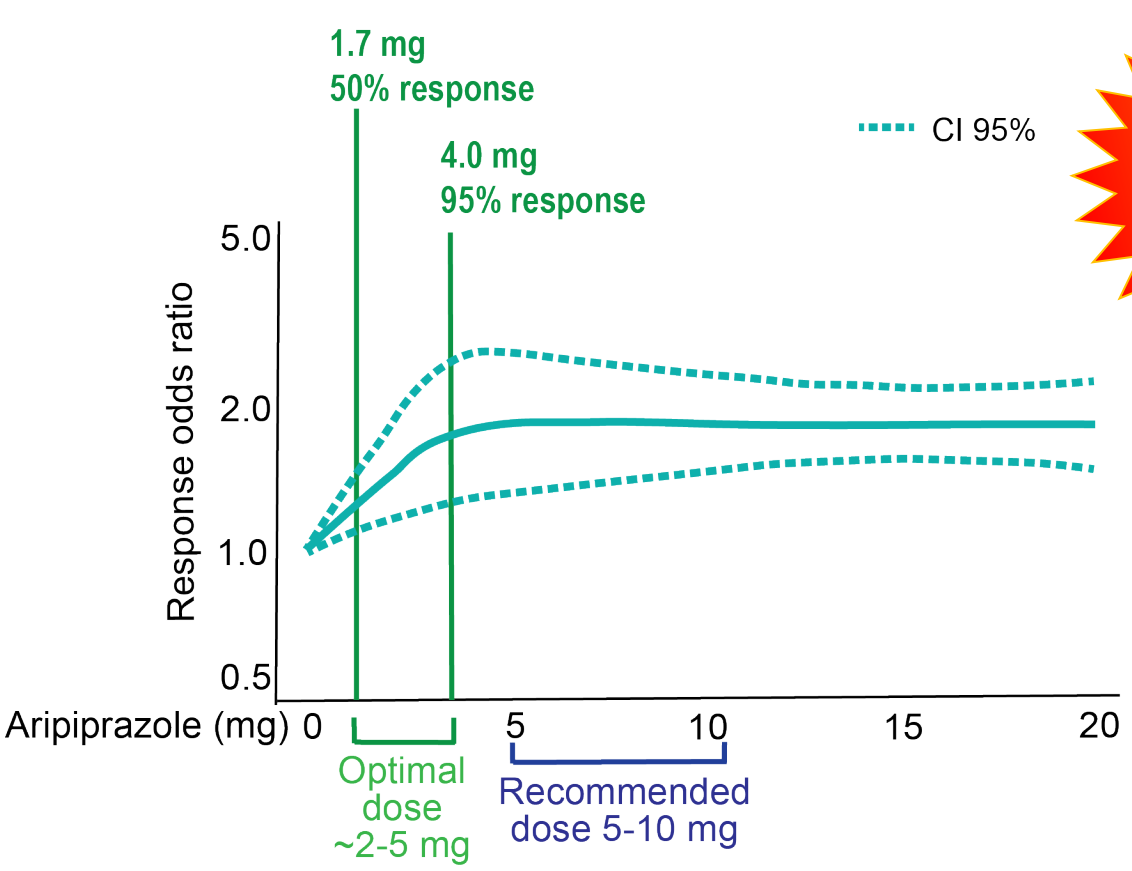
Adverse events in open-label extension (52 weeks, N=2,994)

Weight increase	18%
Somnolence	8%
Headache	7%
Akathisia	7%
Increased appetite	6%
Insomnia	6%
Fatigue	6%
Viral URI	5%
Anxiety	5%
D/C due to AE	9%

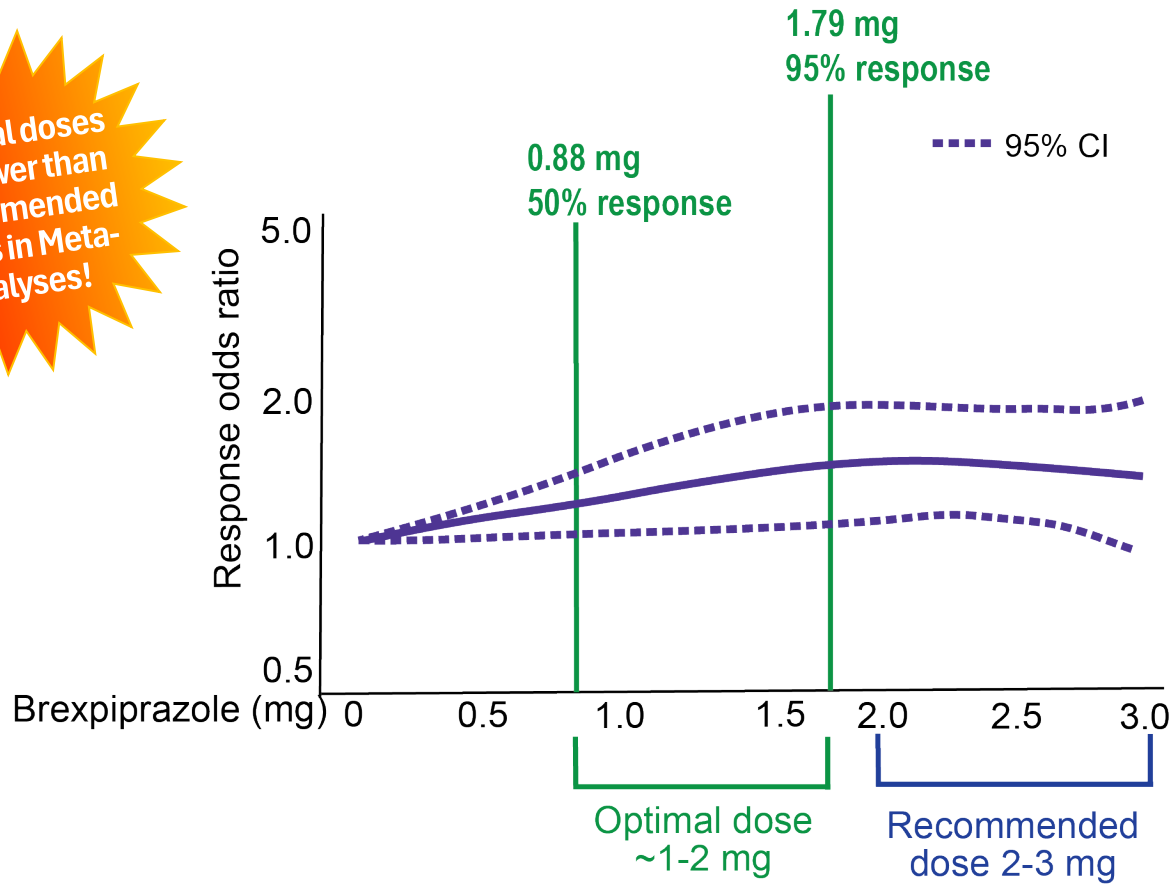
Weight gain ≥7% reported in 26%

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.

Optimal Dose of Adjunctive Antipsychotics for MDD: A Little Dab Will Do Ya!



Optimal doses are lower than recommended doses in Meta-Analyses!



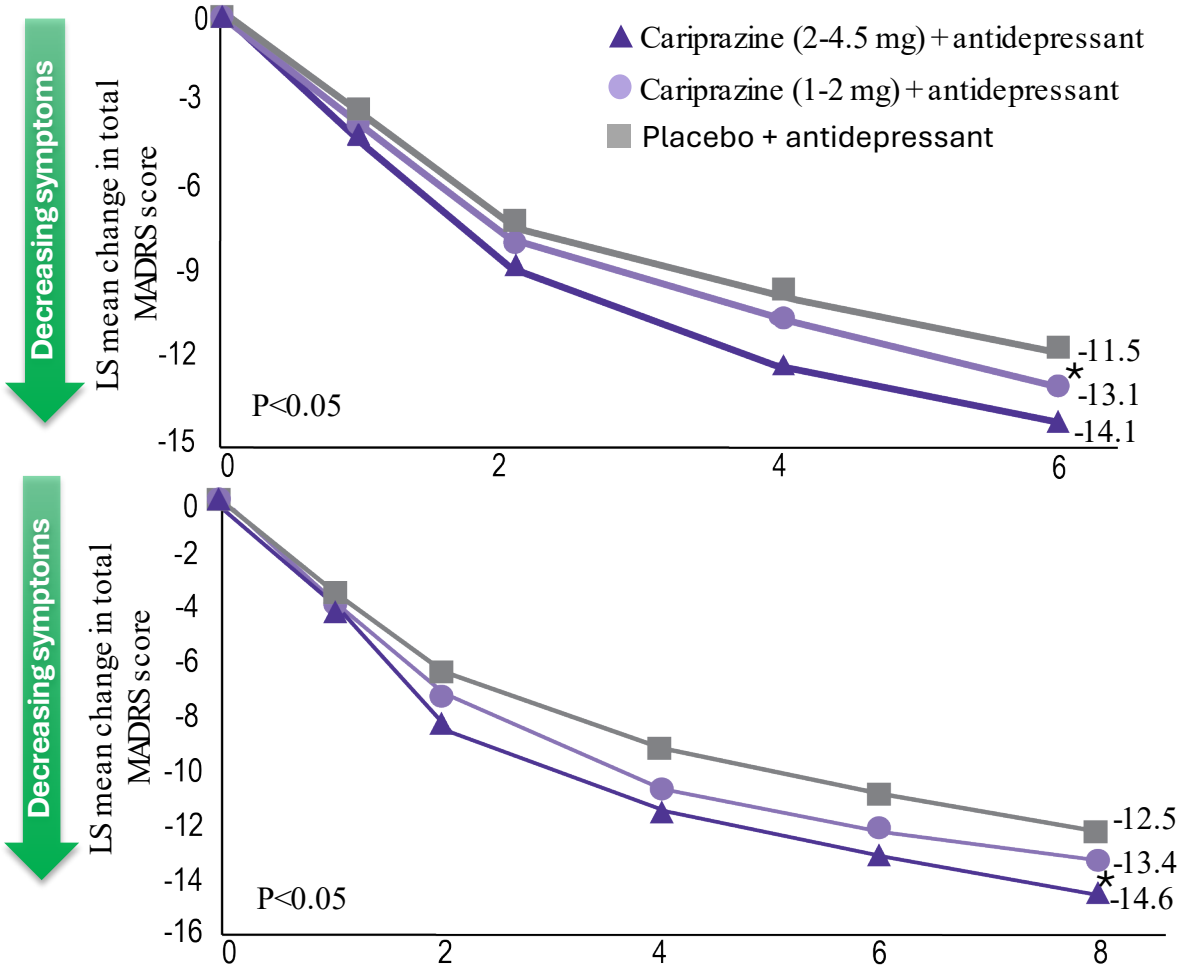
Although individual response varies, higher doses generally do not provide additional benefits

OR = odds ratio; ED50 = 50% effective dose; ED95 = 95% effective dose.

Furukawa Y, et al. *Br J Psychiatry*. 2022;221(2):440-447. Furukawa Y, et al. *Psychiatry Clin Neurosci*. 2022;76(9):416-422.

Pivotal Trials of Adjunctive Cariprazine for MDD

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



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

half-life ~1 week for active metabolite; metabolized primarily by 34A

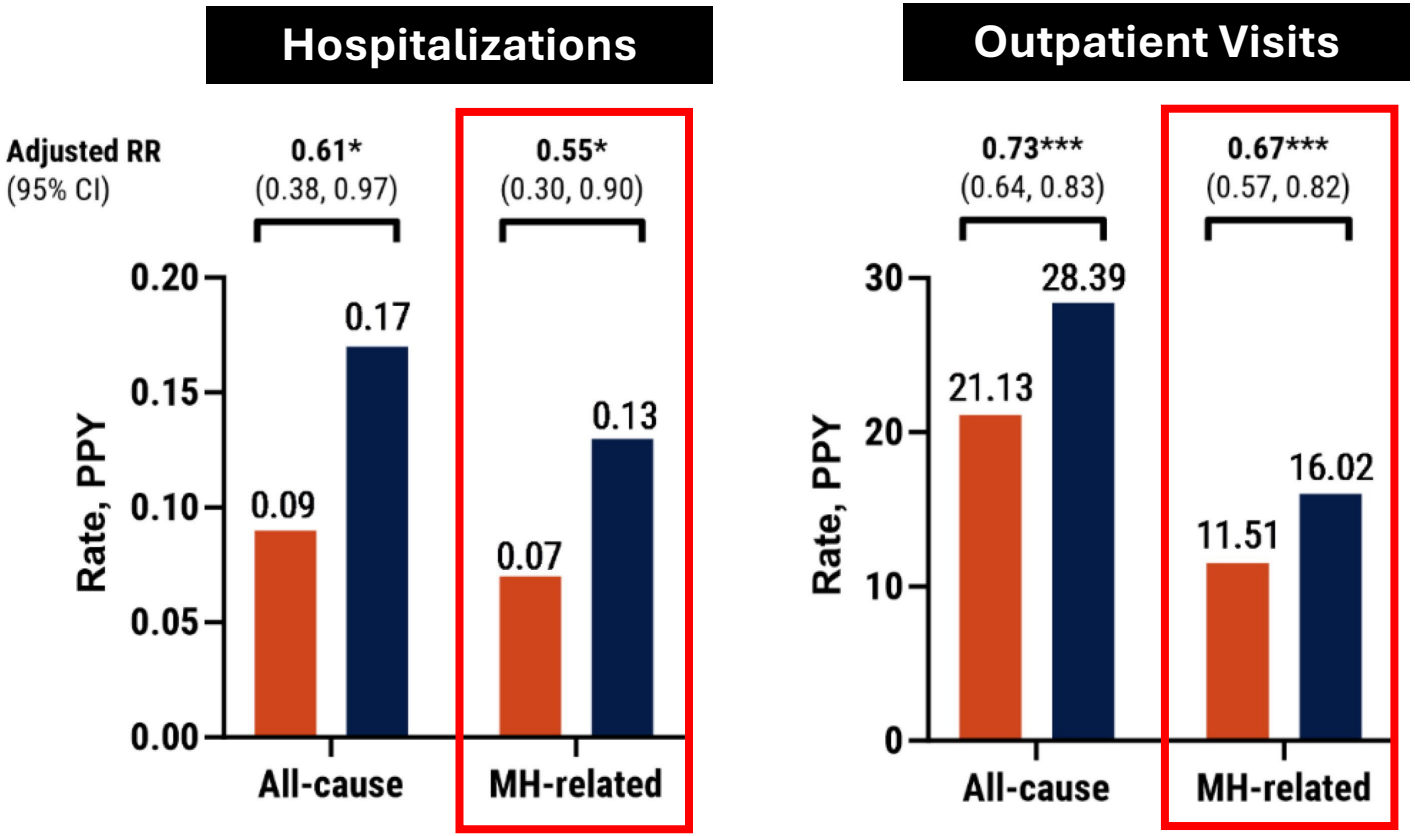
Adverse Events in Pivotal Trials			
	1.5 mg	3 mg	Placebo
Insomnia	9%	10%	5%
Akathisia	7%	10%	2%
Nausea	7%	6%	3%
Somnolence	5%	7%	4%
Weight gain	1.5lb	1.5lb	0.4lb
Weight ≥7%	2%	2%	1%
D/C due to AE	6% pooled		3%

Adverse events in open-label extension (26 weeks, N=345)	
Akathisia	16%
Headache	12%
Anxiety	10%
Insomnia	10%
Restlessness	10%
Weight increase	10%
Fatigue	9%
Nasopharyngitis	9%
Nausea	6%
Dizziness	5%
Sedation	5%
D/C due to AE	14%

Weight gain ≥7% reported in 19%

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.

Retrospective Analysis of Healthcare Resource Utilization Costs Associated with Cariprazine



838

patients received cariprazine

44.7%	55.3%
Initiated as first adjunctive therapy to ADT (n=375)	Initiated as subsequent adjunctive therapy to ADT (n=463)

Those initiating cariprazine first had **significantly lower** rates of MH-related hospitalizations and outpatient visits PPY than those initiating cariprazine subsequently.

Masand PS, et al. *Journal of Medical Economics*. 2025;28(1):235-244.

Dopamine Partial Agonists Have Distinct Pharmacodynamics and Are Not Interchangeable

Cariprazine		Aripiprazole		Brexpiprazole	
0.49 nM	↔	D_2	0.34 nM	↔	0.30 nM
0.085 nM	↑10x ➤	D_3	0.8 nM	↔	1.1 nM
0.58 nM	↔	5-HT_{2B}	0.36 nM	◀ ↓ 5x	1.9 nM
2.6 nM	↔	5-HT_{1A}	1.7 nM	◀ ↑ 14x	0.12 nM
18.8 nM	↓ 6x ➤	5-HT_{2A}	3.4 nM	◀ ↓ 7x	0.47 nM
134 nM	↓ 10 ➤	5-HT_{2C}	15 nM	◀ ↓ 2x	34 nM
111 nM	↓ 3x ➤	5-HT_7	39 nM	◀ ↑ 10x	3.7 nM
-	-	α_{1B}	35 nM	◀ ↑ **200x**	0.17 nM
-	-	α_{2C}	38 nM	◀ ↑ **65x**	0.59 nM
155 nM	↓ 3x ➤	α_{1A}	57 nM	◀ ↑ 15x	3.8 nM
-	-	α_{2A}	74 nM	◀ ↑ 5x	15 nM
-	-	α_{2B}	103 nM	◀ ↑ 6x	17 nM
23.2 nM	↓ 3x ➤	H_1	61 nM	◀ ↓ 3x	19 nM
>1000 nM	↔	M_1	>1000 nM	↔	>1000 nM

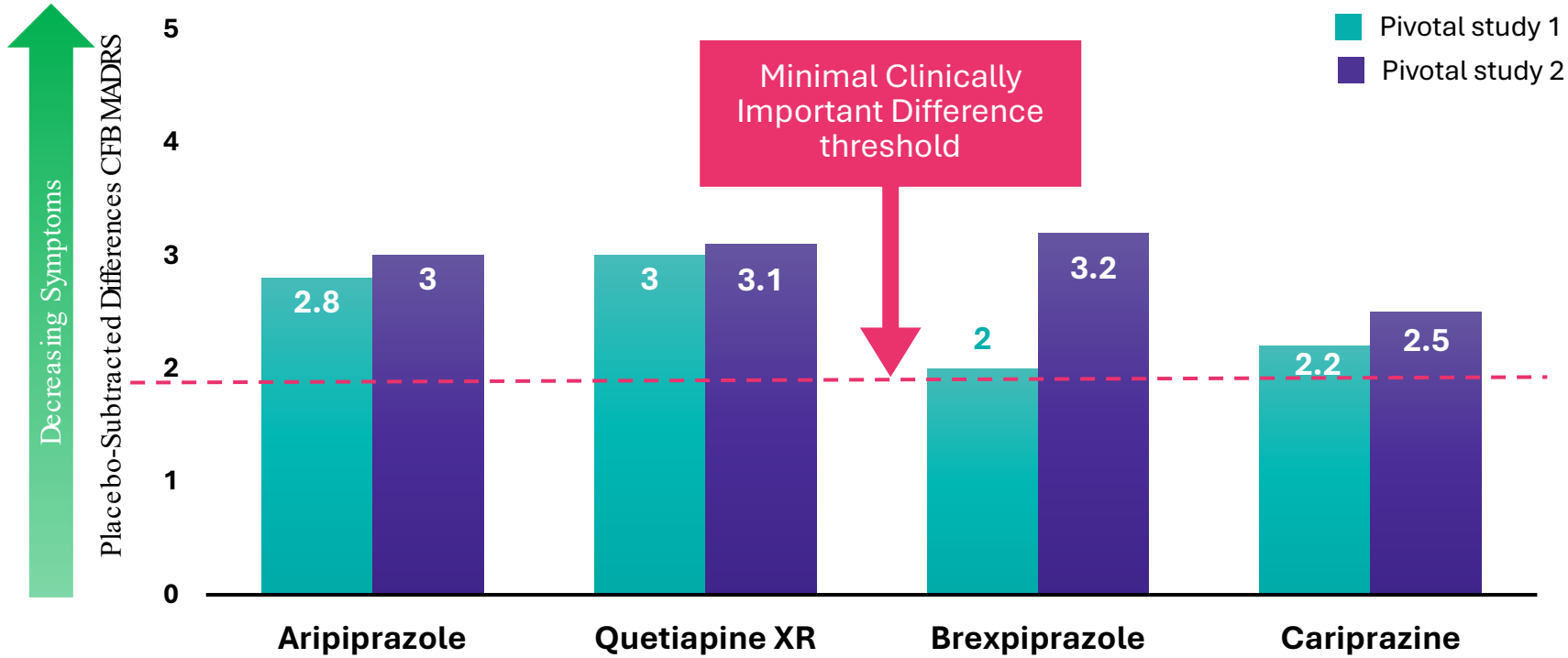
The very different binding affinity profiles of these medications may lead to very different clinical effects

If one adjunct atypical doesn't work, a trial of another may be worthwhile

Citrome L. *Int J Clin Pract*. 2015;69(11):1211-1220. Kiss B, et al. *Drug Design, Development and Therapy*. 2019;13:3229-3248.

Adjunctive Atypical Antipsychotic Pivotal Trials: Placebo-Subtracted Differences

On average, each of the atypical antipsychotics approved for adjunctive treatment of MDD had comparable efficacy in their pivotal trials



Efficacy observed in the clinical trials of one medication ***cannot*** be directly compared to efficacy observed in the clinical trials of another medication

Prescribing Information: Aripiprazole, quetiapine, brexpiprazole, cariprazine. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/. Durgam S. Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomized, Double-blind, Phase 3 Trial. Presented at: 37th Psych Congress Annual Meeting; October 29 - November 2, 2024; Boston, MA. Durgam S, et al. Adjunctive Lumateperone in Patients With Major Depressive Disorder: Results From an Additional Randomized, Double-Blind, Phase 3 Trial. Presented at: 37th Psych Congress Annual Meeting, October 29 - November 2, 2024; Boston, MA. Duru G, et al. Curr Med Res Opin. 2008;24(5):1329-1335.

Common AEs in Pivotal Trials of Approved Doses of Adjunct Antipsychotics in MDD

Aripiprazole	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%

Brexpiprazole	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%

Cariprazine	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%

Quetiapine	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%

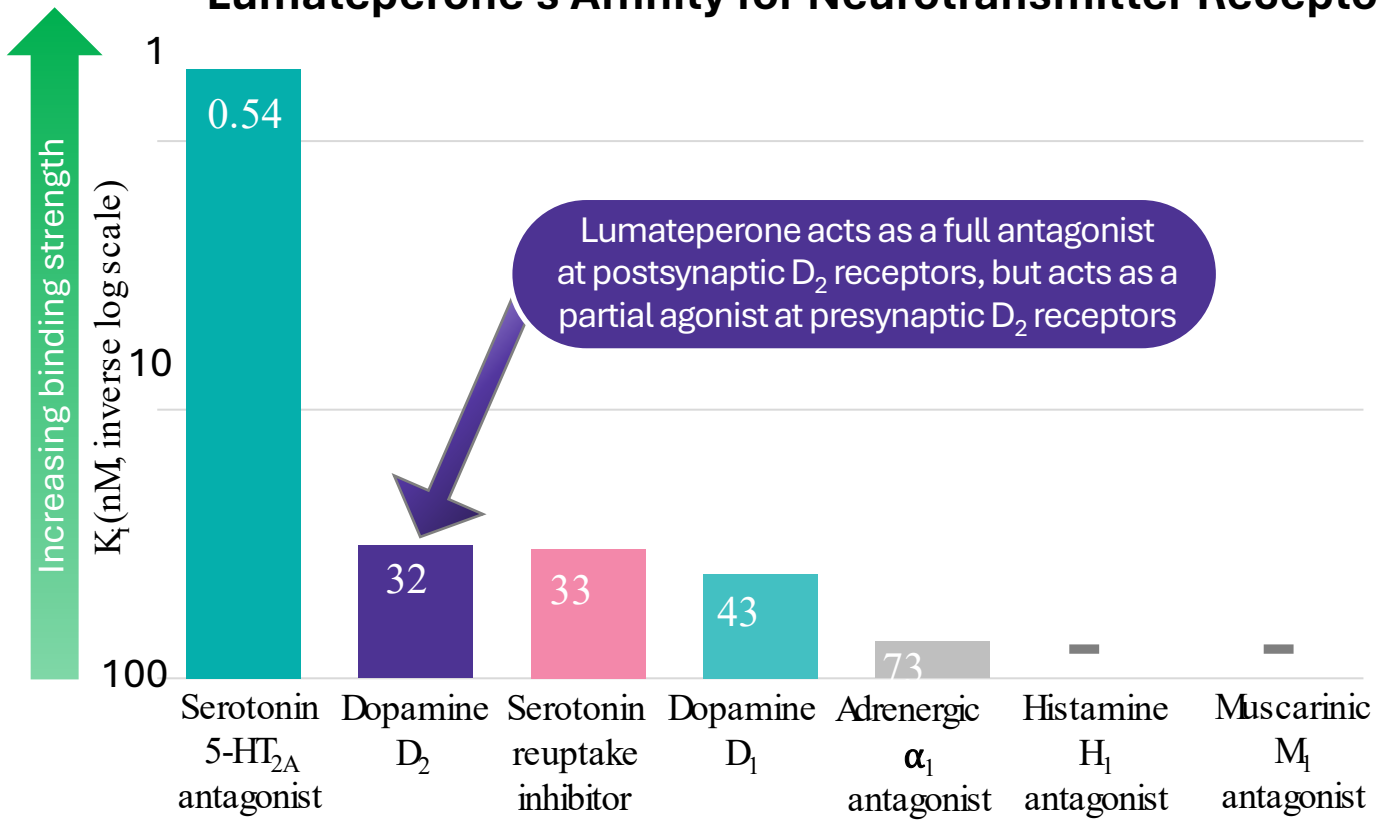
Adverse reaction rates observed in the clinical trials of one medication ***cannot*** be directly compared to rates in the clinical trials of another medication and may not reflect the rates observed in clinical practice.

Prescribing Information: Aripiprazole, brexpiprazole, cariprazine, quetiapine. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/.

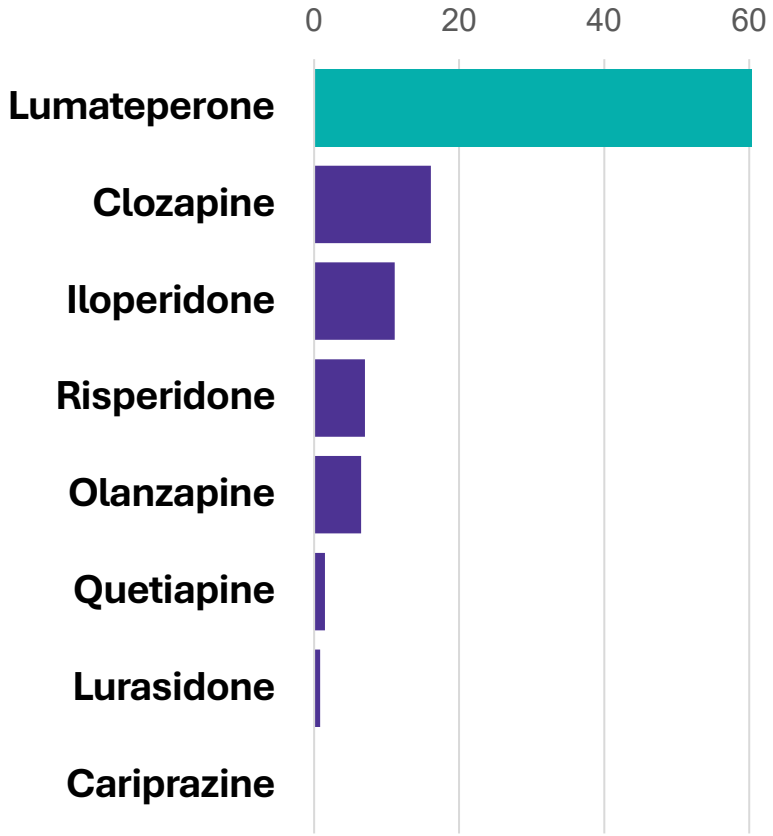
Lumateperone Pharmacology

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



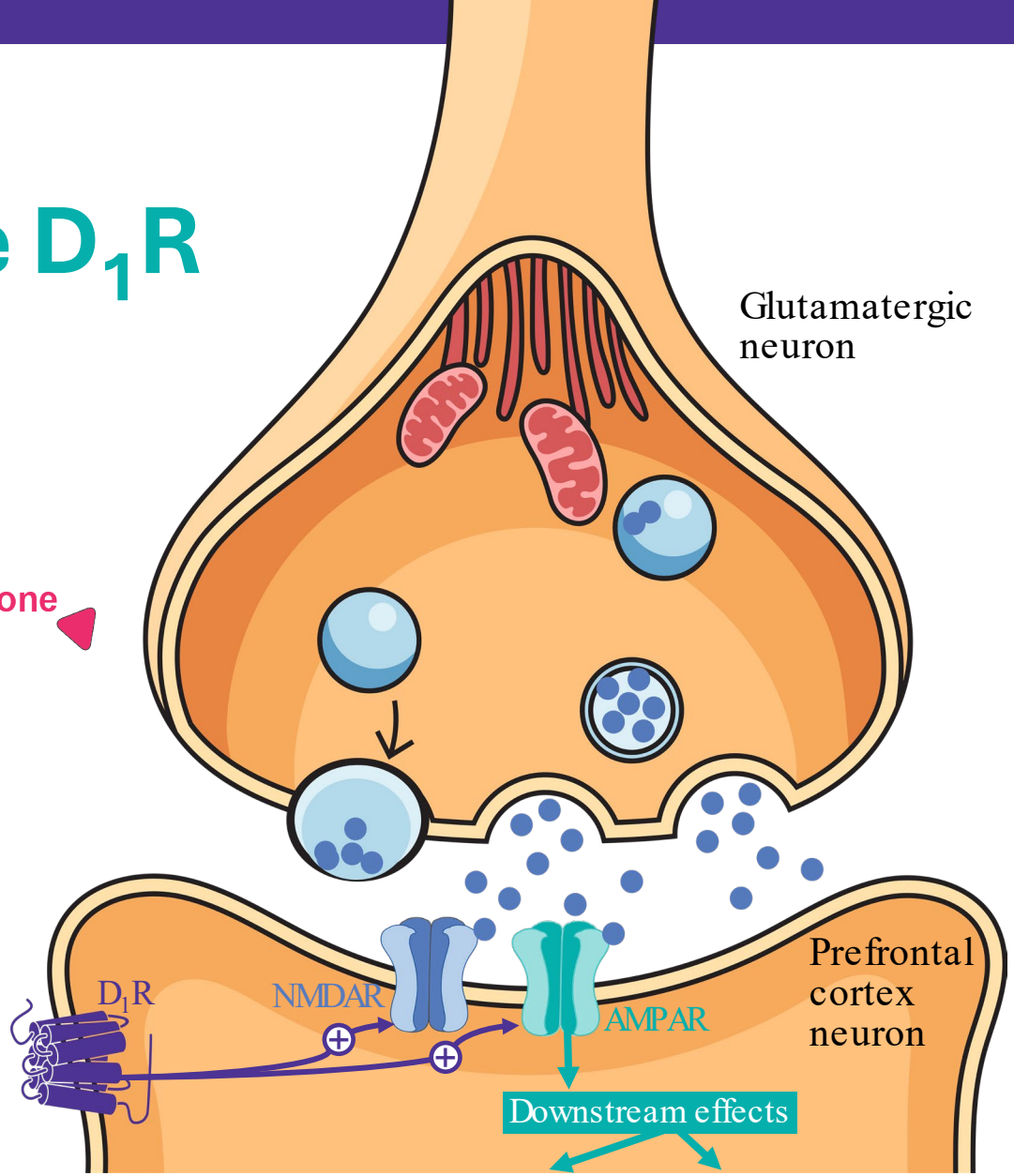
Lumateperone Prescribing information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209500s011lbl.pdf. Li P, et al. *J Med Chem*. 2014;57(6):2670-2682. Kantrowitz JT. *CNS Drugs*. *2020;*34(9):947-959.

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

Scan this QR code to check out a short video that explains the MOA of lumateperone in more detail

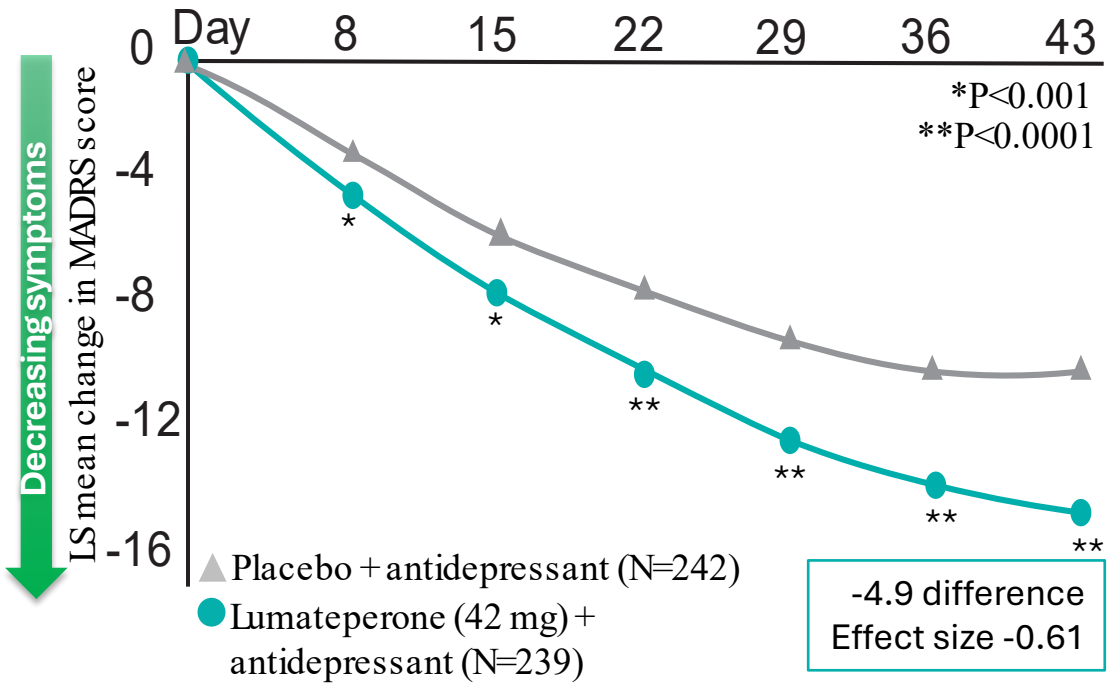


AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor; D1R = D1 dopamine receptor; NMDAR = N-methyl-D-aspartate glutamate receptor.

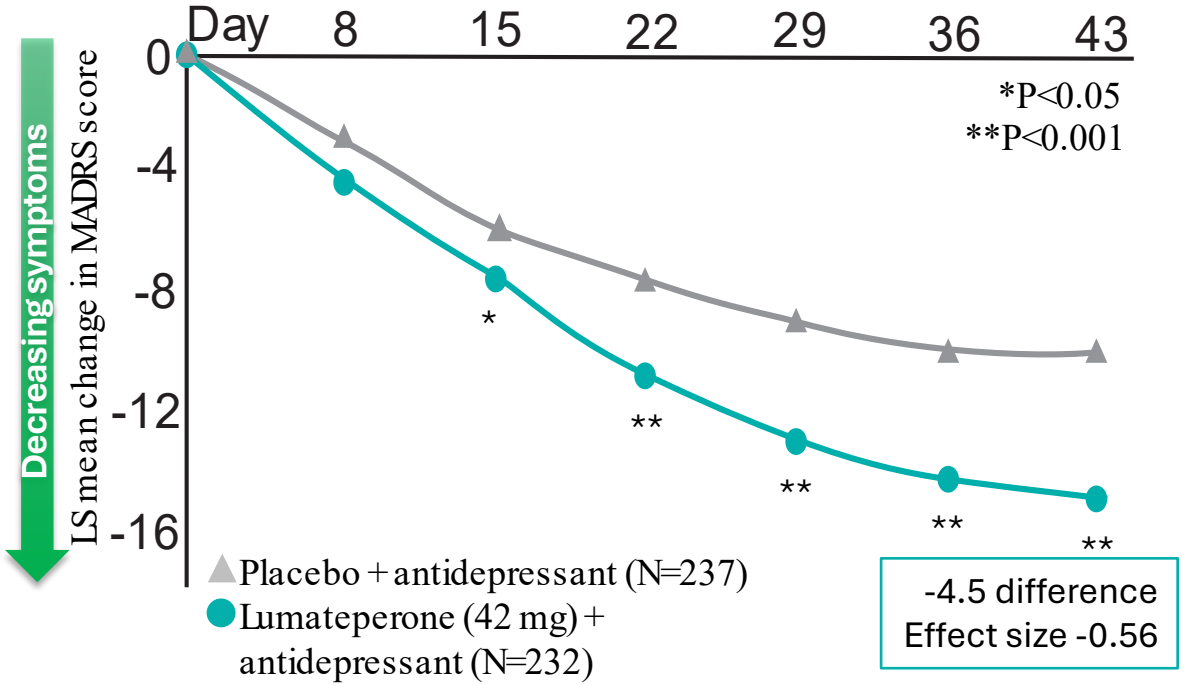
Harvey J, et al. *J Neurosci*. 1997;17(14):5271-5280. Vanover, KE, et al. *European Neuropsychopharmacol*. 2017;27:S660-S661.

Lumateperone Efficacy for Adjunctive MDD Treatment in Investigational 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

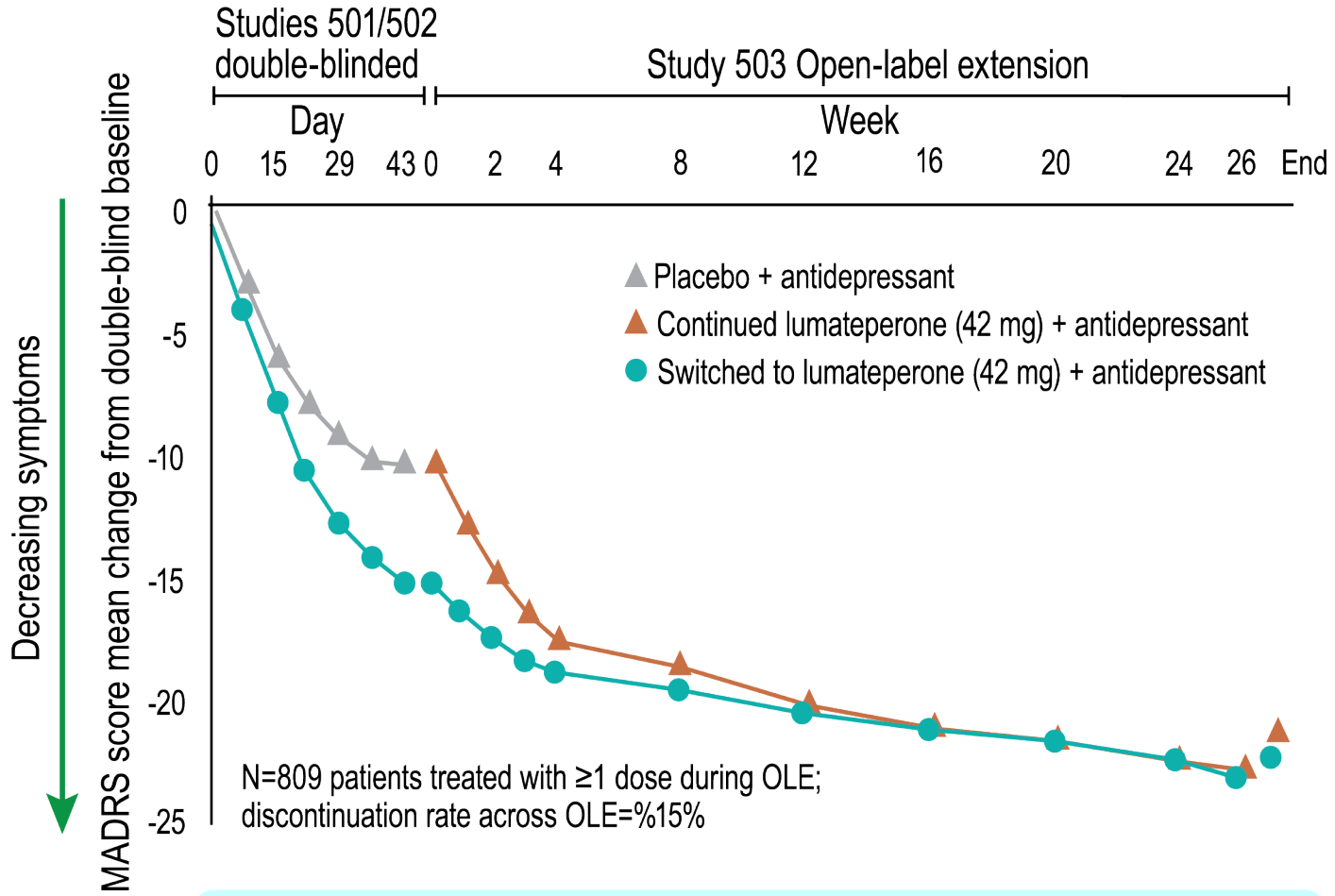
Adverse Events in Study 501		
	Lumateperone 42 mg (N=241)	Placebo (N=243)
All AEs	92 (38%)	53 (21%)
Occurring in >5%		
Dry Mouth	26 (11%)	5 (2%)
Nausea	12 (5%)	10 (4%)
Fatigue	23 (10%)	5 (2%)
Tremor	12 (5%)	1 (0.4%)
Dizziness	25 (10%)	15 (6%)
Headache	38 (16%)	37 (15%)
D/C due to AE	14 (6%)	2 (0.08%)

Adverse Events in Study 502		
	Lumateperone 42 mg (N=242)	Placebo (N=243)
All AEs	138 (57%)	54 (23%)
Occurring in >5%		
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.

Open-Label Extension Study of Lumateperone



No new safety findings emerged, and AEs parameters were consistent with the short-term studies 501 and 502

Mean Change in Body Morphology, Cardiometabolic Parameters, and Prolactin	Baseline N=809	Mean change from baseline
Weight (kg)	79	-0.2
BMI (kg/m^2)	28	-0.1
Waist circumference (cm)	93	-0.5
Cholesterol (mg/dL)		
Total	200	-8
Low-density lipid (LDL)	138	-10
High-density lipid (HDL)	57	0.1
Triglycerides	137	-0.2
Glucose mg/dL	93	1.1
Insulin (mIU/L)	15	-0.4
Prolactin mg/mL	10	1
Potentially clinically significant (PCS) criteria		
≥7% weight increase	9%	
≥7% weight decrease	10%	

OLE = open-label extension; BMI = body mass index; LDL = low-density lipid; HDL = high-density lipid; PCS = potentially clinically significant.

Earley WR, et al. Poster Presented at: American Psychiatric Association (APA) 2025 Annual Meeting; May 17-21, 2025; Los Angeles, CA.

Key Learning Points

- **Augmenting** with an **atypical antipsychotic is more effective** than switching to or adding bupropion

- In a retrospective analysis, patients with MDD who initiated **cariprazine** as their *first* adjunctive therapy had **significantly lower rates of mental health-related hospitalizations and outpatient visits** compared to those who initiated cariprazine as a *subsequent* adjunctive therapy.

- In two placebo-controlled studies, adjunctive treatment of MDD with **lumateperone reduced depressive symptom scores on the MADRS by 4-5 points more than placebo after 6 weeks**

- **Each atypical antipsychotic** approved for adjunctive MDD treatment **has unique** pharmacodynamic **properties** to consider when choosing among adjunctive treatment options

Panel Discussion

Practical Strategies for Determining Partial Response in Patients

- ❑ Use measurement-based care tools
- ❑ Ask about functionality, not just symptoms
- ❑ Talk to family members or close friends

Overcoming Barriers and Managing Side Effects

The term “antipsychotic” can be off-putting to some, increasing stigma

Important to note these medications are not just for psychosis and are approved for adjunctive MDD treatment

Discussing the potential option of adjunctive atypical antipsychotics earlier in treatment course could improve acceptance later

Language shapes perception

- QTc Prolongation
- Diabetes Mellitus
- Hyperlipidemia
- Sexual Side Effects
- Akathisia
- Weight Gain

Patient Advocate Discussion

Practical Takeaways

- **Partial response** to antidepressants in MDD is **more common** than complete response, and a **proactive approach** is important to **avoid settling for symptom reduction instead of return of function**
- **Treat MDD** as **aggressively** as any other illness and **avoid cycling through** medicines with highly **similar mechanisms of action**
- Like most chronic illnesses, **optimal treatment** of MDD **may require more than one medication,** and patient preferences and evidence-based medicine should be taken into account
- **Adjunct antipsychotics** should **take precedence over** combining **antidepressants** when appropriate

Q&A