Augmentation Expectations:

Finding the Right Treatment for Partial Response in MDD

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Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

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

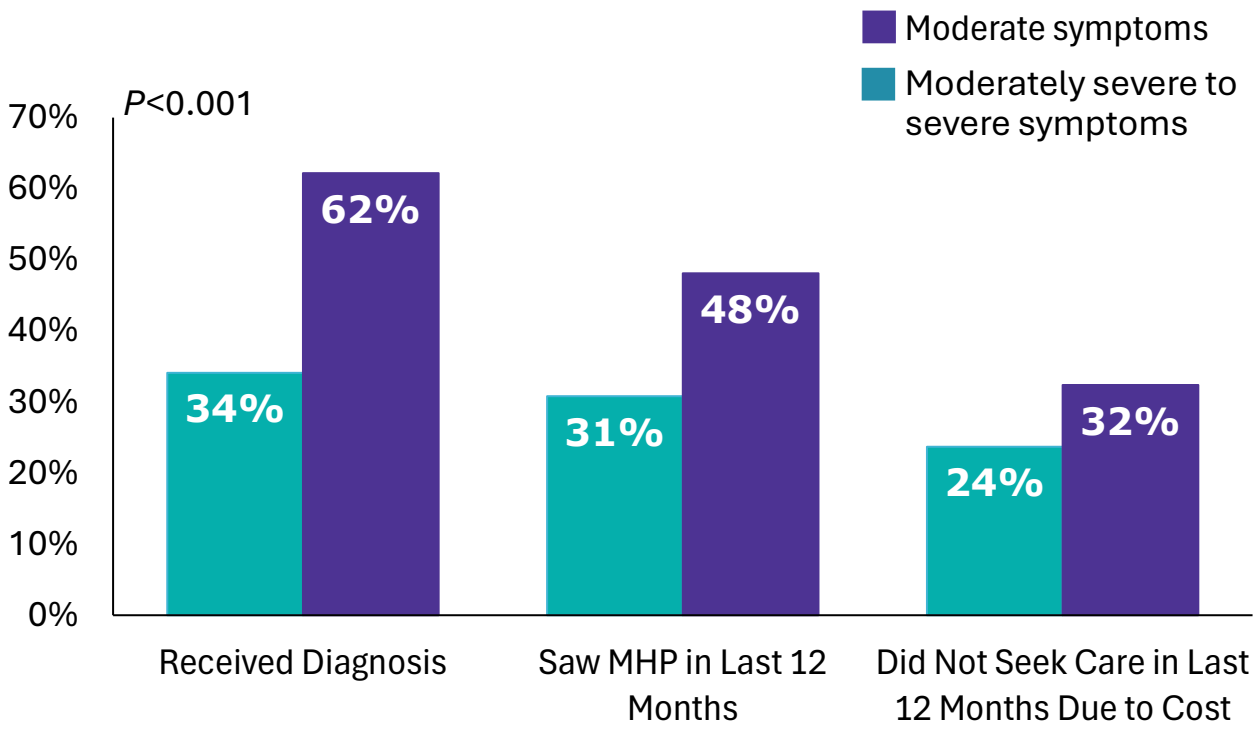
3. Implement strategies for selecting among adjunctive atypical antipsychotics and overcoming barriers to their optimal use in MDD

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

The Remarkable Impact of Primary Care on MDD

Primary care specialists play an *essential* role in caring for patients with MDD

Half of Patients With Moderate MDD Symptoms Did Not See a Mental Health Care Specialist in the Last Year



- Half of U.S. adults live in a MHP shortage area
- Over the last 20 years
  - U.S. population growth: 37%
  - MHP growth: 12%

8.4% 1 of 12	0.5% 1 of 200	60% 3 of 5
Have MDD (more in youth!)	Seek treatment	Who access care receive it from PCP

80% 4 of 5	Antidepressant prescriptions are written by PCPs

MHP = Mental health professional; PCP, primary care professional. Brenner AM, et al. *Acad Psychiatry*. 2017;41(2):202–6. Goodwin RD, et al. *Am J Prevent Med*. 2022;63(5):726–33. https://data.hrsa.gov/Default/GenerateHPSAQuarterlyReport. https://www.nimh.nih.gov/health/statistics/major-depression

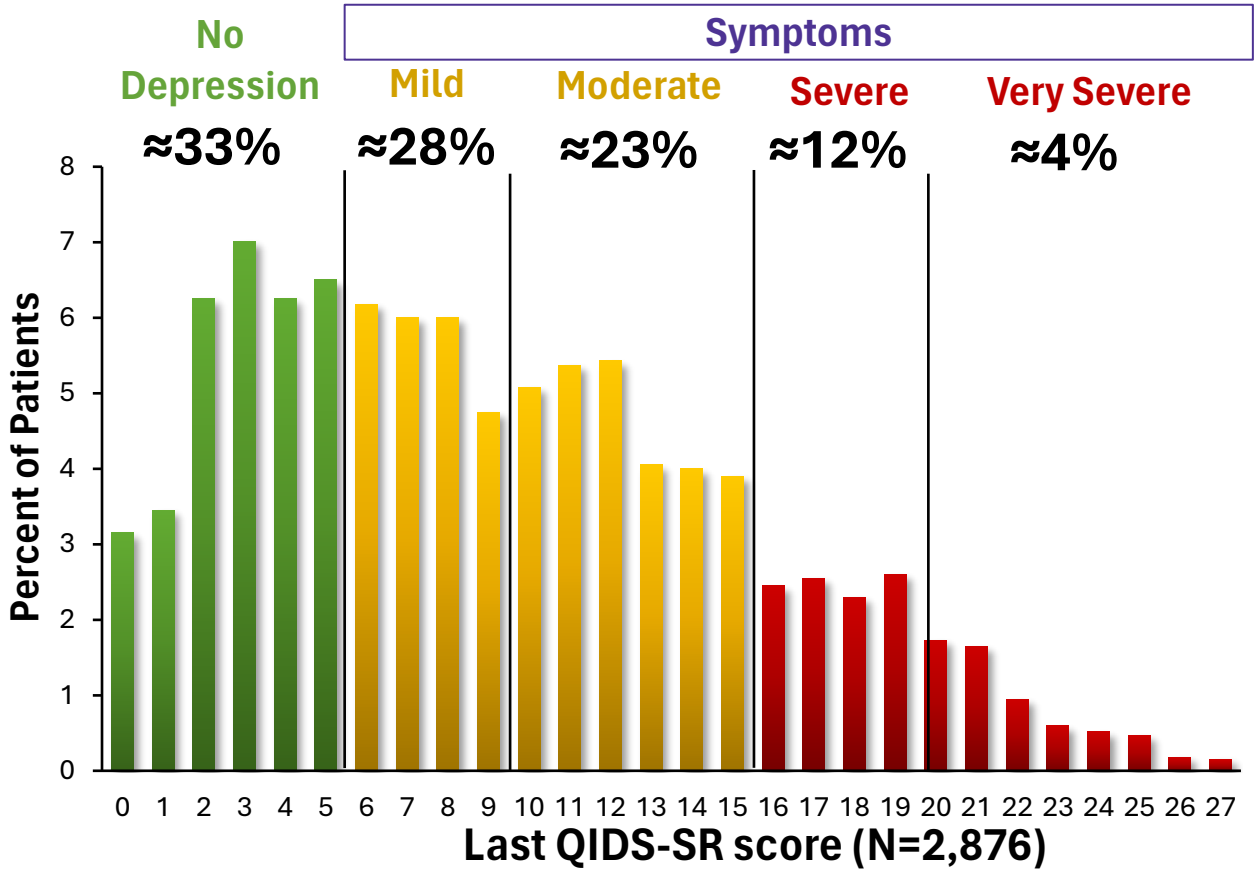
Understanding Inadequate Treatment Response In MDD

Partial Response Is Extremely Common in MDD

- The STAR*D Trial enrolled **4,041** patients with MDD
  - **44%** of study sites were **primary care** practices
- Few exclusion criteria
  - Psychotic symptoms
  - Contraindications to study medications
  - Pregnancy or breastfeeding
- Diverse population
  (~24% Asian, Black, or Hispanic)
- Funded by the NIH

Participants completed QIDS-SR, a standardized self-report scale to report MDD symptoms

The majority were symptomatic after receiving a first-line antidepressant as monotherapy for up to 14 weeks.

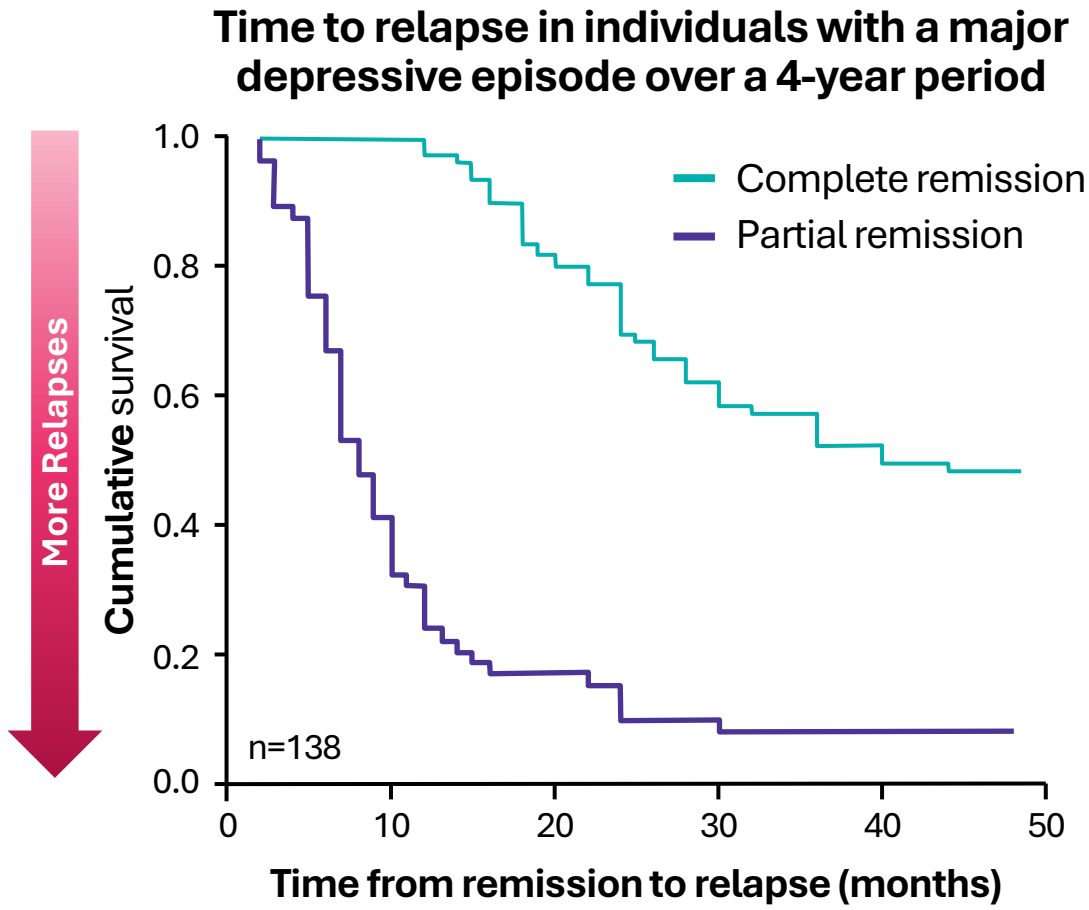


STAR*D = Sequenced Treatment Alternatives to Relieve Depression. QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

Rush et al., *Am J Psychiatry.* 2006;163(11):1905-17. Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

Settling for Partial Response Worsens Outcomes

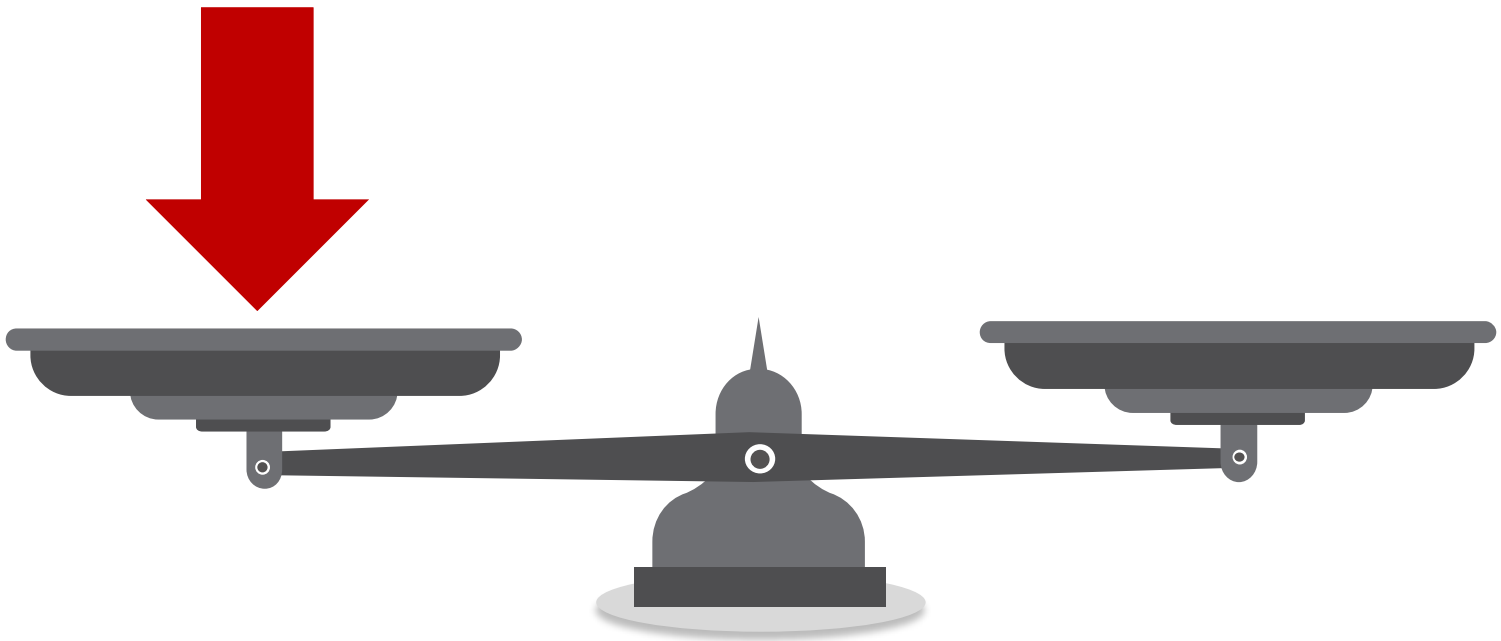
- Increases risk of relapse
- Increases the number of depressive episodes
- Increases frequency of depressive episodes
- Continues impairment in work and relationships
- Associated with increased all-cause mortality risk



Judd. *Am J Psychiatry*. 2000;157:1501-4. McLaughlin. *Prev Sci*. 2011;12:361. Hare. *Eur Heart J*. 2014;35:1365-72. Murphy. *Arch Gen Psychiatry*. 1987;44:473-80. Miloyan B, et al. *World Psychiatry*. 2017;16:219-20. van Dooren. *PLoS One*. 2013;8:e57058. de Groot M, et al. *Psychosom Med*. 2001;63:619-30. Pence BW, et al. *JAMA Psychiatry*. 2018;75:379-85. Ickovics JR, et al. *JAMA*. 2001;285:1466-74. Pintor L, et al. *J Affect Disord*. 2004;82(2):291–6.

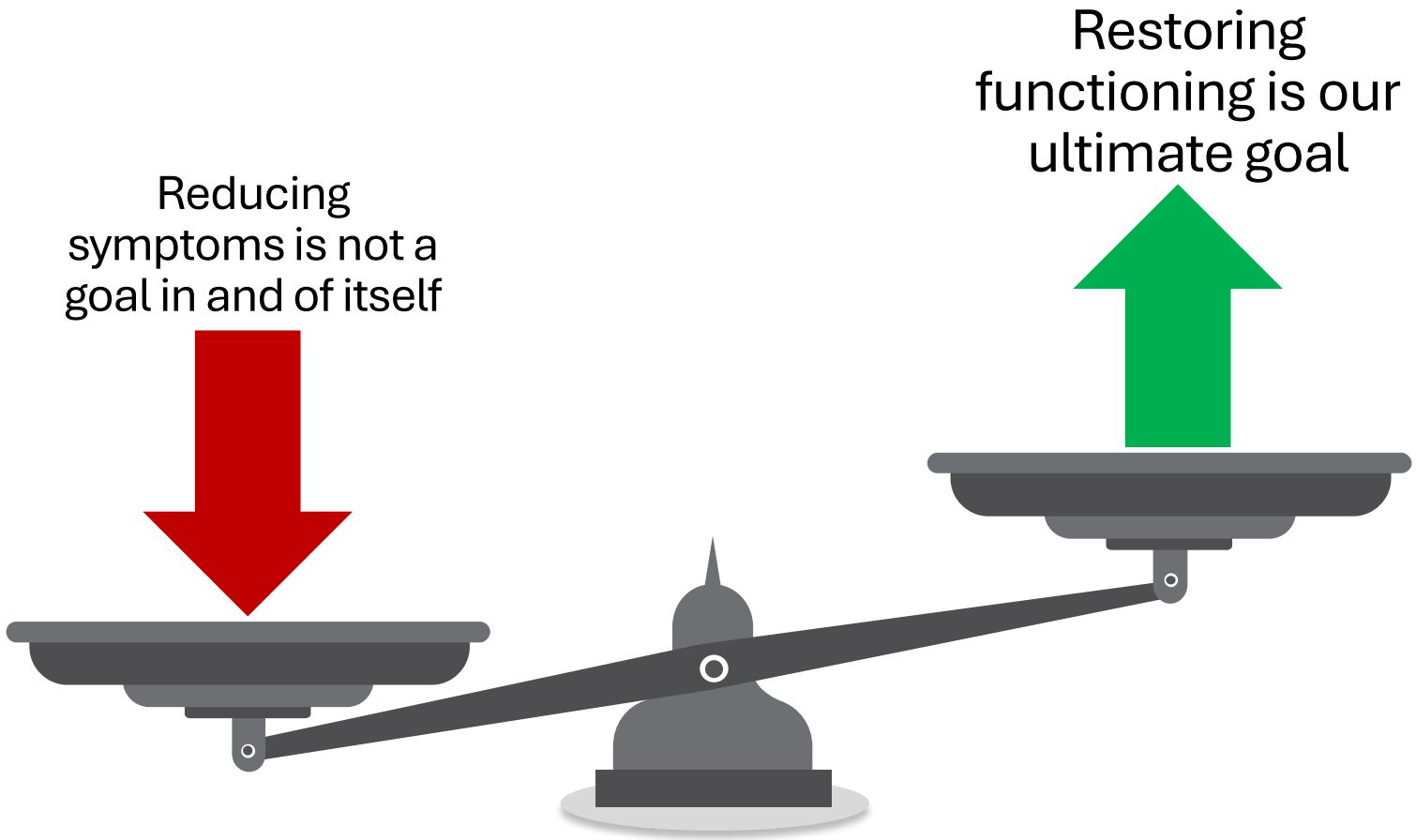
The Goal of Treating Major Depressive Disorder Is Not Simply to Reduce Symptoms

Reducing symptoms is not a goal in and of itself



Papakostas. *J Clin Psychiatry.* 2016;77:e1009. Trivedi. *Int Clin Psychopharmacol.* 2009;24:133-8. Work Group on Major Depressive Disorder. *Am J Psychiatry.* 2010;157:1.

The Goal of Treating MDD Is to Restore Function



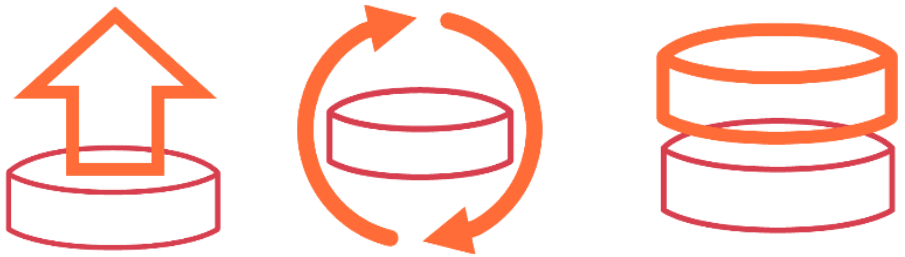
Papakostas GI. *J Clin Psychiatry.* 2016;77:e1009. Trivedi. *Int Clin Psychopharmacol*. 2009;24:133-8. Working Group on Major Depressive Disorder. APA Press. 2010. Accessed May 2, 2025. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf

Key Learning Points

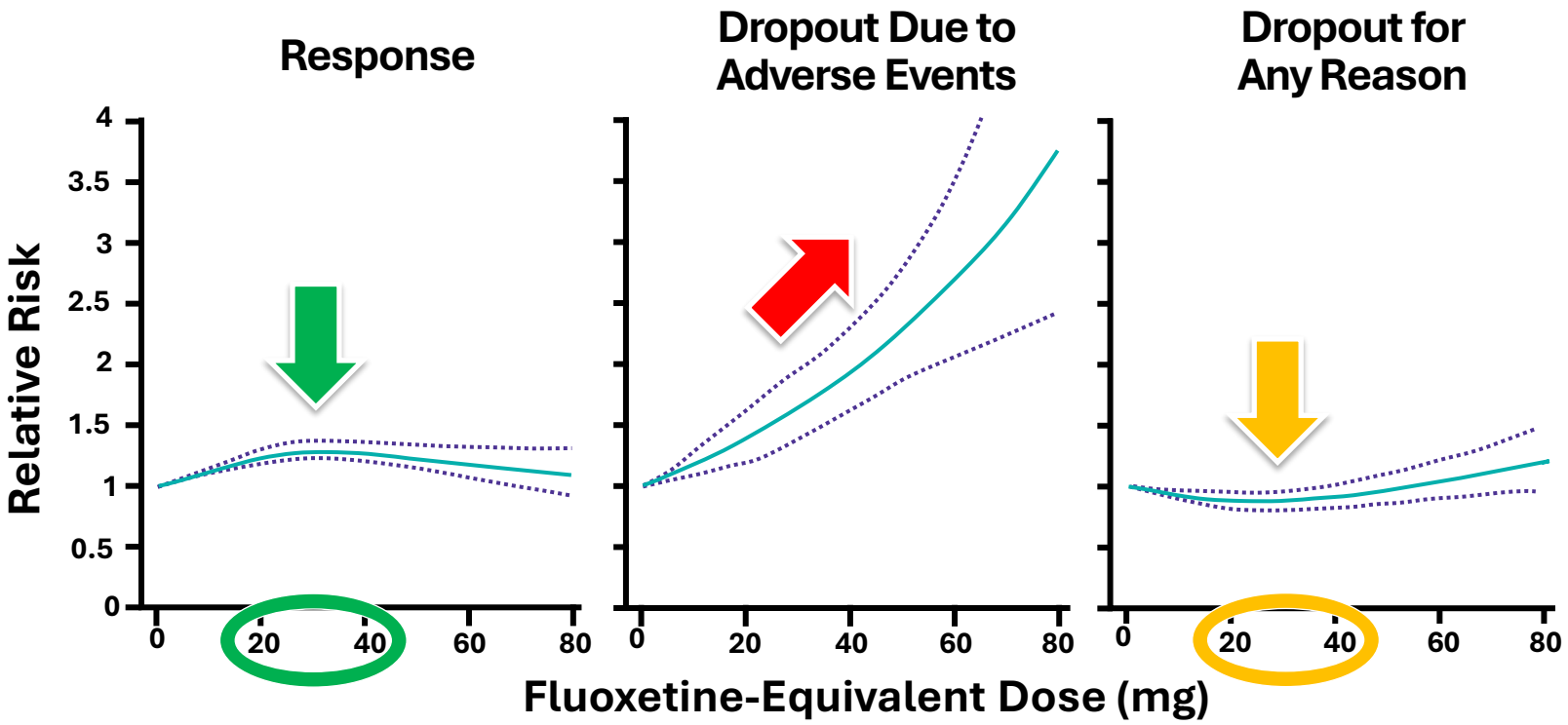
- Results of the STAR*D trial indicated that **the majority** of patients with MDD **remained symptomatic after** first-line **antidepressant monotherapy** for up to 14 weeks
- **Partial response** leaves patients at **higher risk of relapse** and **recurrence** and may increase **all-cause mortality**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

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

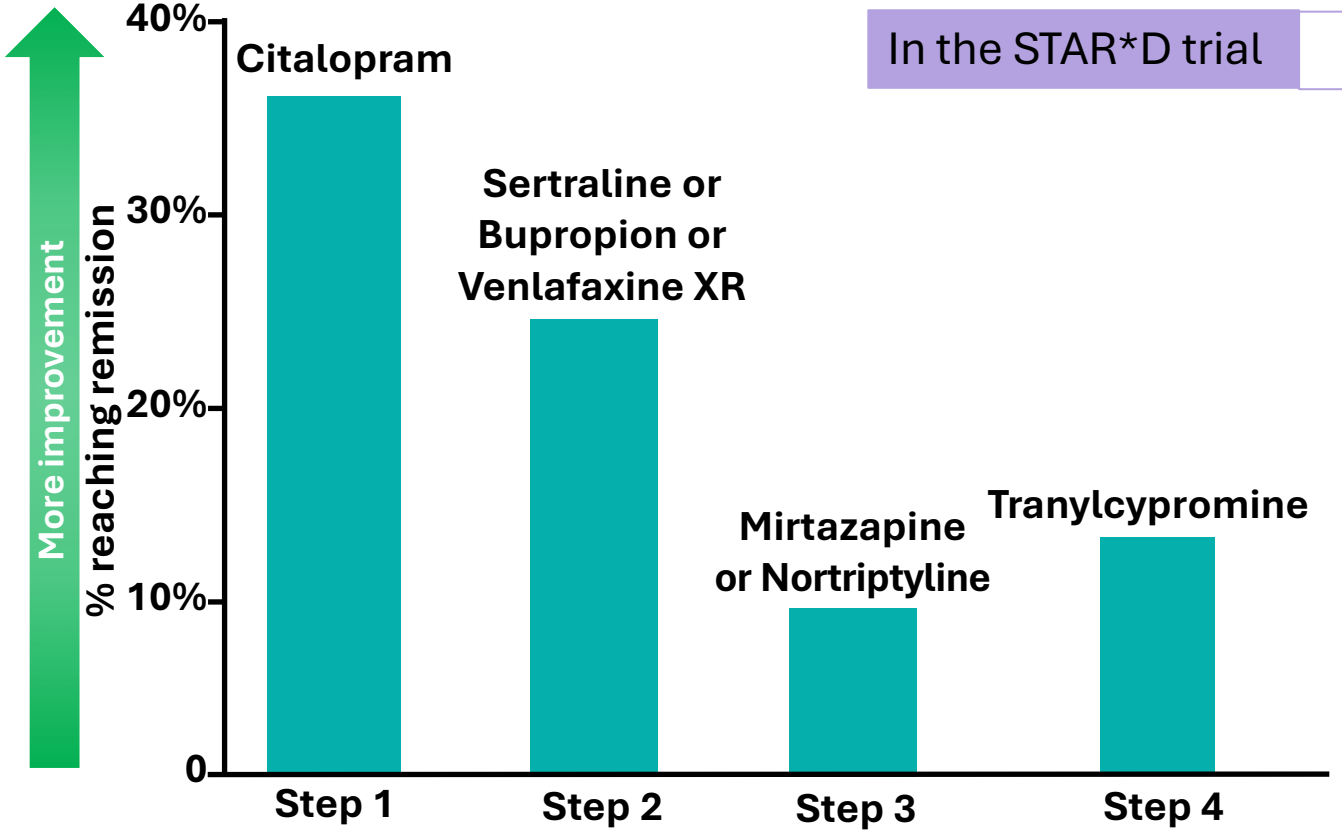


Approximate Optimal Doses	
Citalopram	20-40 mg
Escitalopram	10-20 mg
Fluoxetine	20-40 mg
Paroxetine	17-34 mg
Sertraline	50-100 mg

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):601-9. Hayasaka Y, et al. *J Affect Dis*. 2015;180:179-84.

Switching Antidepressants Produces Diminishing Returns



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

If not, or if response partial, or medicine intolerable, they could switch (left) or augment (not shown)

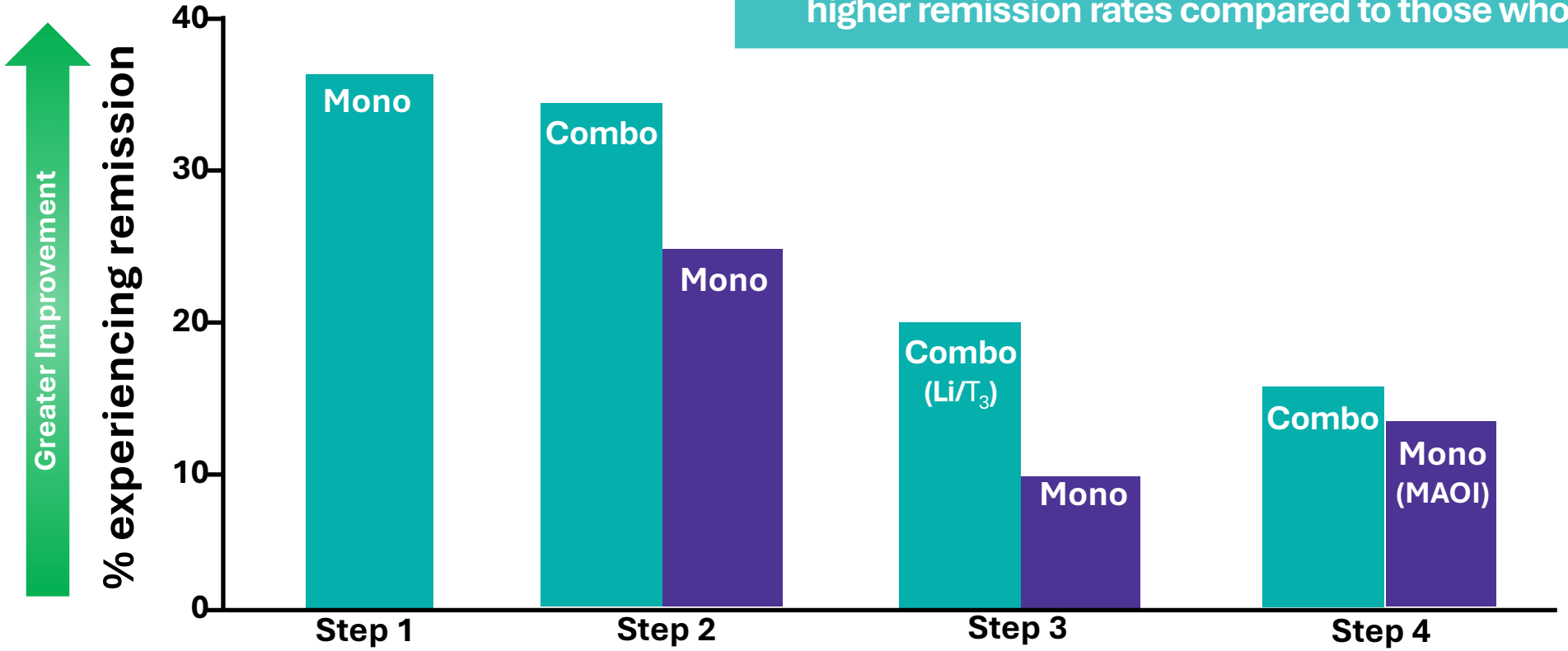
Remission rates decreased or did not significantly change (steps 3 and 4) after switching to a different medication

Similar results are seen whether switching between medicines in
- Different classes (e.g., citalopram to bupropion)
- The same class (e.g., citalopram to sertraline)

Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40. Trivedi MH, et al. *N Engl J Med*. 2006;354(12):1243-52. Rush AJ, et al. *N Engl J Med*. 2006;354(12):1231-42. Nierenberg AA, et al. *Am J Psychiatry*. 2006;163(9):1519-30. Fava M, et al. *Am J Psychiatry*. 2006;163(7):1161-72. McGrath PJ, et al. *Am J Psychiatry*. 2006;163(9):1531-41.

Adding a Treatment May Be Better Than Switching

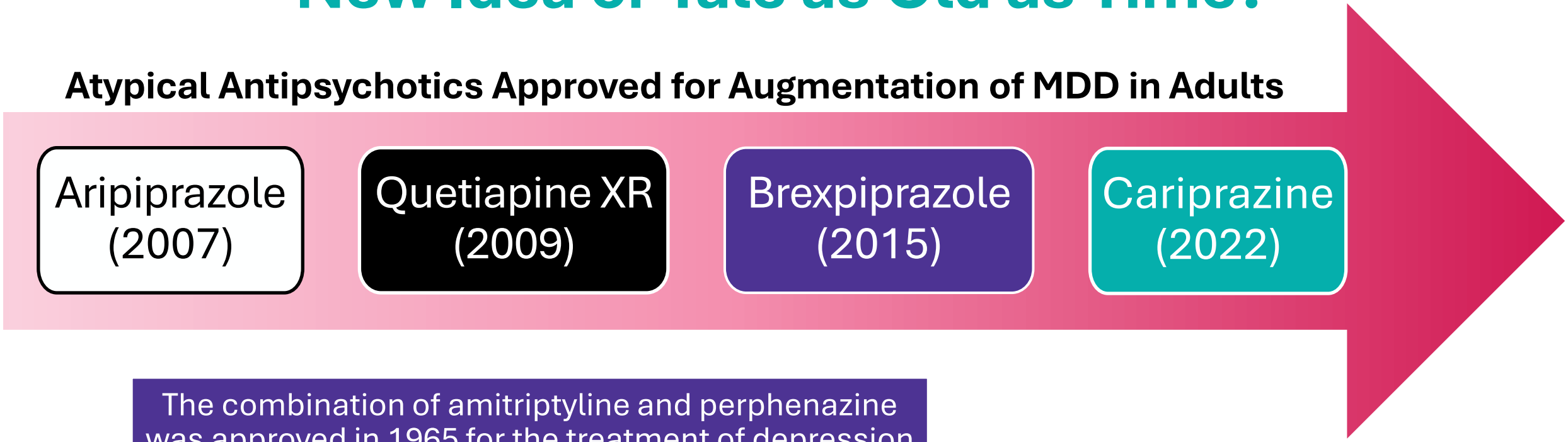
Although STAR*D was not powered to compare options against one another, people who added a treatment had numerically higher remission rates compared to those who switched.



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):1243-52. Rush AJ, et al. *N Engl J Med*. 2006;354(12):1231-42. Nierenberg AA, et al. *Am J Psychiatry*. 2006;163(9):1519-30. Fava M, et al. *Am J Psychiatry*. 2006;163(7):1161-72. McGrath PJ, et al. *Am J Psychiatry*. 2006;163(9):1531-41.

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

Atypical Antipsychotics Approved for Augmentation of MDD in Adults

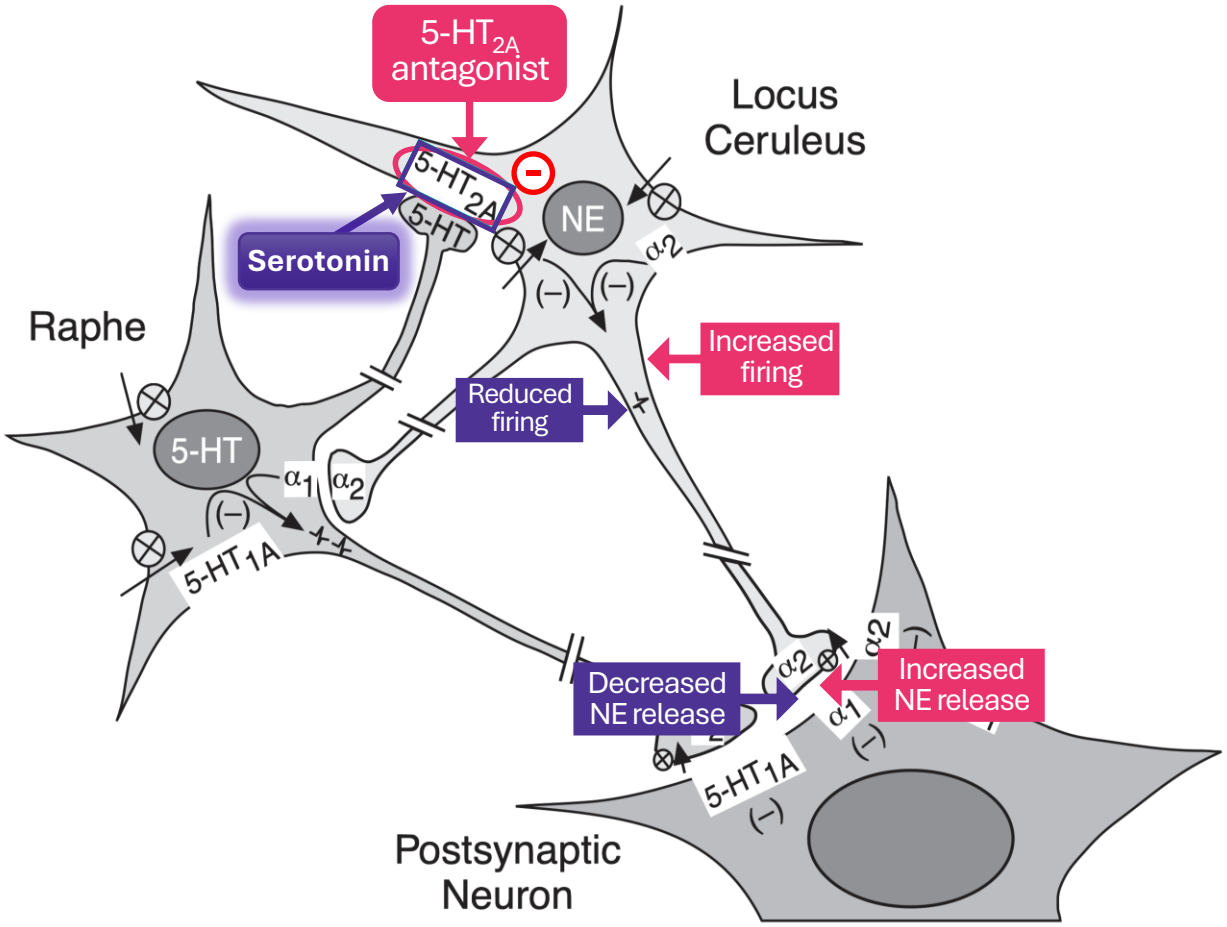


The combination of amitriptyline and perphenazine was approved in 1965 for the treatment of depression comorbid with anxiety and/or agitation

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

PI = prescribing information; XR = extended release. Perphenazine and amitriptyline hydrochloride tablets Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed February 28, 2025. www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Nelson JC, et al. *Am J Psychiatry*. 2009;166(9):980-91.

5-HT_{2A} Receptor Antagonism May Play a Role in Atypical Antipsychotic Augmentation in MDD



5-HT_{2A} receptors are inhibitory

The increased synaptic serotonin produced by SSRIs and SNRIs can **indirectly stimulate** 5-HT_{2A} receptors

The net effect is **suppression of norepinephrine** transmission

Antagonism of 5-HT_{2A} receptors by atypical antipsychotics may **restore norepinephrine signaling**

NE = Norepinephrine. Blier P, et al. *J Clin Psychiatry*. 2005;66(Suppl 8):30-40. Blier P, et al. *J Affect Disord*. 2011;128(Suppl 1):S3-S10. Szabo ST, et al. *J Pharmacol Exp Ther*. 2002;302(3):983-91.

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

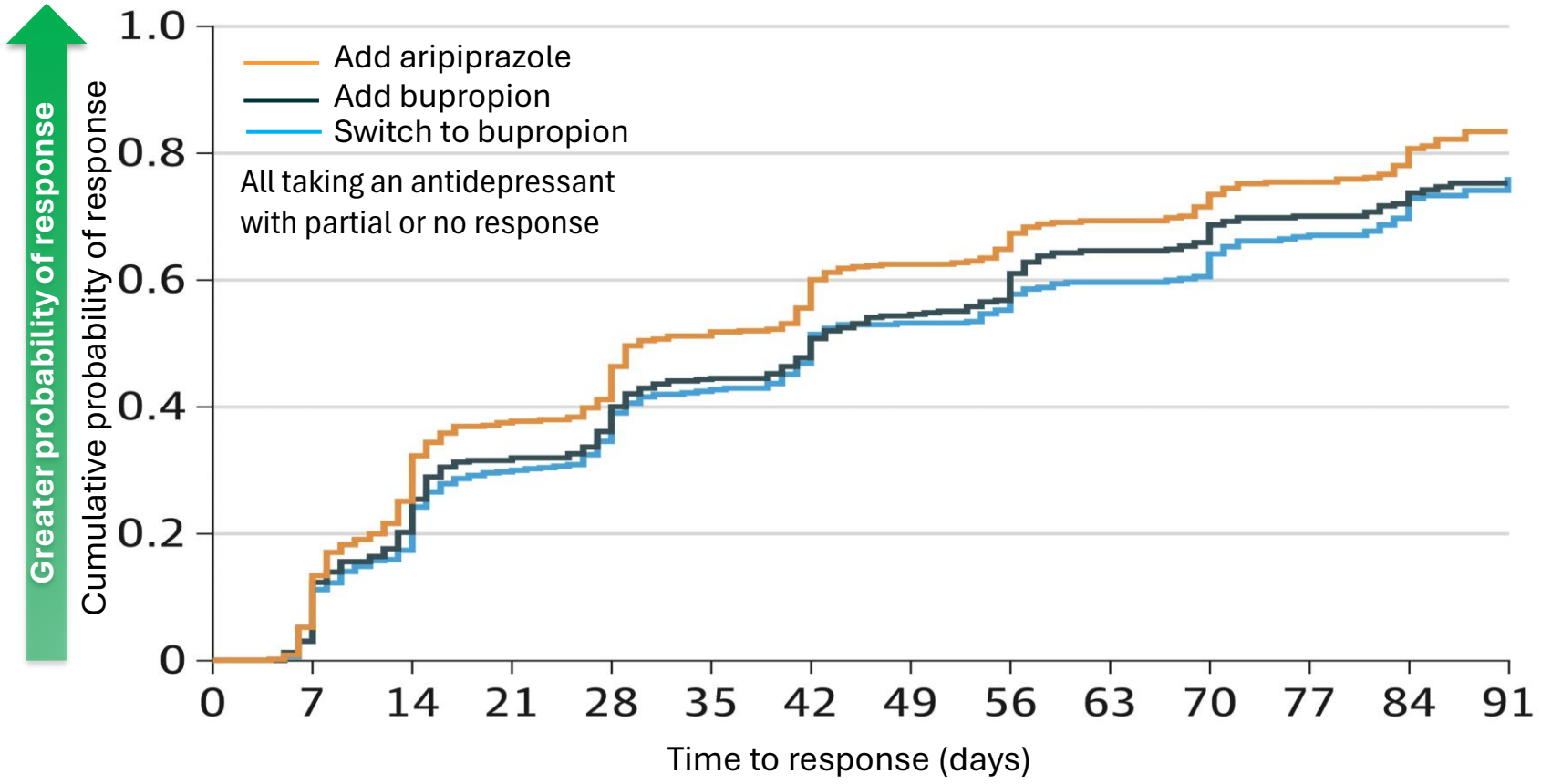
- The **maximum dose** for an SSRI **may not be the optimal dose** for a particular patient; **consider tolerability** and **customize** treatment **to the individual**

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

Approved Treatments for Adjunctive Treatment of MDD

Augmenting with an Atypical Antipsychotic Is Superior to Switching to or Adding Bupropion

Randomized controlled trial in VA population showed adding aripiprazole increased response to treatment more than switching to or adding bupropion



Most common adverse events

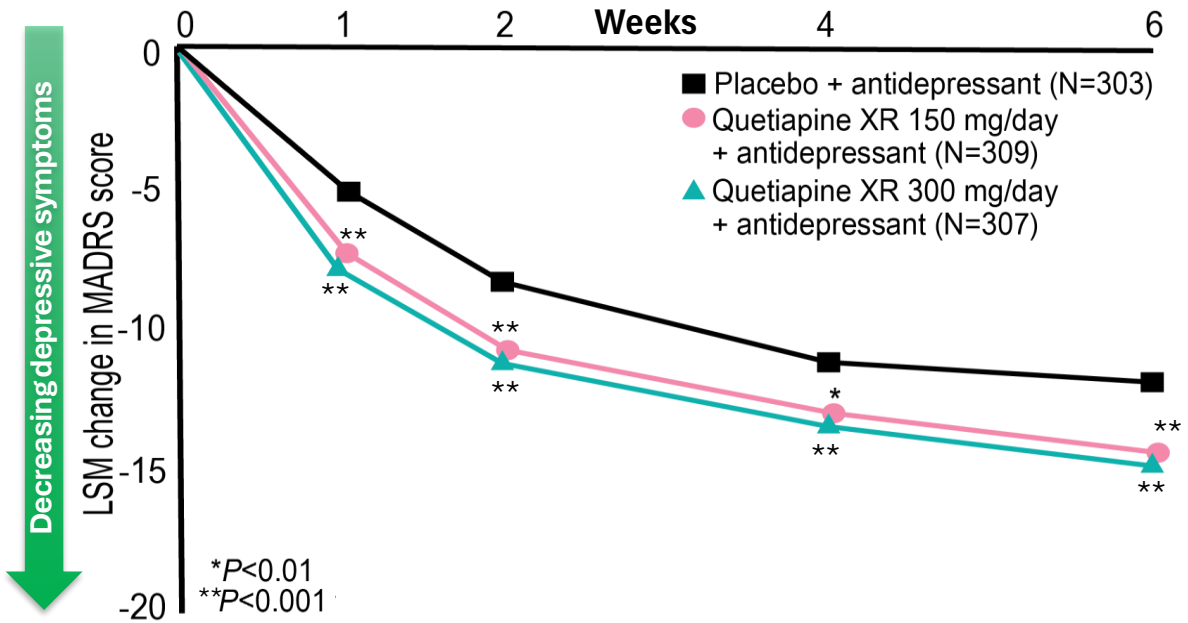
Bupropion	Aripiprazole
anxiety	somnolence
irritability	akathisia
insomnia	weight gain

Dropout rates were lowest with aripiprazole augmentation

VA = Veterans Affairs; AE = adverse event. Mohamed S, et al. *JAMA*. 2017;318(2):132-45.

Pivotal Trials of Adjunctive Quetiapine XR for MDD

Adjunctive quetiapine in MDD decreased depressive symptoms more than placebo, primarily by improving sleep



At week 6, there were statistically significant differences in 4 and 5 of 6 "core" MADRS items with 150 mg or 300 quetiapine, respectively, vs placebo; however, much of the overall separation was still driven by sleep improvement

Quetiapine and quetiapine XR have similar half-lives (elimination), but XR reaches max 4.5 hours later

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

Pro Tip!
Take before dinner

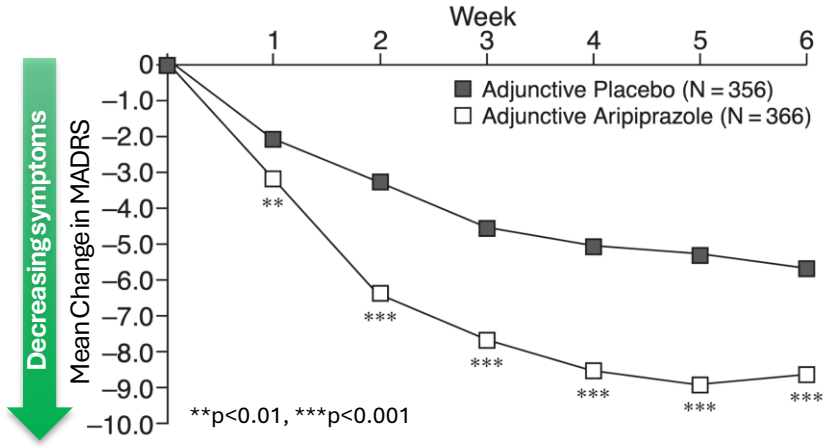
Approved doses: 150 and 300 mg in the evening, *without* food (<300 cal)

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

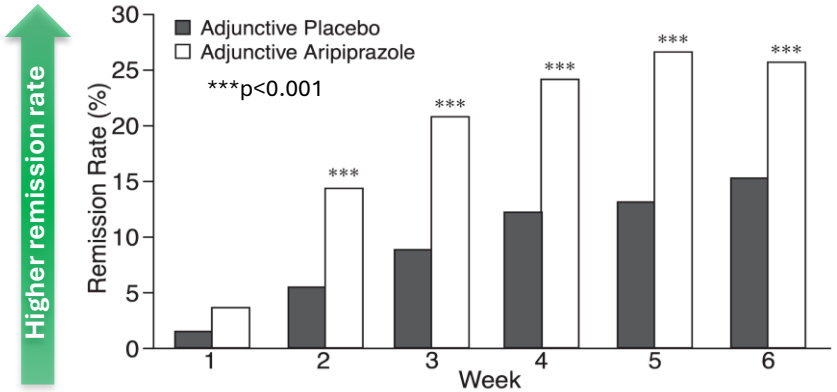
AE = Adverse event; D/C = Discontinued; LSM = Least squares mean. Bauer M, et al. *J Affect Disord*. 2010;127(1-3):19-30. Rummel-Kluge C, et al., *Schizophr Bull*. 2012;38(1):167-77. Citrome L, et al. *J Clin Psychiatry*. 2023;84:22r14631. Seroquel XR (quetiapine) Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed February 28, 2025. www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

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%

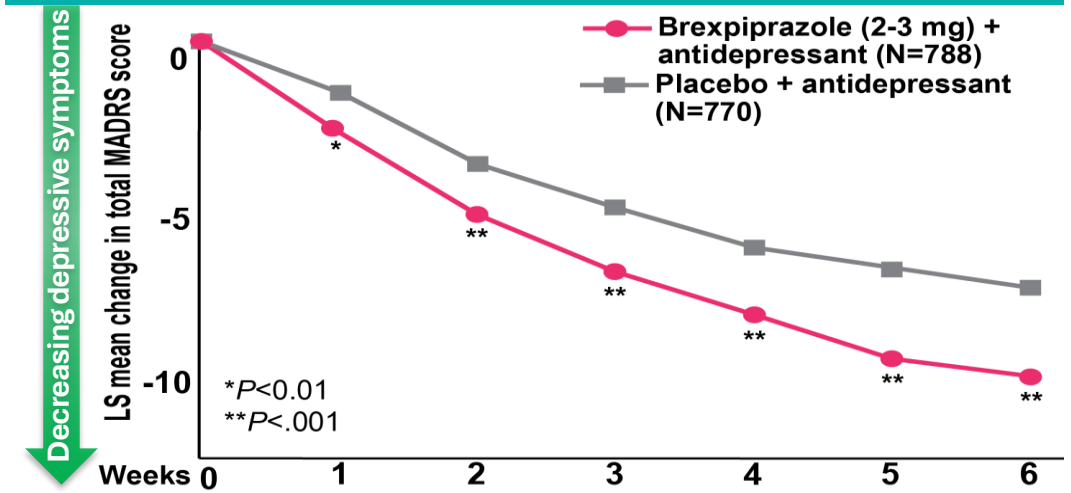
Adverse events in Open-Label Extension (52 weeks, N=994)	
Akathisia	26%
Fatigue	18%
Weight increase	17%
Restlessness	14%
Somnolence	14%
Insomnia	12%
URI	11%
Nausea	9%
Dizziness	9%
D/C due to AE	23%

Weight gain ≥7% reported in 26%

MADRS = Montgomery Åsberg Depression Rating Scale; D/C = discontinuations; AE = adverse events. Abilify (aripiprazole) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed Jan 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/. Berman RM et al. *Neuropsychiatry Dis Treat*. 2011;7:303-12. Pae et al., CNS Drugs. 2011;25:109-27. Thase ME., et al. *Prim Care Companion. J Clin Psychiatry.* 2008;10(6): 440-7.

Pivotal Trials of Adjunctive Brexpiprazole for MDD

Adjunctive brexpiprazole reduced depressive symptoms significantly more than placebo



	Pooled 2-3 mg	Pooled 2mg
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%

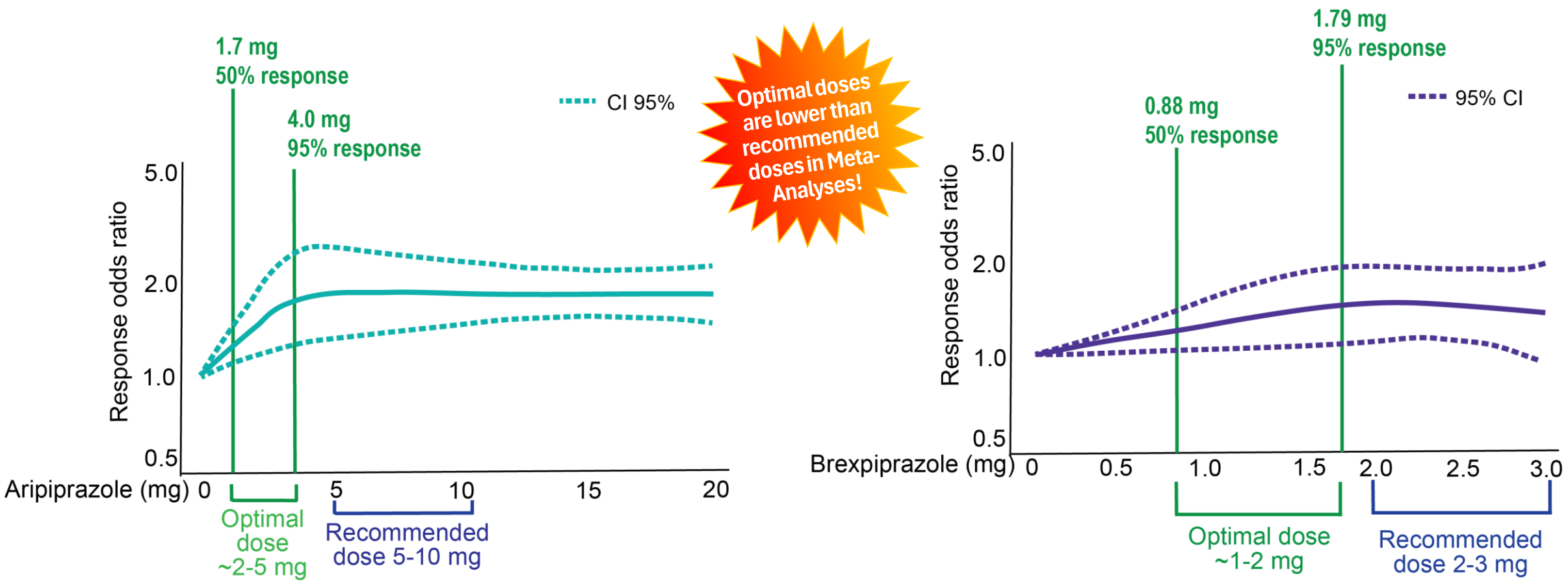
Adverse events in open-label extension (52 weeks, N=2,994)

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%

Rexulti (brexpiprazole) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/. Hobart M, et al. *J Clin Psychopharmacol*. 2019;39(3):203-9. Thase ME, et al. *Expert Opinion on Pharmacotherapy*. 2019;20(15):1907-16.

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

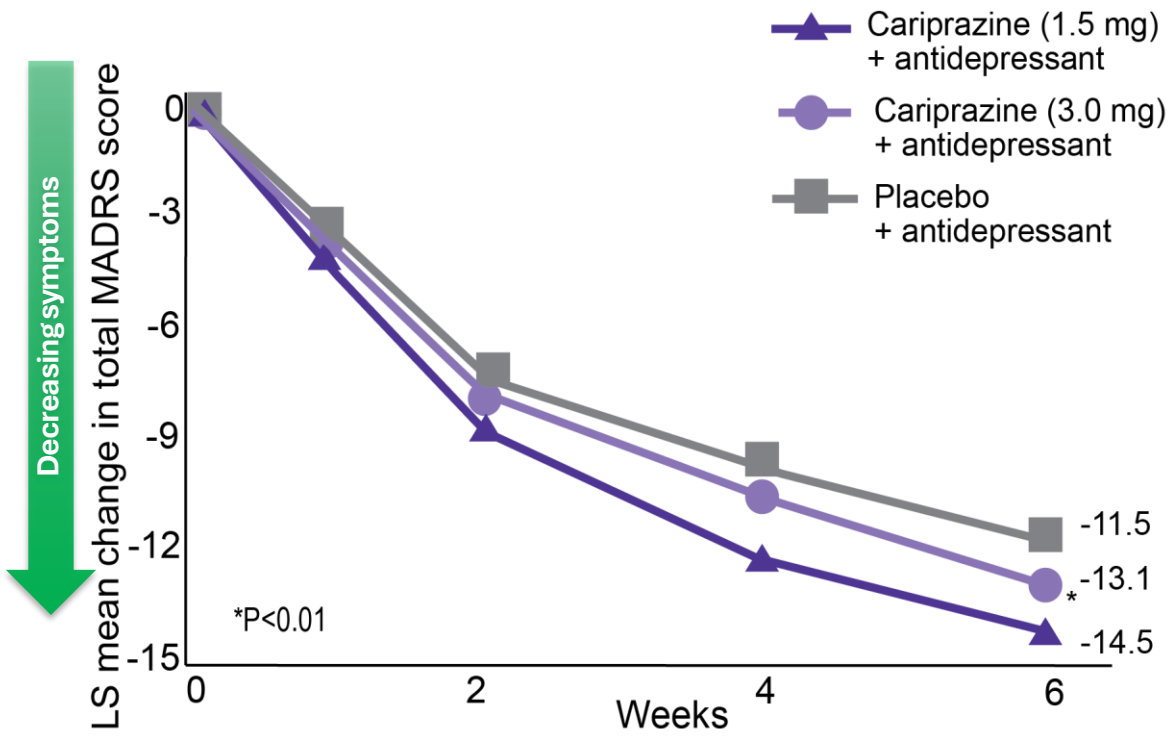


Although individual response varies, higher doses generally do not provide additional benefits

OR = odds ratio; ED50 = 50% effective dose; ED95 = 95% effective dose; PI = prescribing information. Furukawa Y, et al. *Br J Psychiatry*. 2022;221(2):440-7. Furukawa Y, et al. *Psychiary Clin Neurosci*. 2022;76(9):416-22.

Pivotal Trials of Adjunctive Cariprazine forMDD

Adjunctive treatment with cariprazine decreased depressive symptoms significantly more than placebo



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

48-96 -hour half-life; metabolized by 34A and 2D6

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%

Vraylar (cariprazine) [package insert]. Madison, NJ: Allergan USA; 2022. Durgam, S, et al. *J Clin Psychiatry.* 2016;77(3):371-8. Sachs, GS, et al. *Am J Psychiatry.* 2023;180(3):241-51. Earley, WR., et al. *Psychopharmacol Bull.* 2018;48(4):62-80. Vieta E, et al. *Int J Clin Psychopharmacol.* 2019;34(2):76-83. https://clinicaltrials.gov/ct2/show/NCT03739203.

Each Dopamine Partial Agonist Has Distinct Pharmacodynamics

All atypical antipsychotics are not equal!

They differ in pharmacologic profiles and receptor binding

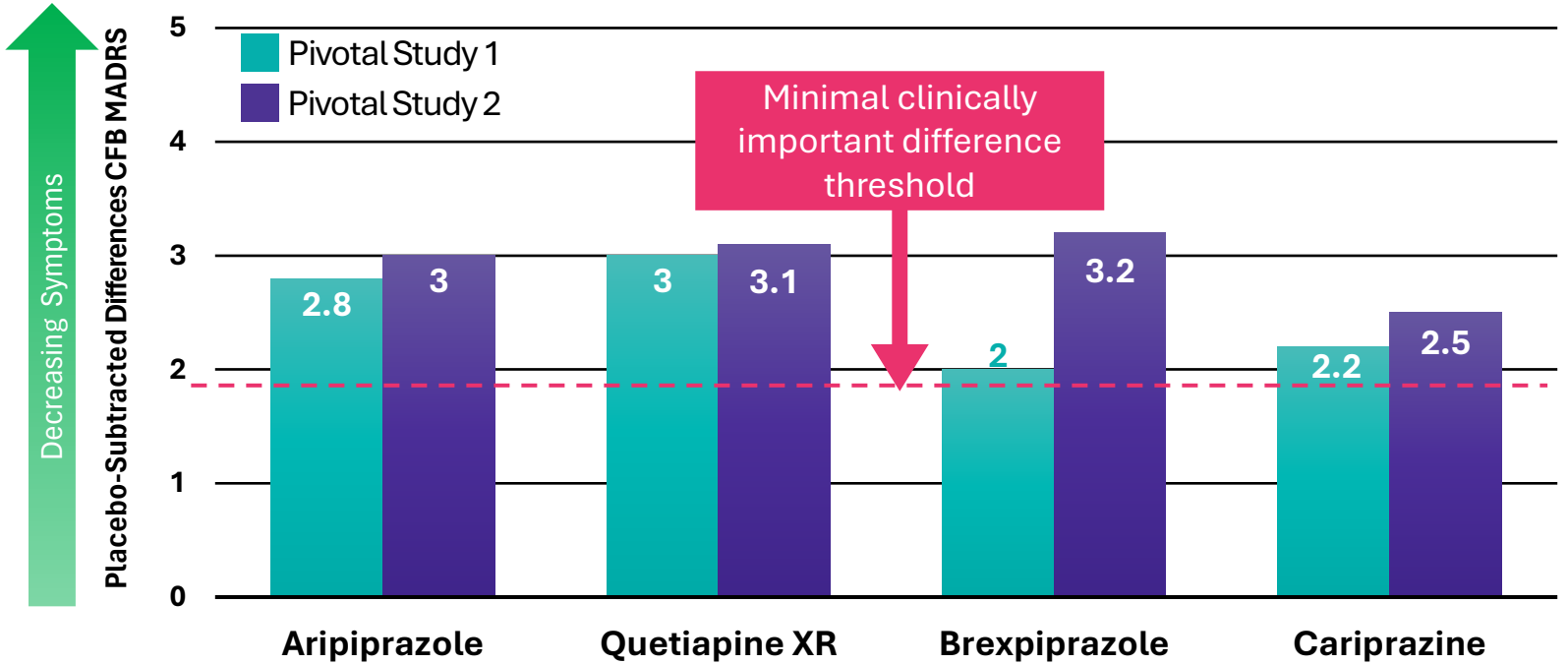
Hot Take! If one doesn't work, it may make sense to try another

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	↔	$5\text{-}HT_{2B}$	0.36 nM	◀ ↓ 5x	1.9 nM
2.6 nM	↔	$5\text{-}HT_{1A}$	1.7 nM	◀ ↑ 14x	0.12 nM
18.8 nM	↓ 6x ➤	$5\text{-}HT_{2A}$	3.4 nM	◀ ↓ 7x	0.47 nM
134 nM	↓ 10 ➤	$5\text{-}HT_{2C}$	15 nM	◀ ↓ 2x	34 nM
111 nM	↓ 3x ➤	$5\text{-}HT_7$	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

Citrome L. *Int J Clin Pract*. 2015;69(11):1211-20. Kiss B, et al. *Drug Design, Development and Therapy*. 2019;13:3229-48.

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

Abilify (aripiprazole), Seroquel XR (quetiapine), Rexulti (brexpiprazole), and Vraylar (cariprazine) prescribing information: 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 the 37th Psych Congress Annual Meeting, 10/29-11/2/2024, 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 the 37th Psych Congress Annual Meeting, 10/29-11/2/2024, Boston, MA. Duru G, et al. *Curr Med Res Opin*. 2008;24(5):1329-35.

Approved Atypical Antipsychotics for Adjunctive MDD Treatment : Adverse Events in Short-term Studies

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.

Aripiprazole		
	All doses*	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%

*pooled

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 XR			
	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%

Abilify (aripiprazole), Rexulti (brexpiprazole), Vraylar (cariprazine), and Seroquel XR (quetiapine) prescribing information: Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/.

Approved Atypical Antipsychotics for Adjunctive MDD Treatment : Adverse Events in Open-Label Extension Studies

Aripiprazole 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%

26% had weight gain ≥7%

Brexpiprazole 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%

26% had weight gain ≥7%

Caripiprazine 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%

19% had weight gain ≥7%

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.

High-quality data on the long-term tolerability of quetiapine is limited

Berman RM et al. *Neuropsychiatr Dis Treat*. 2011;7:303-12. Hobart et al., *J Clin Psychopharmacol*. 2019;39(3):1907-16. Vieta E, et al. *Int Clin Psychopharmacol*. 2019;34(2):76-83.

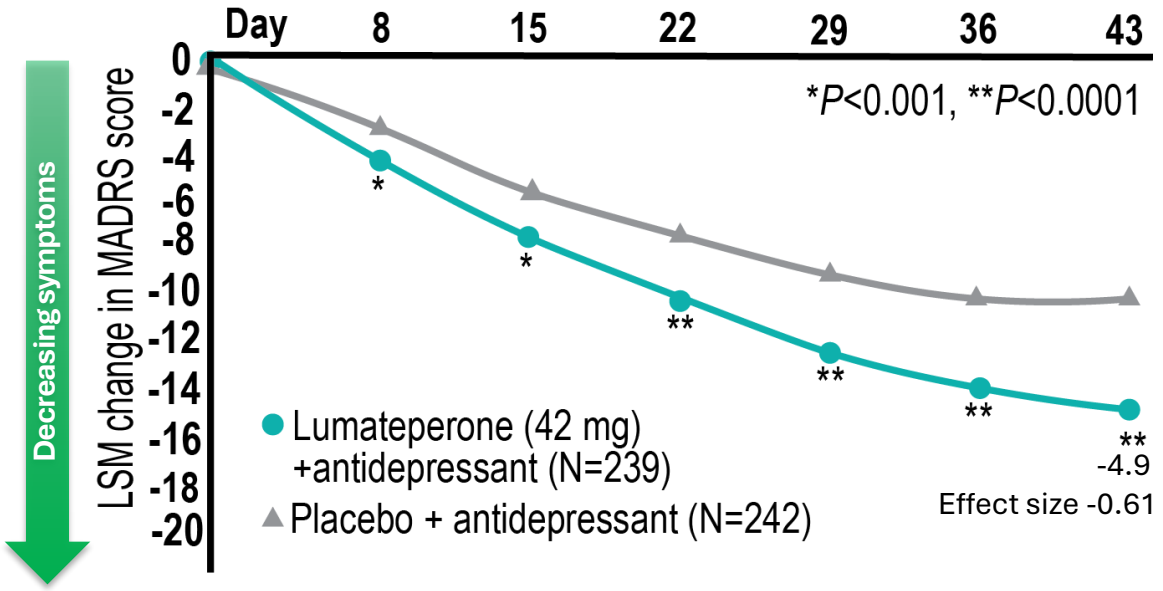
Key Learning Points

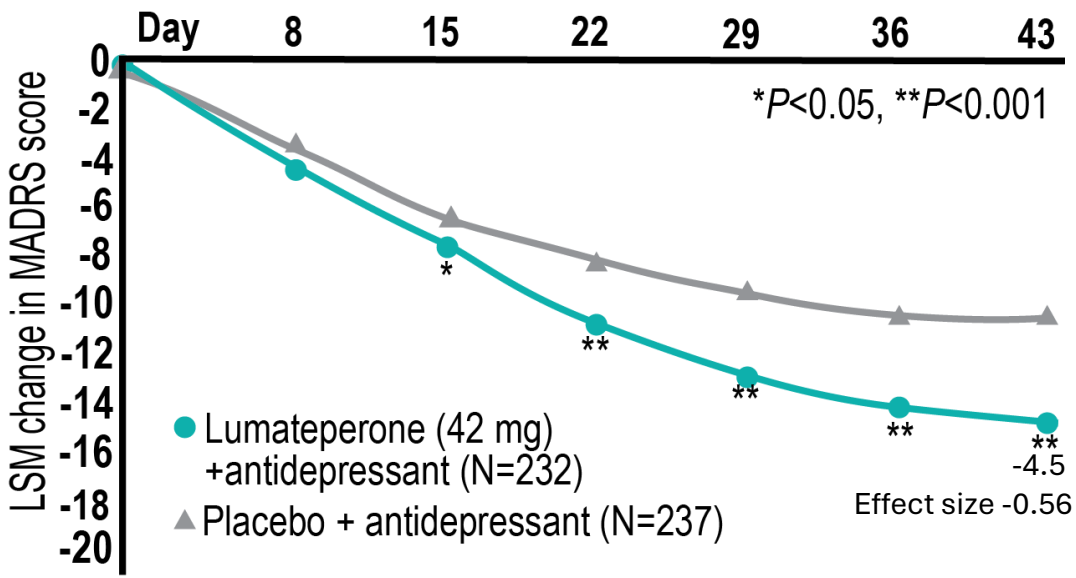
- **Adding** an **atypical antipsychotic** to antidepressant treatment **is more effective** than switching to or adding bupropion
- The **optimal dose** of an atypical antipsychotic for adjunctive MDD treatment **may be lower than the recommended dose**
- **Increasing** atypical antipsychotic **doses** above recommended amounts **does not always provide benefits**
- **Each atypical antipsychotic** approved for adjunctive MDD treatment **has unique** pharmacodynamic **properties** to consider when choosing among adjunctive treatment options

Emerging Agents for Adjunctive Treatment of MDD: Lumateperone

Phase 3 Studies of Lumateperone for Adjunctive MDD Treatment

In two placebo-controlled studies, adjunctive lumateperone decreased depressive symptoms vs placebo as early as day 8 and day 15, respectively





In two studies, adjunctive lumateperone reduced MADRS score by 4.5 to 4.9 points compared with placebo

Durgam S. Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomized, Double-blind, Phase 3 Trial. Presented at the 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 the 37th Psych Congress Annual Meeting, October 29-November 2, 2024, Boston, MA.

Phase 3 Studies of Lumateperone for Adjunctive MDD Treatment

Dry mouth, dizziness, fatigue, nausea, somnolence and tremor occurred at least twice as often with adjunctive lumateperone vs placebo.

Most were mild-to-moderate

No clinically relevant increases in prolactin or cardiometabolic parameters

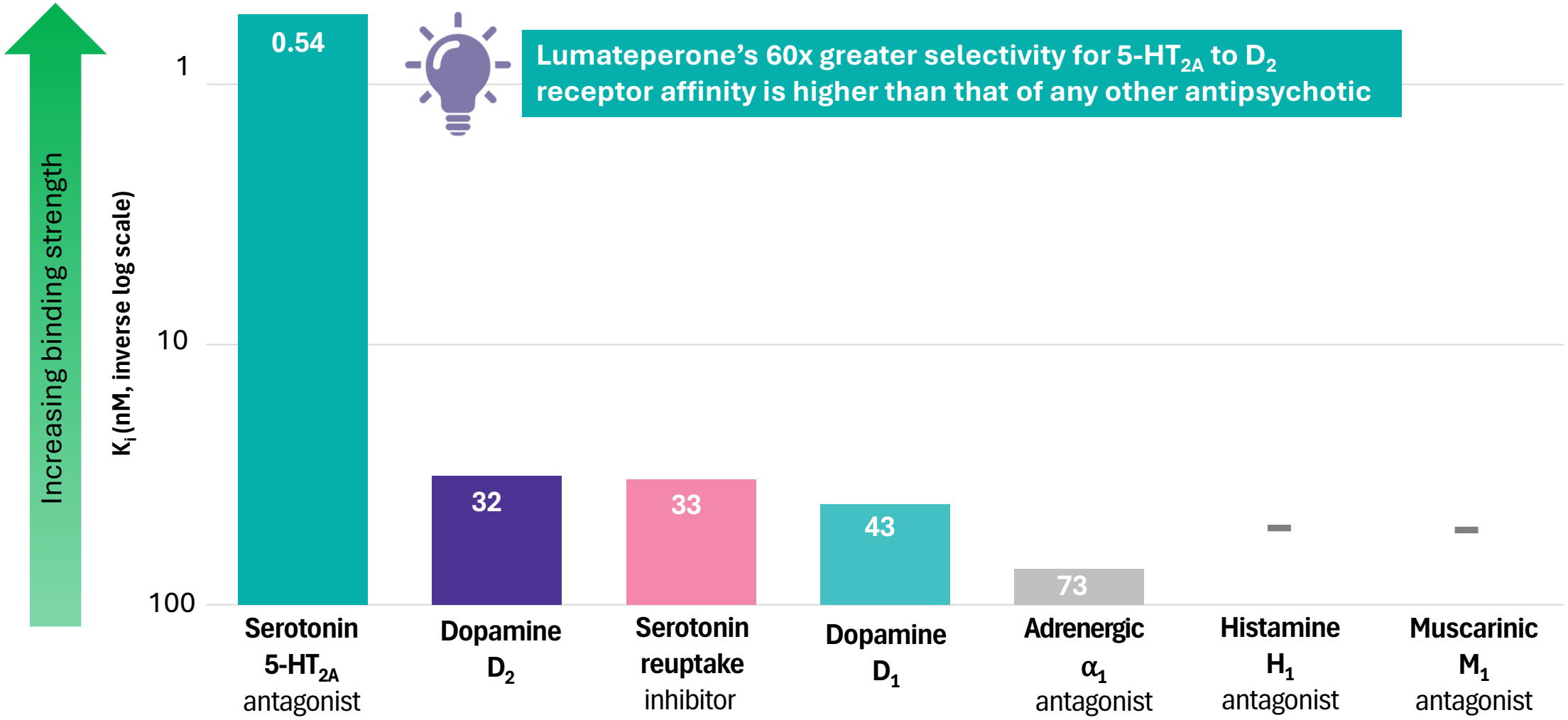
No weight gain

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%)

Durgam S. Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder: Results From a Randomized, Double-blind, Phase 3 Trial. Presented at the 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 the 37th Psych Congress Annual Meeting, October 29-November 2, 2024, Boston, MA. Clinical Trial Record: https://clinicaltrials.gov/study/NCT05061706 Clinical Trial Record: https://clinicaltrials.gov/study/NCT04985942

Lumateperone Pharmacology

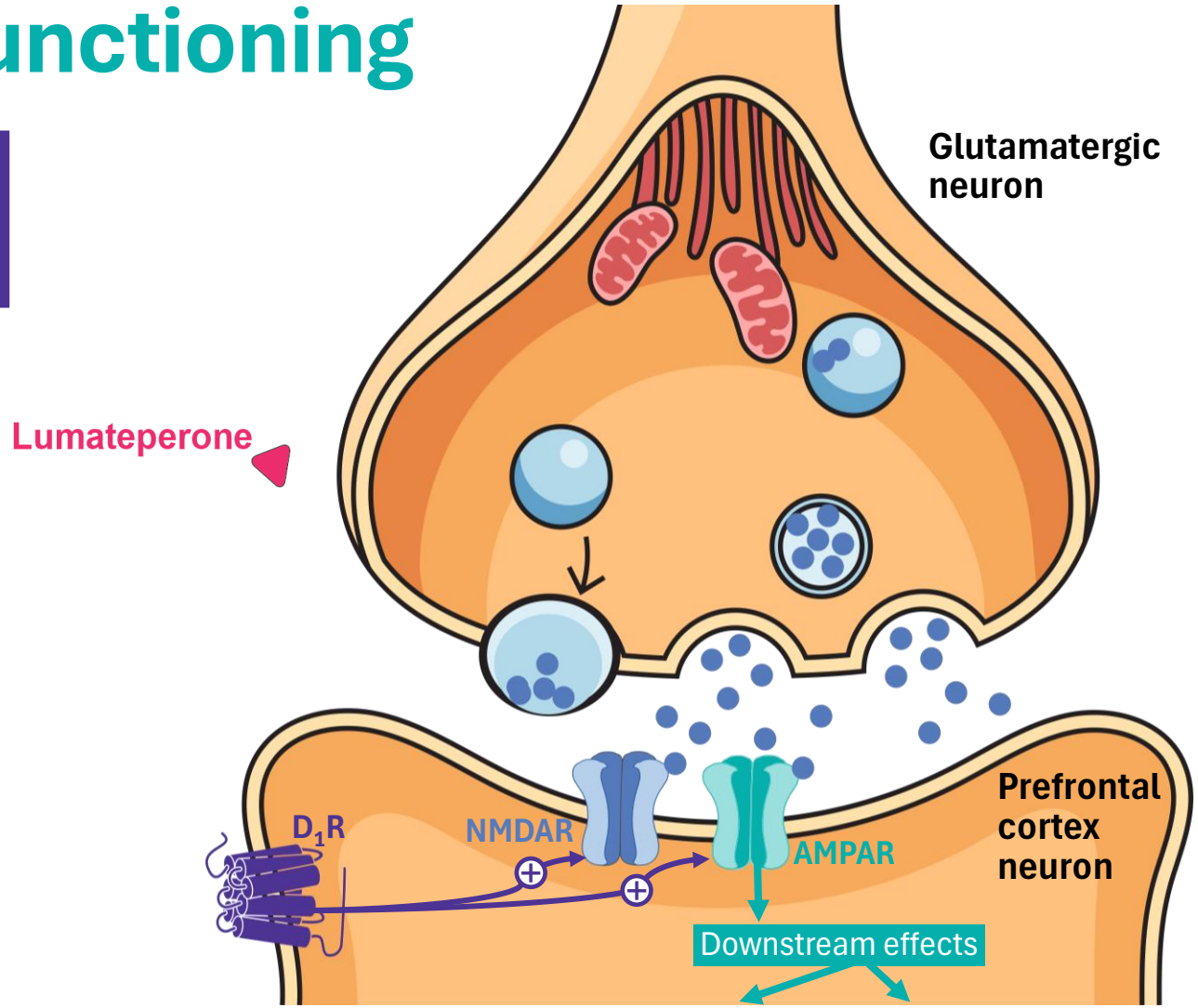


Caplyta (lumateperone) Prescribing information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/.
Li P, et al. J *Med Chem*. 2014;57(6):2670-82. Kantrowitz JT. *CNS Drugs*. *2020;*34(9):947-9.

Lumateperone's Effects on D1 May Indirectly Modulate Glutamate Functioning

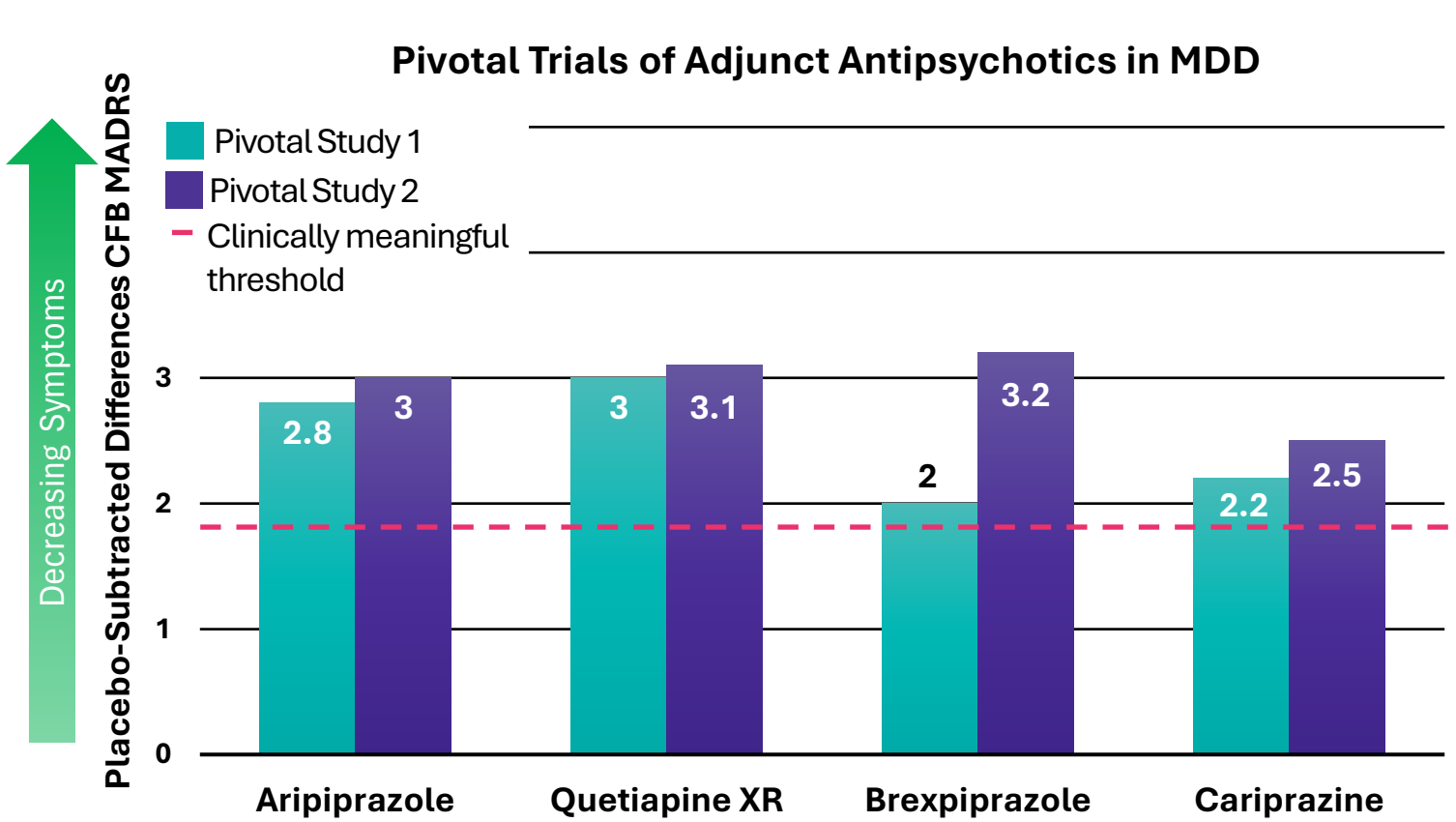
In preclinical studies, lumateperone indirectly activates both NMDA and AMPA glutamate receptors in the prefrontal cortex

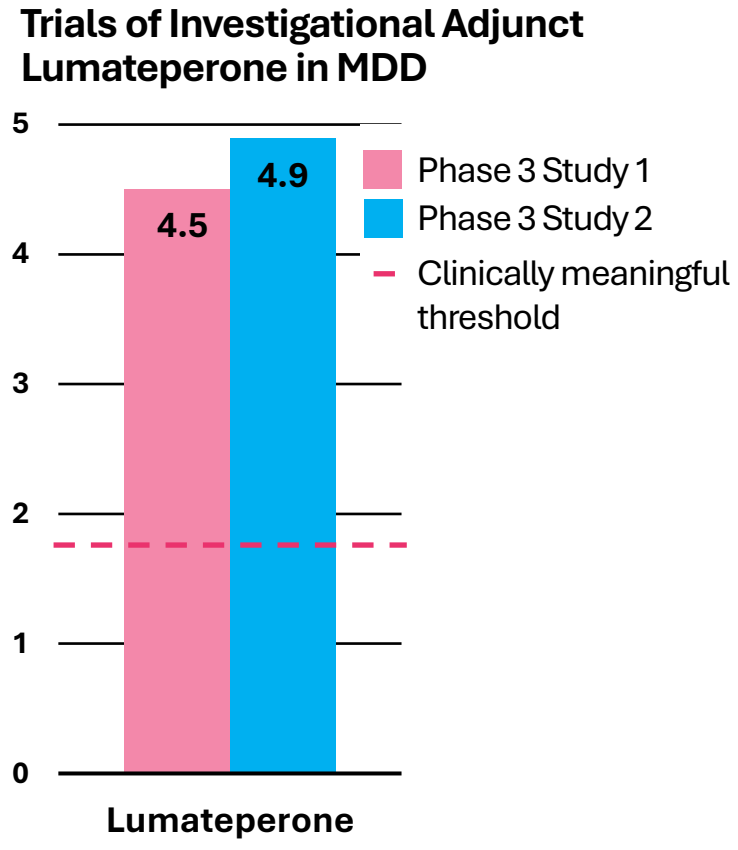
1. Lumateperone binds the D_1R receptor
2. Activation of the D_1R receptor strengthens AMPA and NMDA glutamate signaling
3. The AMPA receptor activates multiple downstream processes that are important for learning, memory, and recovery



AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor; D1R = D1 dopamine receptor; NMDAR = *N*-methyl-D-aspartate glutamate receptor; PFC = Prefrontal Cortex. Harvey J, et al. *J Neurosci*. 1997;17(14):5271-80. Vanover, KE, et al. *European Neuropsychopharmacol*. 2017;27:S660-1.

Adjunctive Atypical Antipsychotic Pivotal Trials: Placebo-Subtracted Differences





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

Abilify (aripiprazole), Seroquel XR (quetiapine), Rexulti (brexpiprazole), and Vraylar (cariprazine) prescribing information: 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 the 37th Psych Congress Annual Meeting, 10/29-11/2/2024, 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 the 37th Psych Congress Annual Meeting, 10/29-11/2/2024, Boston, MA.

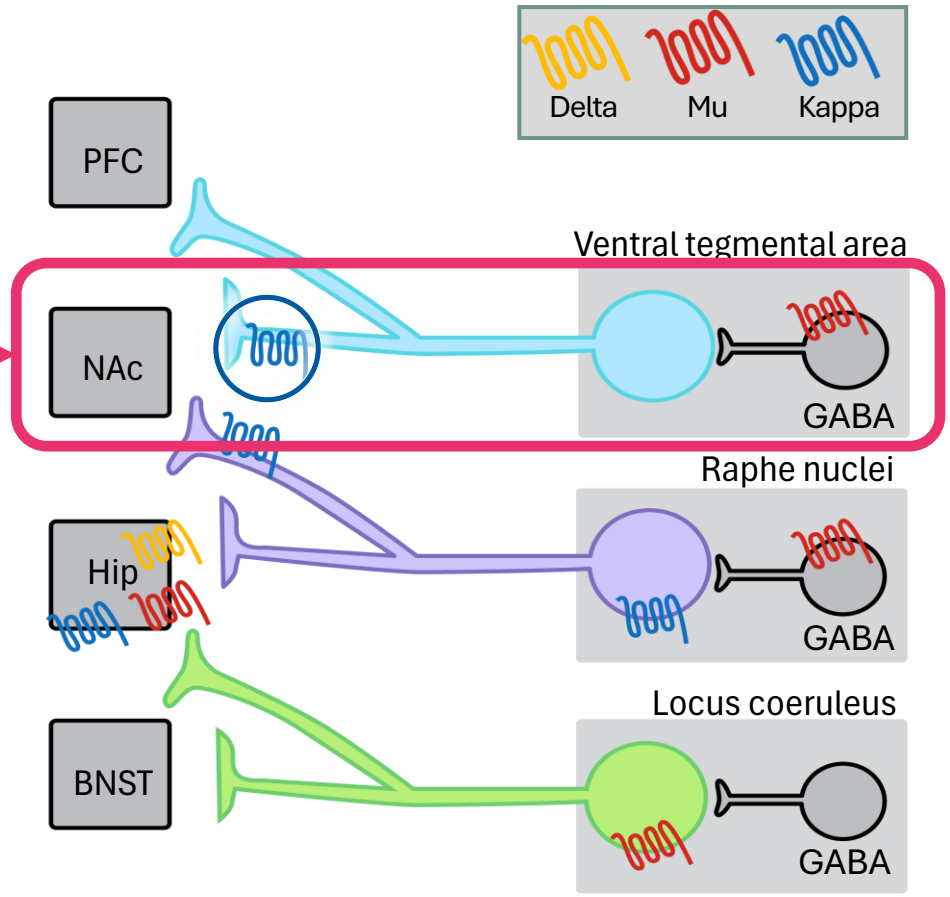
Key Learning Points

- The most prominent feature of the **lumateperone's** mechanism of action is **high-affinity 5-HT_{2A} serotonin receptor antagonism**
- During pivotal clinical trials of lumateperone for adjunctive treatment of MDD, **side effects** were similar to previous lumateperone studies and **did NOT include akathisa, weight gain, or metabolic symptoms**
- In clinical trials, **lumateperone** had a robust effect on **reducing depressive symptoms** compared with placebo that was **well above the minimal important clinical difference**

Emerging Agents for Adjunctive Treatment of MDD: Aticaprant

The Endogenous Opioid System Interacts with Systems Related to Anhedonia and Mood

- Anhedonia is a significant loss of interest or pleasure in all or almost all activities and is a very common core symptom of MDD
- Antagonism of **kappa opioid receptor** may address anhedonia by increasing release of dopamine in reward pathways



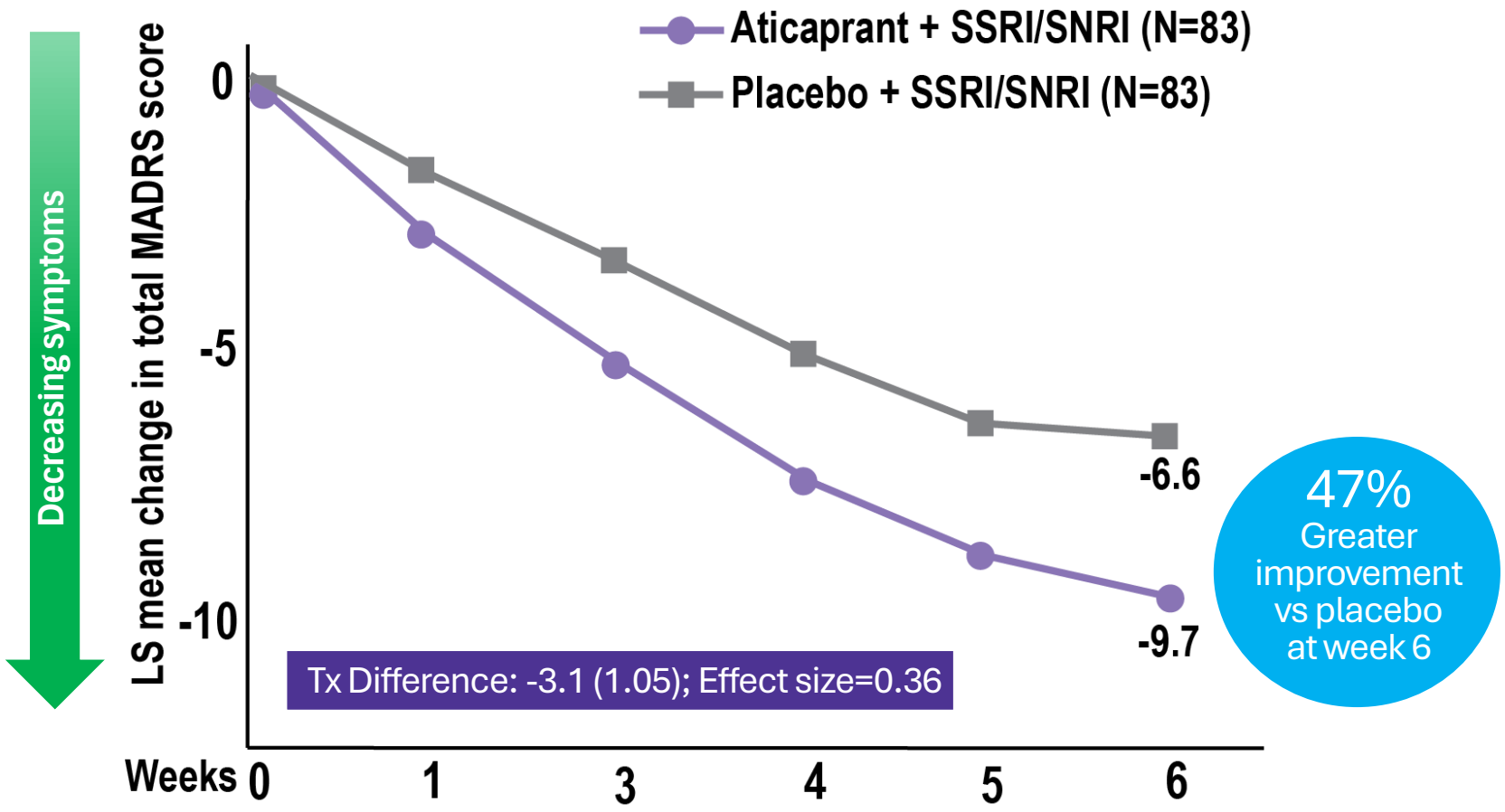
Kappa opioid antagonism is potentially associated with antidepressant and pro-reward effects, without abuse potential

BNST = Bed nucleus of stria terminalis; Hip = Hippocampus; NAc = Nucleus accumbans; PFC = Prefrontal cortex. Lutz P-E, Kieffer BL. *Trends Neurosci*. 2013;36(3):195-206. Tao R, Auerbach SB. *J Pharmacol Exp Ther*. 2002;303(2): 549-56. Schmidt ME, et al. *Neuropsychopharmacology*. 2024:1-11.

Phase 2 Clinical Study of Aticaprant for Adjunctive MDD Treatment

Adjunctive aticaprant improved depressive symptoms more than placebo in people with moderate-to-severe MDD

Subanalyses showed mprovement with aticaprant vs placebo was larger in people with higher than median anhedonia



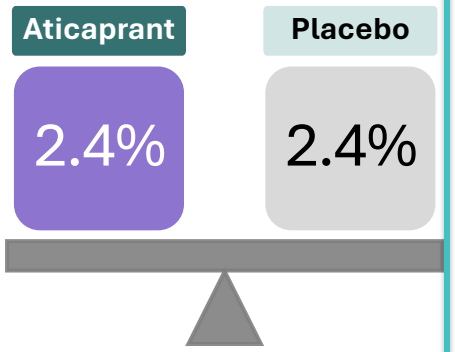
Schmidt ME, et al. *Neuropsychopharmacol.* 2024:1-11.

Aticaprant Adverse Events in Phase 2a

Adverse Events ≥ 5% in any arm	Aticaprant + SSRI/SNRI	Placebo + SSRI/SNRI
Headache	10 (11.8%)	6 (7.1%)
Diarrhea	7 (7.2%)	2 (2.4%)
Nasopharyngitis	5 (5.9%)	2 (2.4%)
Pruritis	5 (5.9%)	0
D/C due to AE	1 (1.2%)	1 (1.2%)
No weight/metabolic changes or sexual AEs		

Human Studies Similar to Preclinical Findings

Aticaprant showed **no difference** for adverse events suggestive of abuse potential compared to placebo



Aticaprant was efficacious and well-tolerated as an adjunctive treatment in phase 2, but phase 3 studies showed insufficient efficacy in the MDD population, and the program was discontinued

Schmidt, ME., et al. *Neuropsychopharmacology* (2024): 1-11. https://www.jnj.com/media-center/press-releases/johnson-johnson-statement-on-ventura-program. Accessed 3/10/2025.

Panel Discussion

Practical Strategies for Determining Partial Response in Patients

Things to Address

- Inaccurate diagnosis
- Unaddressed co-occurring medical or psychiatric disorders, including substance use disorders
- Inappropriate selection of therapeutic modalities
- Complicating psychosocial and psychological factors
- Nonadherence to treatment

Things to Monitor

- Inadequate duration of treatment
- Treatment adherence
- Persistent or poorly tolerated side effects
- Inadequate dose of medication
- Pharmacokinetic/pharmacodynamic factors affecting medication action
- Poor therapeutic alliance

American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd ed. American Psychiatric Publishing, Inc.; 2010.

Case Presentation

- **HISTORY**
  - Consuela is a 47-year-old Hispanic woman with a 17-month history of depressed mood
  - Reports depressive episode 10-15 years ago after job loss and romantic relationship challenges
- **SYMPTOMS:** she expresses or endorses
  - Insomnia
  - Anhedonia
  - Fatigue
  - Increased tearfulness
  - Increased appetite
  - Feelings of guilt for not wanting to keep her new grandchild for visits
  - NO rapid thoughts or speech differences
  - NO decreased need for sleep
- **EVALUATION**
  - PHQ-9 score = 23 and negative Rapid Mood Screener
  - Clinical examination, lab values within normal limits

➢ **DIAGNOSIS: MDD**

- **TREATMENT**
  - A first-degree relative responded to sertraline
  - Treatment initiated with 25 mg sertraline, titrated to 100 mg over 6 weeks
- **RESPONSE**
  - PHQ-9 =16 (7-point reduction)
  - Good adherence, misses~2 doses per month
  - Mild nausea
  - Reduced libido with emergent anorgasmia

DISCUSSION

Does this treatment journey represent remission, response, partial response, or failure? What would be some of your next steps?

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

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