



The Road to Recovery in MDD:
**From Partial Response
to Remission and Beyond**

MasterClass

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Faculty

Christoph U. Correll, MD

Clinical Professor of Psychiatry,
Zucker School of Medicine at
Hofstra/Northwell
New York, NY

Brooke Kempf, PMHNP-BC

Adjunct Faculty, Indiana
University, Indianapolis
Brazil, Indiana

Ricky Reding

Patient Advocate

Faculty Disclosures

- **Christoph U. Correll, MD:** Advisory Board – AbbVie, Alkermes, Allergan, Angelini, BoehringerIngelheim, Bristol Myers Squibb, Cerevel, Compass, Gedeon Richter, Janssen/J&J, Karuna, LBPharmaceuticals, Lundbeck, Medincell, Merck, Neuraxpharm, Neurelis, Neurocrine Biosciences, Newron, Novo Nordisk, Otsuka, Recordati, Rovi, Sage, Seqirus, SK LifeScience, Sunovion, Supernus, Teva, Vertex, Viatris; Consultant – AbbVie, Alkermes, Allergan, Angelini, Autobahn, Boehringer Ingelheim, Bristol Myers Squibb, Cerevel, Compass, Denovo, Eli Lilly, Gedeon Richter, GH, Intra-Cellular Therapies, Janssen/J&J, Karuna, Kuleon Bioscience, LB Pharmaceuticals, Lundbeck, Medincell, Medlink, Merck, Mindpax, Neuraxpharm, Neurelis, Neurocrine Biosciences, Newron, Novo Nordisk, Otsuka, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sunovion, Supernus, Teva, Vertex, Viatris; Grant/Research Support – BoehringerIngelheim, Janssen, Takeda
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Learning Objectives

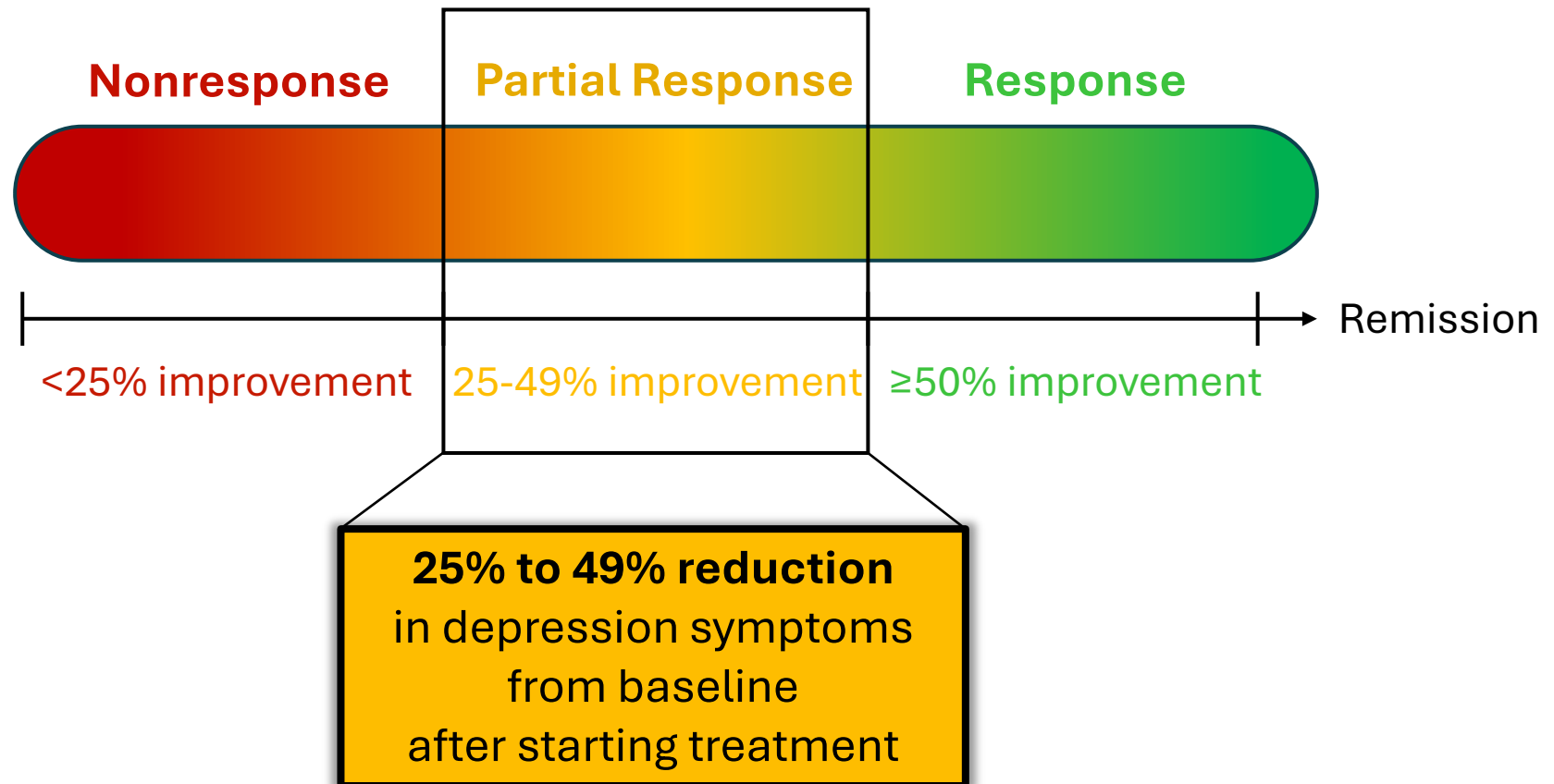
- Detect partial treatment response in patients with MDD with attention to the impact of specific residual symptoms such as anhedonia, anxiety, sleep disturbance, or cognitive dysfunction
- Evaluate the latest clinical evidence associated with available and emerging adjunctive pharmacotherapies, specifically focusing on atypical antipsychotics for patients with partial response in MDD, including their efficacy for specific residual symptoms
- Implement evidence-based and patient-centered adjunctive treatment strategies to address residual symptoms and improve outcome for patients with partial response in MDD

Understanding Partial Response in MDD



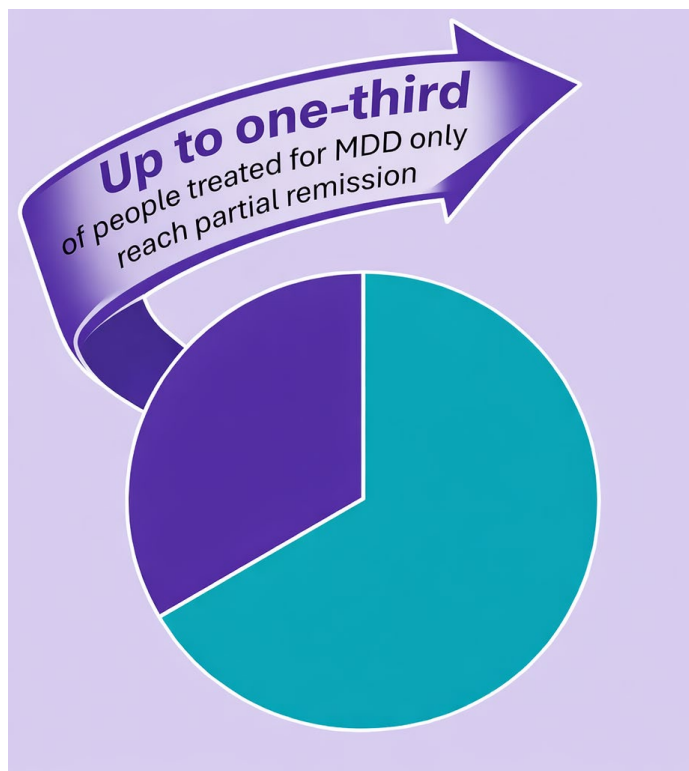
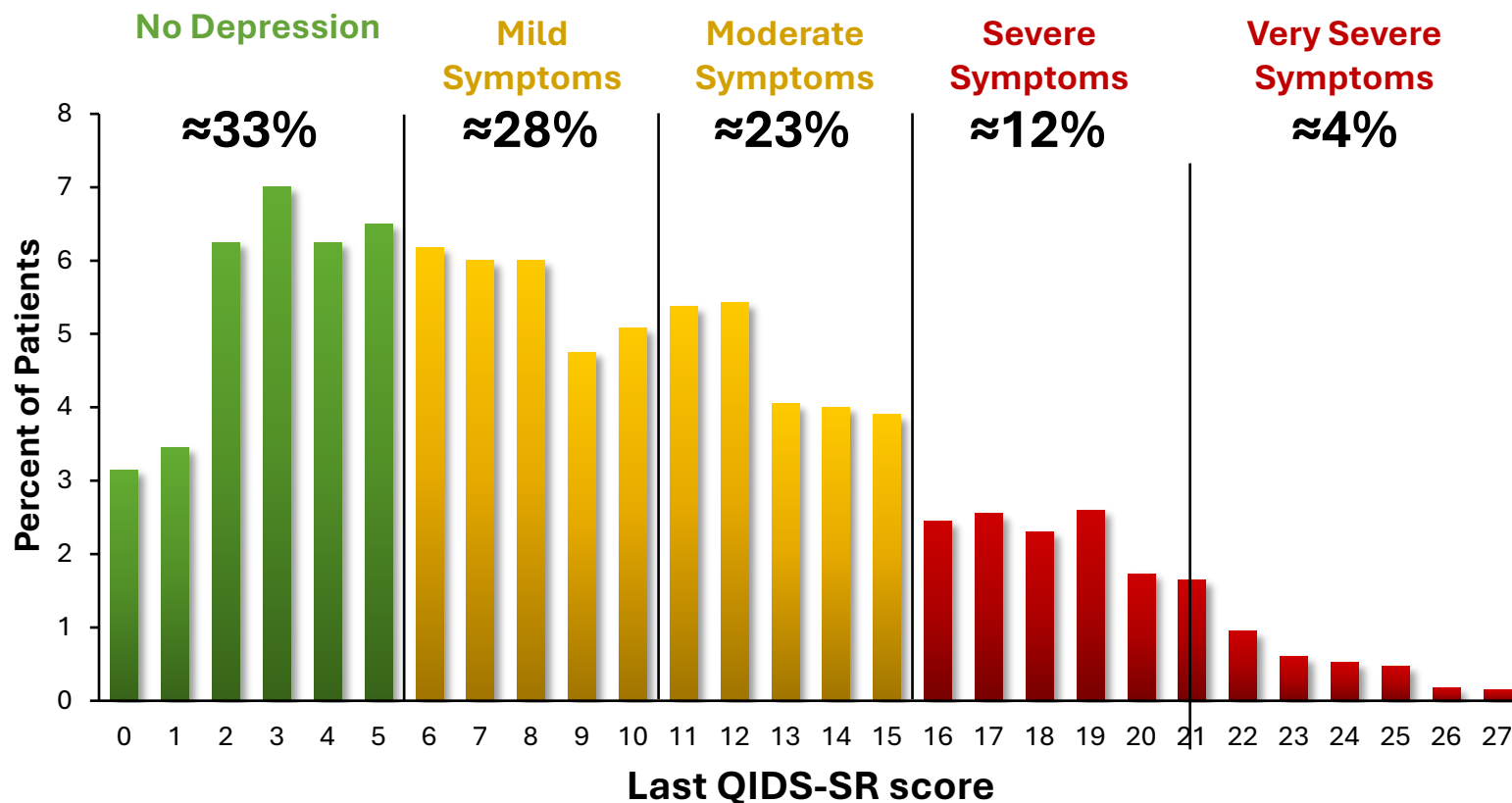
What Is Partial Response in MDD?

Treatment Response Continuum in MDD



Partial Response Is Extremely Common in MDD

Total distribution of exit scores on QIDS-SR for outpatients with MDD (N=2876)

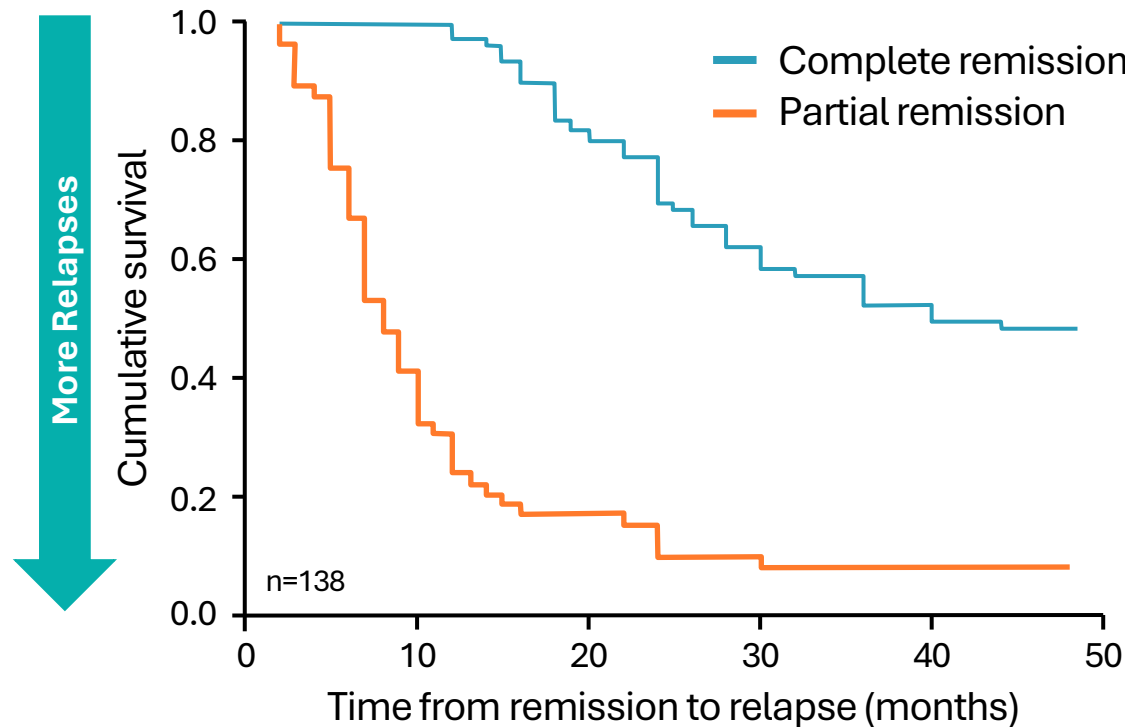


The majority of participants in STAR*D remained symptomatic after receiving a first-line antidepressant as monotherapy for up to 14 weeks.

QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.
Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

Settling for Partial Response Has Substantial Consequences: Why “Better” Is Not Enough

Time to relapse in individuals with an MDE over a 4-year period



Greater risk of
relapse or
recurrence

More chronic
depressive
episodes

Shorter
durations between
episodes

Ongoing
impairment
in work and
relationships

Associated with an
increased risk of
all-cause mortality

Judd. *Am J Psychiatry*. 2000;157:1501. McLaughlin. *Prev Sci*. 2011;12:361. Hare. *Eur Heart J*. 2014;35:1365. Murphy. *Arch Gen Psychiatry*. 1987;44:473. Miloyan. *World Psychiatry*. 2017;16:219. van Dooren. *PLoS One*. 2013;8:e57058. de Groot. *Psychosom Med*. 2001;63:619. Pence. *JAMA Psychiatry*. 2018;75:379. Ickovics. *JAMA*. 2001;285:1466. Pincus L, et al. *J Affect Disord*. 2004;82(2):291–296

The Remission-Recovery Gap in MDD

Depression affects ~350 million people worldwide and is the leading cause of disability, Yet treatment success is measured primarily by symptom reduction, not **functional recovery**

97%

of patients with MDD during
a
12-month period reported
**some level of functional
impairment in ≥ 1 domain**

60%

report
severe or very severe
impairment

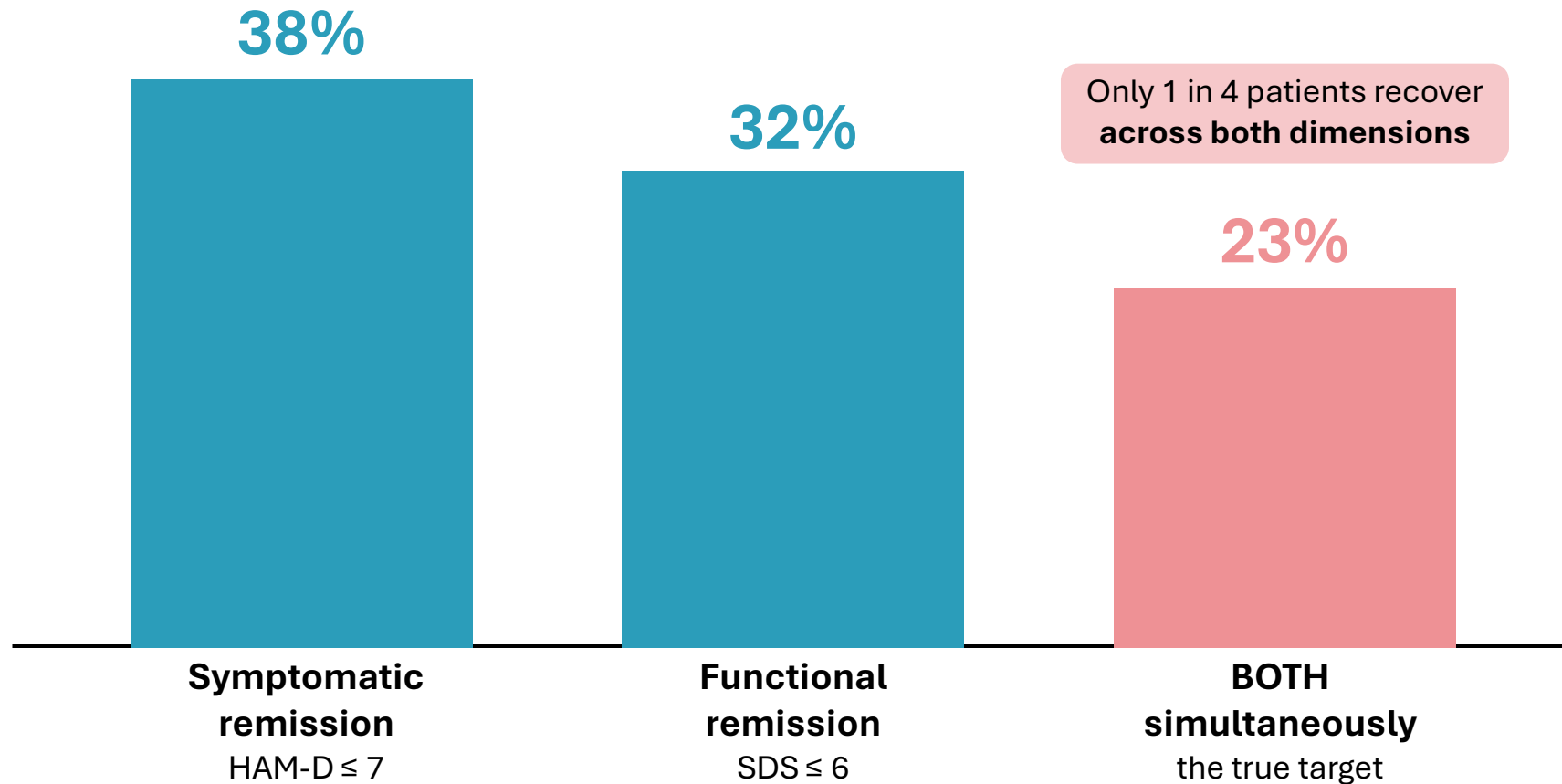
\$36.6B

annual lost work
productivity in the US

Patients lose an average of 27 workdays per year, equal to 225 million lost workdays annually in the US

The Critical Gap: Symptoms vs Function

Why do many patients achieve symptom remission yet continue to experience **functional impairment**?



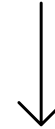
What This Means for Depression Treatment

The Functional Impairment Problem

- Current treatment goals focus on **symptom remission** ($\text{HAM-D} \leq 7$)
- **Functional remission** ($\text{SDS} \leq 6$) should be equally important
- Residual functional impairment predicts **relapse risk**
- Cognitive deficits may require targeted **cognitive rehabilitation**

Symptom-Centric Model

“Do you feel better?”
 $\text{HAM-D} \leq 7$



Functional Model

“Can you work and connect?”
 $\text{SDS} \leq 6$

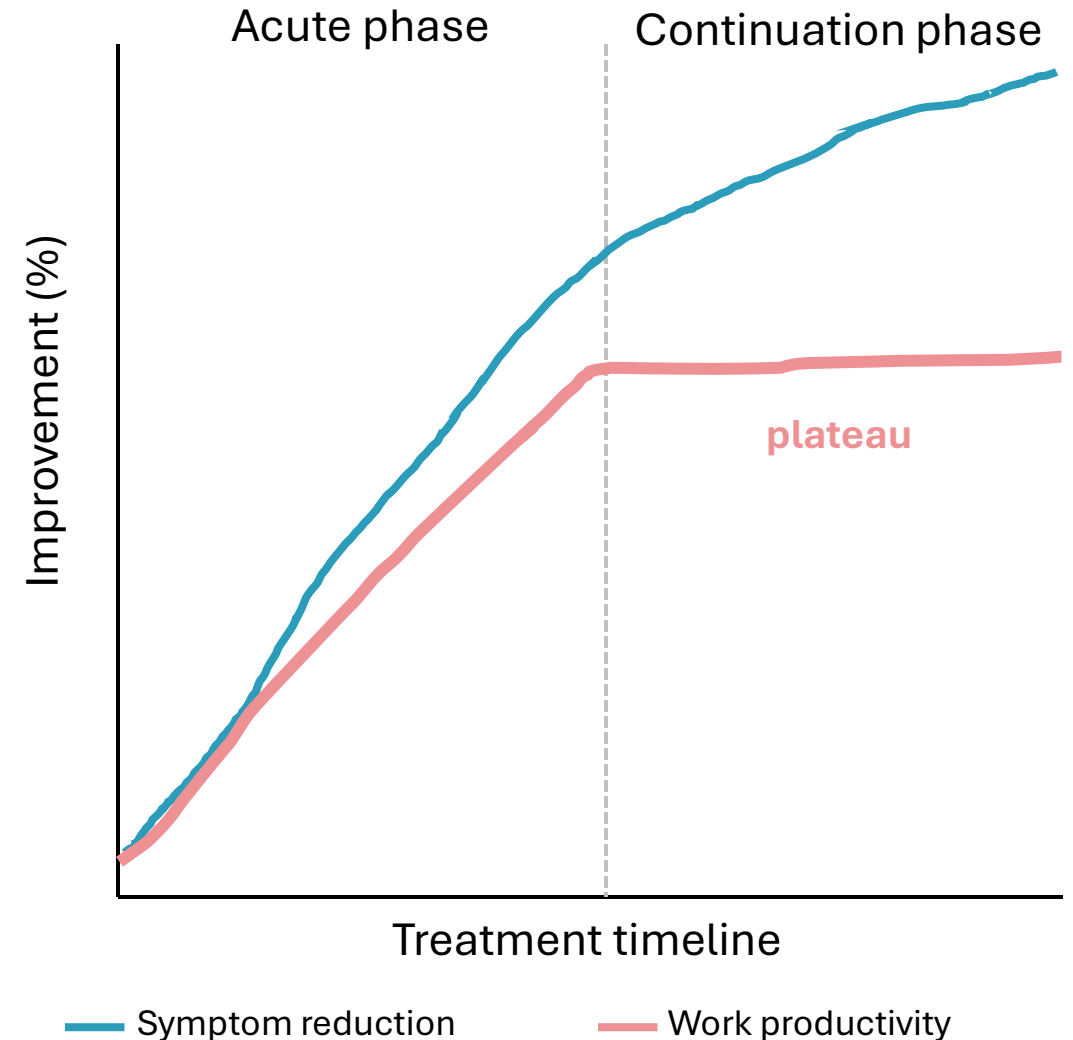
Bottom line: Feeling better is not the same as functioning well; recovery must be redefined.

Work and Social Function

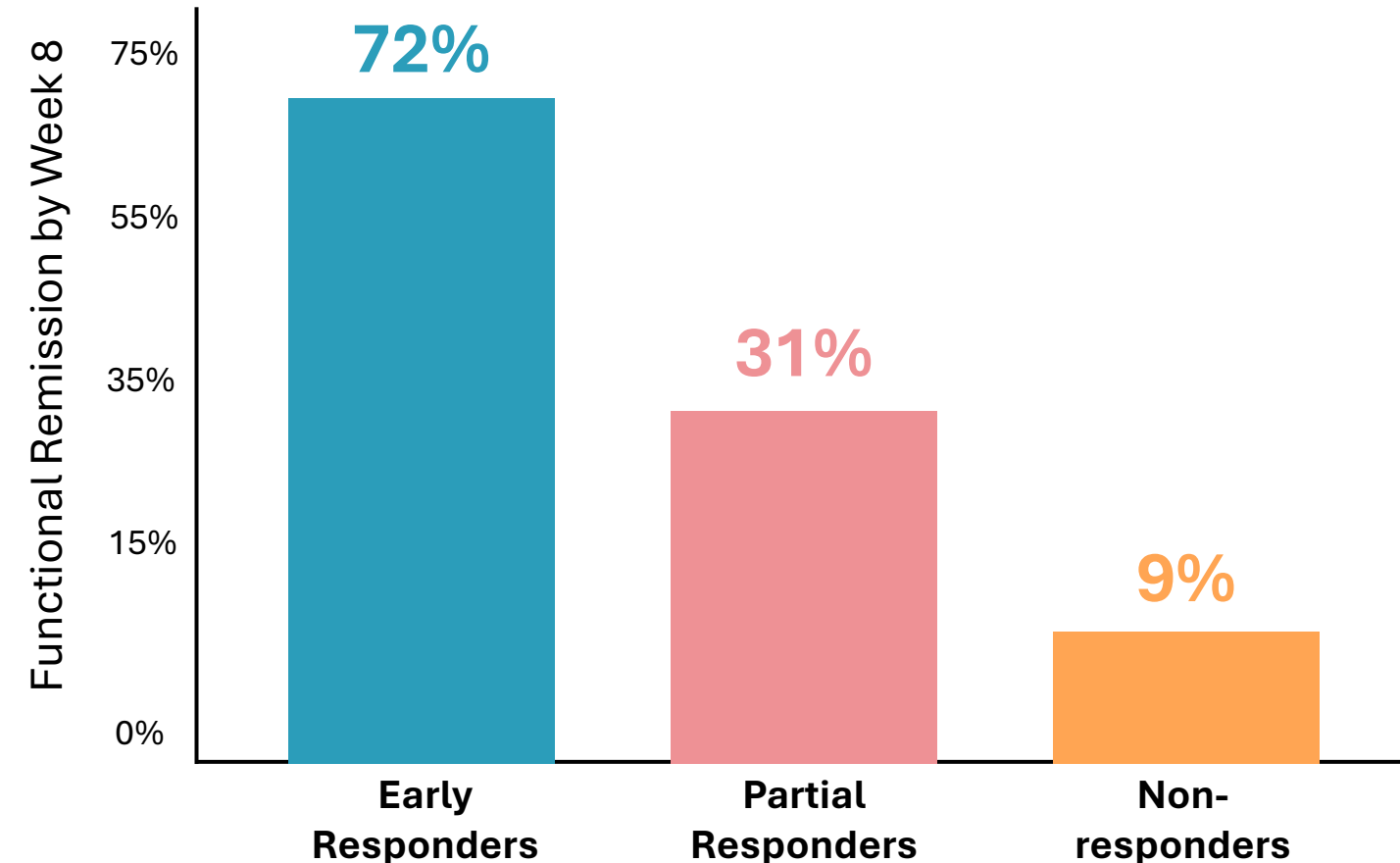
- 27 workdays lost per employee per year with MDD
- Even mild symptoms reduce productivity by 1.65% per PHQ-9 point
- Productivity gains parallel symptom reduction during acute phase only

The Paradox

Without early symptom remission, work productivity plateaus despite continued improvement in mood symptoms



Early Response Predicts Functional Recovery



- Baseline depression severity did **NOT** predict functional improvement
- Early treatment response was highly predictive of functional outcomes
- Partial responders remained functionally impaired despite symptom reduction

Clinical implication:

Week 2 assessment identifies likely treatment failures early, enabling timely intervention

Residual Symptoms Drive Poor Outcomes



Depressed mood,
Anxiety



Emotional Blunting/
Anhedonia



Cognitive
Problems



Eating
Problems



Sleeping Problems/
Insomnia



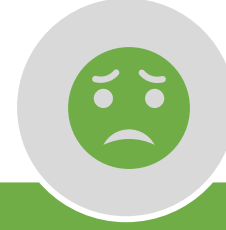
Psychomotor
Problems



Fatigue or
Lack of Energy



Worthlessness
And/or Guilt



Suicidal Ideations



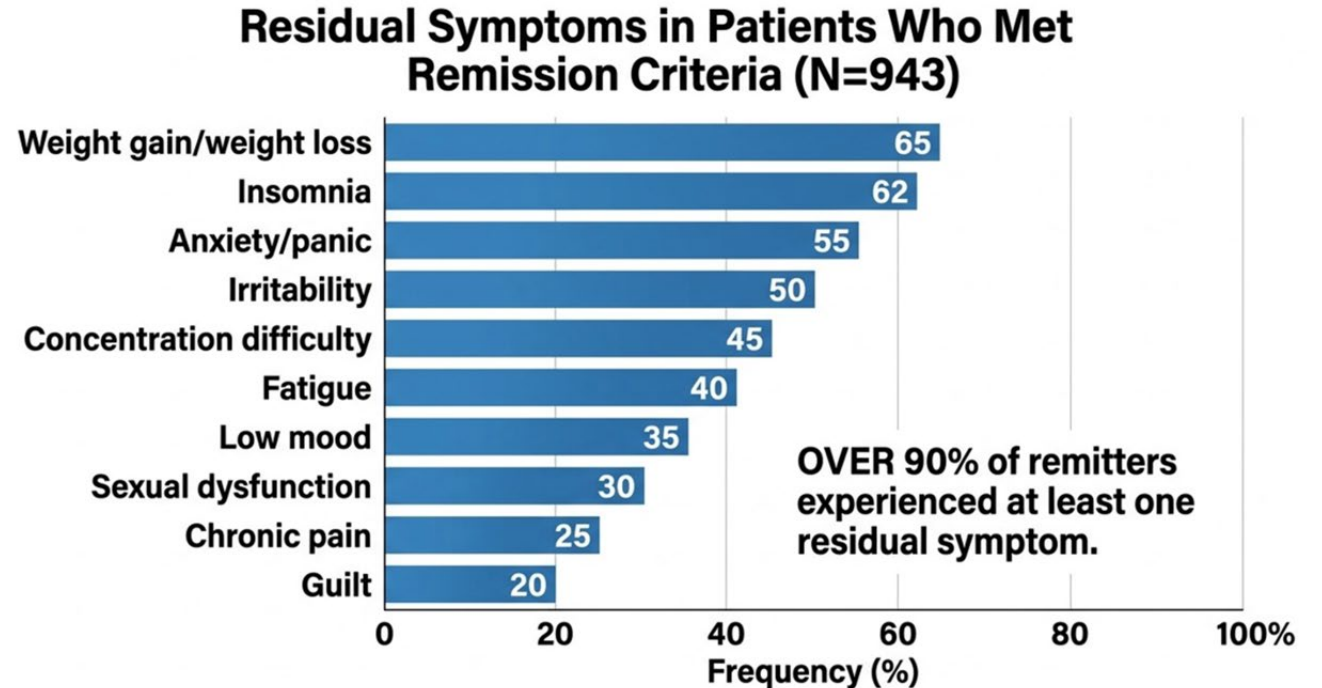
Lack of Motivation

Residual Symptoms in Remission

Over 90% of even remitted patients have at least one residual symptom

Most common: weight gain, insomnia, and anxiety

Other significant symptoms: irritability, fatigue, cognitive impairment, and guilt



STAR*D Trial: Residual Symptoms Despite Remission (Nierenberg et al)



HIGH-IMPACT RESIDUAL SYMPTOMS



Anhedonia

Directly correlates with persistent work and social disability.



Sleep Disturbances & Insomnia

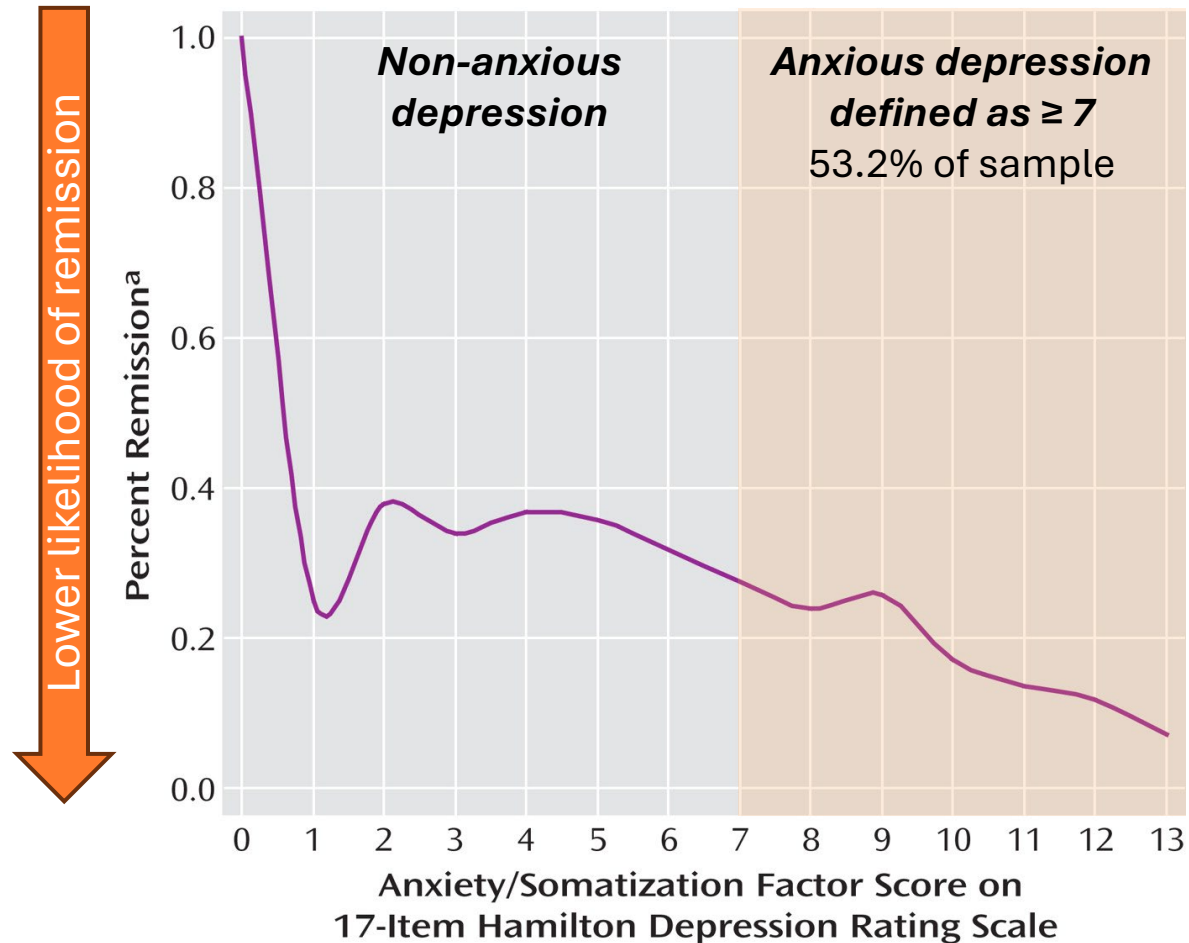
Present in 66.6% of cases.
Dominant contributor to cognitive deficits and physical fatigue.



Residual Anxiety

Increases overall relapse risk by 3x and accelerates time to relapse.

Remission Is Significantly Less Likely for Individuals with MDD + Higher Anxiety, Even With Antidepressant Treatment



Among STAR*D Level 1 outpatients treated with citalopram (N=2,876), 53% met criteria for anxious depression at baseline.

Higher baseline anxiety/somatization scores were associated with significantly lower likelihood of remission, demonstrating that **co-occurring anxiety predicts poorer antidepressant outcomes**



Key Learning Points

- Partial response is defined as **meaningful improvement in symptoms but less than 50%**. It is very common and associated with poorer short- and long-term outcomes
- Residual symptoms, such as anhedonia, anxiety, sleep disturbance, or cognitive dysfunction, contribute to functional impairment, relapse risk, and adverse mental and physical health outcomes
- The therapeutic goal in MDD is full symptom remission and functional recovery, not simply symptom reduction

Detection and Evaluation of Partial Response in MDD

Examples of Residual Symptoms of MDD

Persistent Low Mood

Subthreshold depressive affect persisting after initial treatment response

Anhedonia

Reduced capacity for pleasure; often under-detected in routine follow-up

Sleep Difficulties and Cognitive Difficulties

Insomnia, hypersomnia, poor concentration, and memory impairment

Anxiety Symptoms

Comorbid anxiety is common; use GAD-7 to monitor severity over time

**Residual symptoms predict relapse and functional impairment.
Systematic monitoring beyond mood is essential to guide treatment toward full remission.**

Generalized Anxiety Disorder-7 (GAD-7): A Standardized Scale to Detect and Monitor Anxiety

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
Feeling nervous, anxious or on edge	0	1	2	3
Not being able to stop or control worrying	0	1	2	3
Worrying too much about different things	0	1	2	3
Trouble relaxing	0	1	2	3
Being so restless that it is hard to sit still	0	1	2	3
Becoming easily annoyed or irritable	0	1	2	3
Feeling afraid as if something awful might happen	0	1	2	3
Total Score (add column totals)				
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely Difficult ☐				

Total Score

Anxiety Symptoms

- 0–4: None to minimal
- 5–9: Mild
- 10–14: Moderate
- 15–21: Severe

The GAD-7 is **quick to administer (<2 minutes)**, **validated**, and **provides immediate scoring** of anxiety symptoms

MADRS Anhedonia Score

The **MADRS** is a 10-item clinician-administered questionnaire to measure the severity of depressive episodes in adults

Five items from the MADRS are often used to measure anhedonia:



Apparent
sadness



Reported
sadness



Concentration
difficulties



Lassitude



Inability
to feel

MADRS = Montgomery-Åsberg Depression Rating Scale.

Montgomery SA, et al. *Br J Psychiatry*. 1979;134:382-389. Cao B, et al. *Front Psychiatry*. 2019;10:17.

Validated Anhedonia Rating Scales

Question	SHAPS
1. I would enjoy my favorite television or radio program	14 item self-reported scale assessing consummatory anhedonia
2. I would enjoy being with my family or close friends*	
3. I would find pleasure in my hobbies and pastimes	A higher score indicates higher levels of anhedonia
4. I would be able to enjoy my favorite meal*	
5. I would enjoy a warm bath or refreshing shower*	
6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread	
7. I would enjoy seeing other people's smiling faces*	
8. I would enjoy looking smart when I have made an effort with my appearance	
9. I would enjoy reading a book, magazine, or newspaper*	
10. I would enjoy a cup of tea or coffee or my favorite drink	
11. I would find pleasure in small things, eg, bright sunny day, telephone call from a friend	
12. I would be able to enjoy a beautiful landscape or view	
13. I would get pleasure from helping others	
14. I would feel pleasure when I receive praise from other people	

*Reverse scored with answer choices: strongly agree, agree, disagree, strongly disagree

SHAPS = Snaith-Hamilton Pleasure Scale; DARS = Dimensional Anhedonia Rating Scale.

Nakonezny PA, et al. *Int Clin Psychopharmacol*. 2010;25(6):328-333. Rizvi SJ, et al. *Psychiatry Res*. 2015;229(1-2):109-119.

List at least 2:	DARS	
A. List at least 2 of your favorite pastimes/hobbies that are NOT primarily social:		
1. I would enjoy these activities	17 item self-reported scale assessing anticipatory and consummatory anhedonia in 4 domains	
2. I would spend time doing these activities		
3. I want to do these activities		
4. These activities would interest me		
B. List at least 2 of your favorite foods or drinks:		A higher score indicates higher levels of anhedonia
5. I would make an effort to get/make these foods/drinks		
6. I would enjoy these foods/drinks		
7. I want to have these foods/drinks		
8. I would eat as much of these foods as I could		
C. List at least 2 of your favorite social activities:		
9. Spending time with doing these things would make me happy		
10. I would be interested in doing things that involve other people		
11. I would be the one to plan these activities		
12. I would actively participate in these social activities		
D. List at least 2 of your favorite sensory experiences		
13. I would actively seek out these experiences		
14. I get excited thinking about these experiences		
15. If I were to have these experiences, I would savor every moment		
16. I want to have these experiences		
17. I would make an effort to spend time having these experiences		

Translating Patient Language into Domain Probes

The DARS Framework Probing Domains:

Hobbies

Food & Drink

Sensory

Social Activities

Spontaneous Patient Phrases:

"I don't care anymore."

"Nothing sounds fun."

"I'm just going through the motions."

"I feel numb."

"I can't enjoy anything."

"What's the point?"

Note Keywords: Detached, Bored, Numb, Mechanical, Uninspired, "Grey."

Targeted Interviewing Strategies

Probe Anticipatory Anhedonia (Wanting)

"When you think about doing something you used to enjoy, do you feel any excitement or looking forward to it?"

Probe Consummatory Anhedonia (Liking)

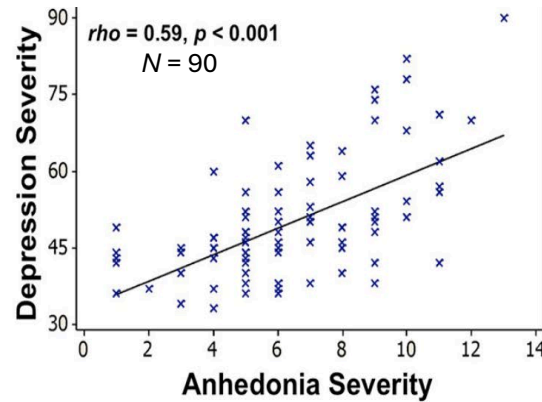
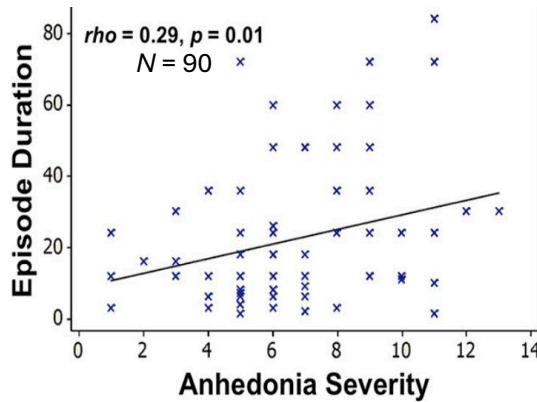
"When you actually do something that used to be enjoyable, can you feel pleasure in the moment?"

Probe Motivation and Effort

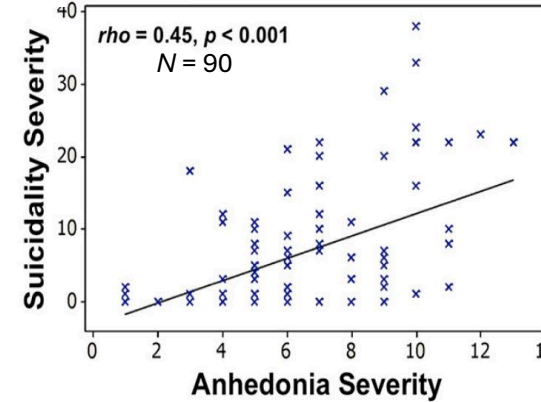
"Do you find it hard to get yourself to start activities, even ones you know you might enjoy?"

In Adolescents, Anhedonia Is Associated with...

Greater Depression Severity Longer Episode Duration

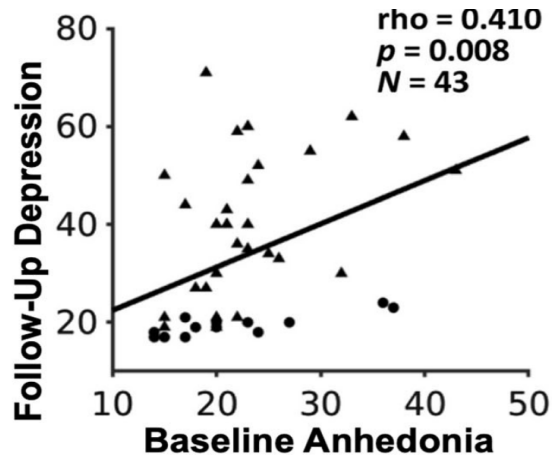


Greater Suicidality

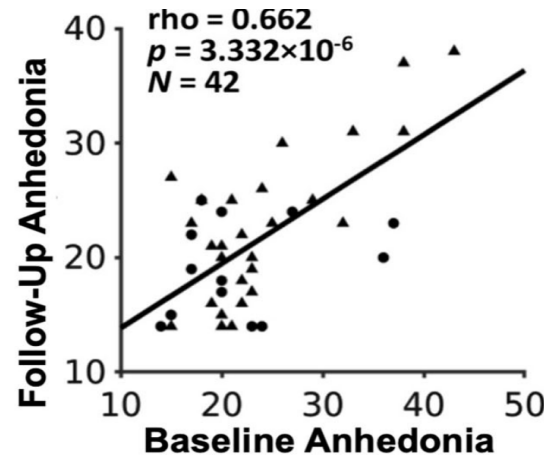


✕ N=90 depressed adolescents

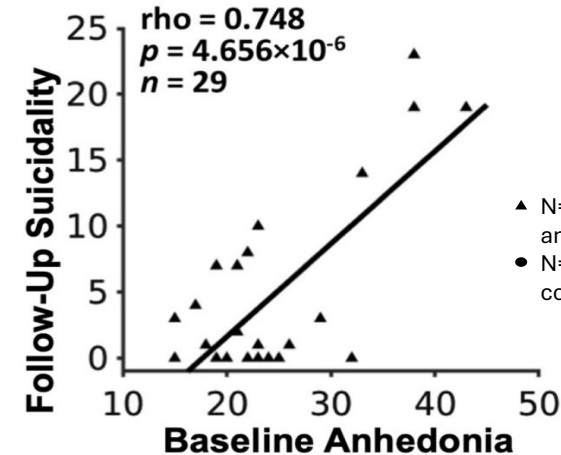
Future* Depression Severity



Future Anhedonia



Future Suicidality



▲ N=29 adolescents with mood and anxiety symptoms
● N=14 healthy adolescent controls

*Assessed after 24 months

Ely BA, et al. *Frontiers in Psychiatry*. 2021;12(678709).

Clinical Interviewing Skills to Detect Anhedonia

- Anhedonia is a core symptom of MDD, yet often missed
 - In routine follow-up, watch for:
 - Flat affect
 - Disengaged responses
 - Vague answers about daily activities
 - Use open, empathetic questioning and validate the patient's experience to encourage disclosure



“What activities have you lost interest in lately?”

“Do you still find pleasure in things you used to enjoy?”

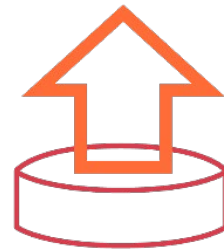
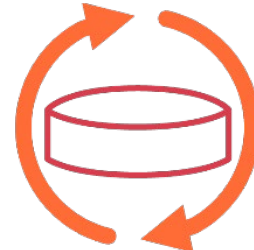
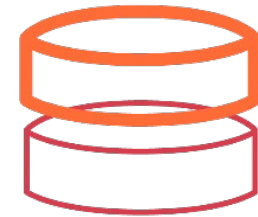
“How has your motivation changed since treatment began?”

Key Learning Points

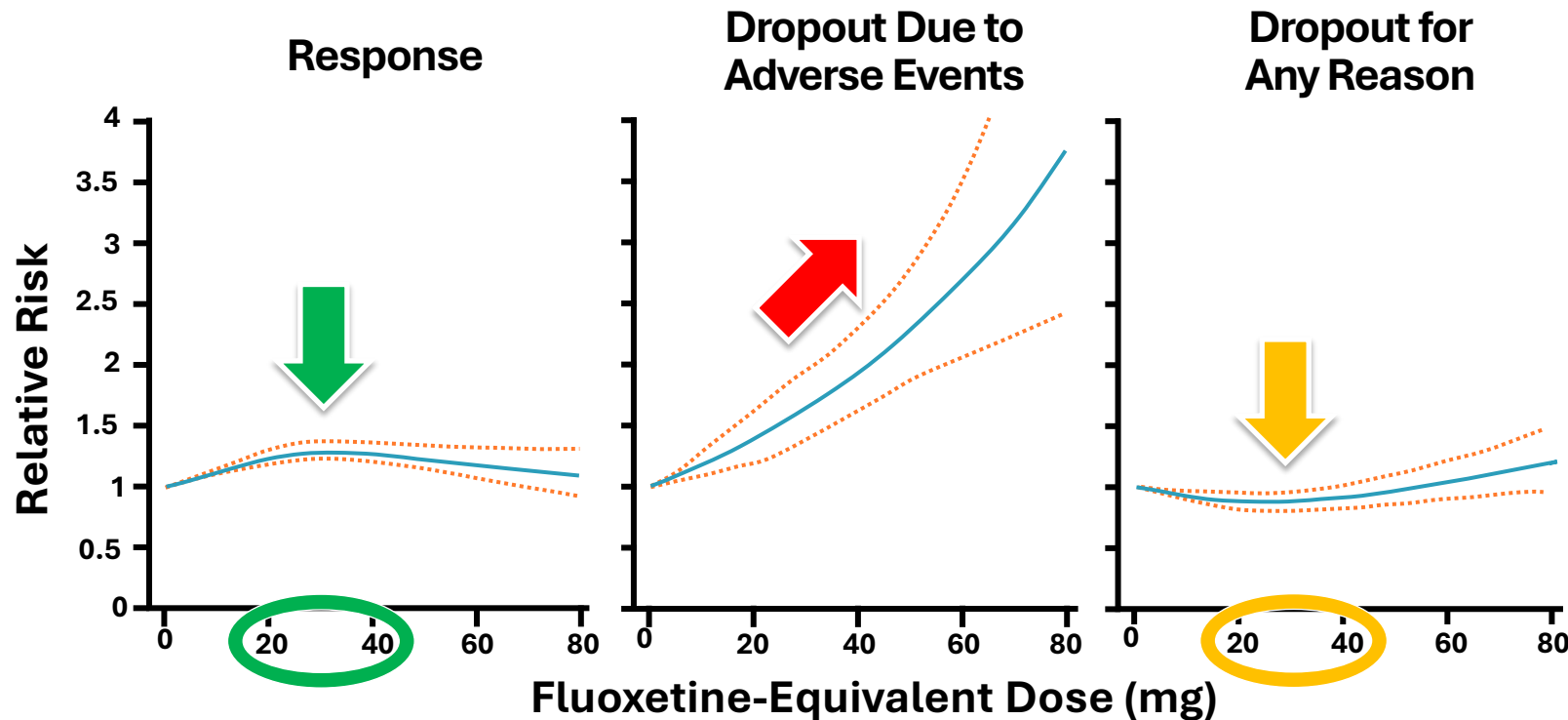
- Before declaring treatment failure, consider reasons for partial response, including partial adherence, or delayed onset of clinically noticeable improvement
- Higher baseline anxiety in individuals with MDD is associated with a significantly lower likelihood of achieving remission. Routine screening for comorbid anxiety symptoms (e.g., GAD-7) is recommended.
- Residual anhedonia is associated with greater depressive severity, longer episode duration, functional impairment, and increased suicidality risk
- Anhedonia can be assessed using validated instruments, including the MADRS anhedonia score, the Snaith-Hamilton Pleasure Scale (SHAPS), and the Dimensional Anhedonia Rating Scale (DARS)

Treatment Options for Partial 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

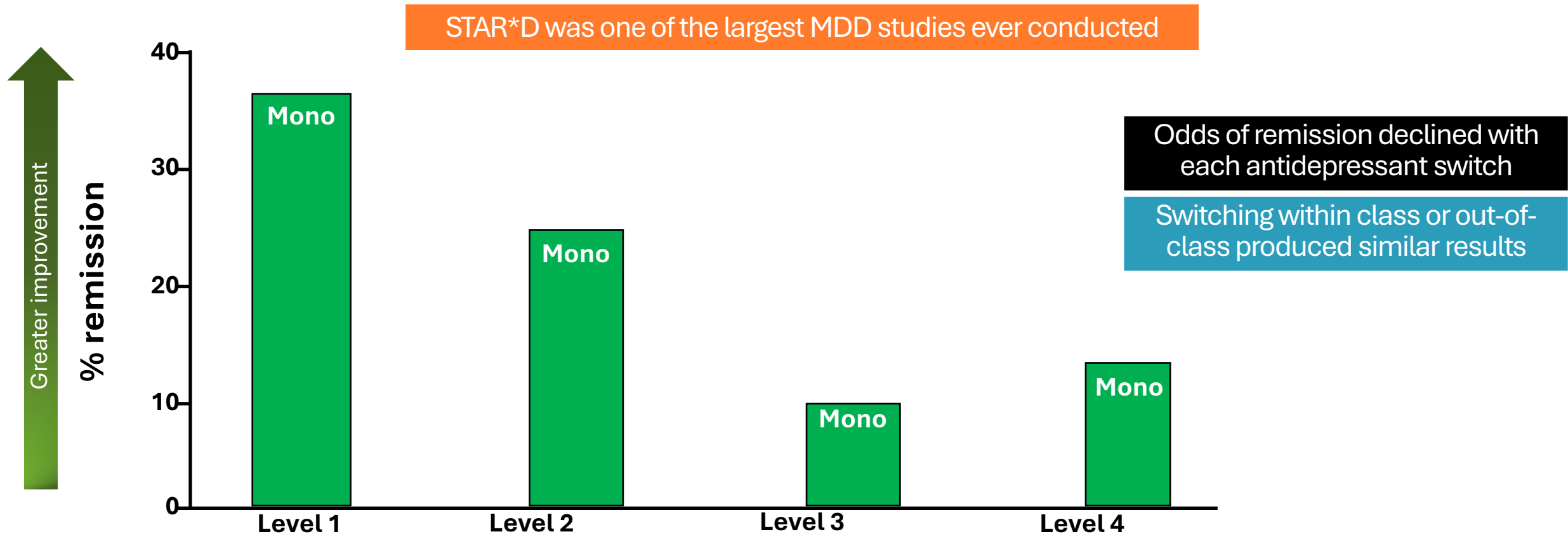
Citalopram	20-40 mg
Escitalopram	10-20 mg
Fluoxetine	20-40 mg
Paroxetine	17-34 mg
Sertraline	50-100 mg

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.

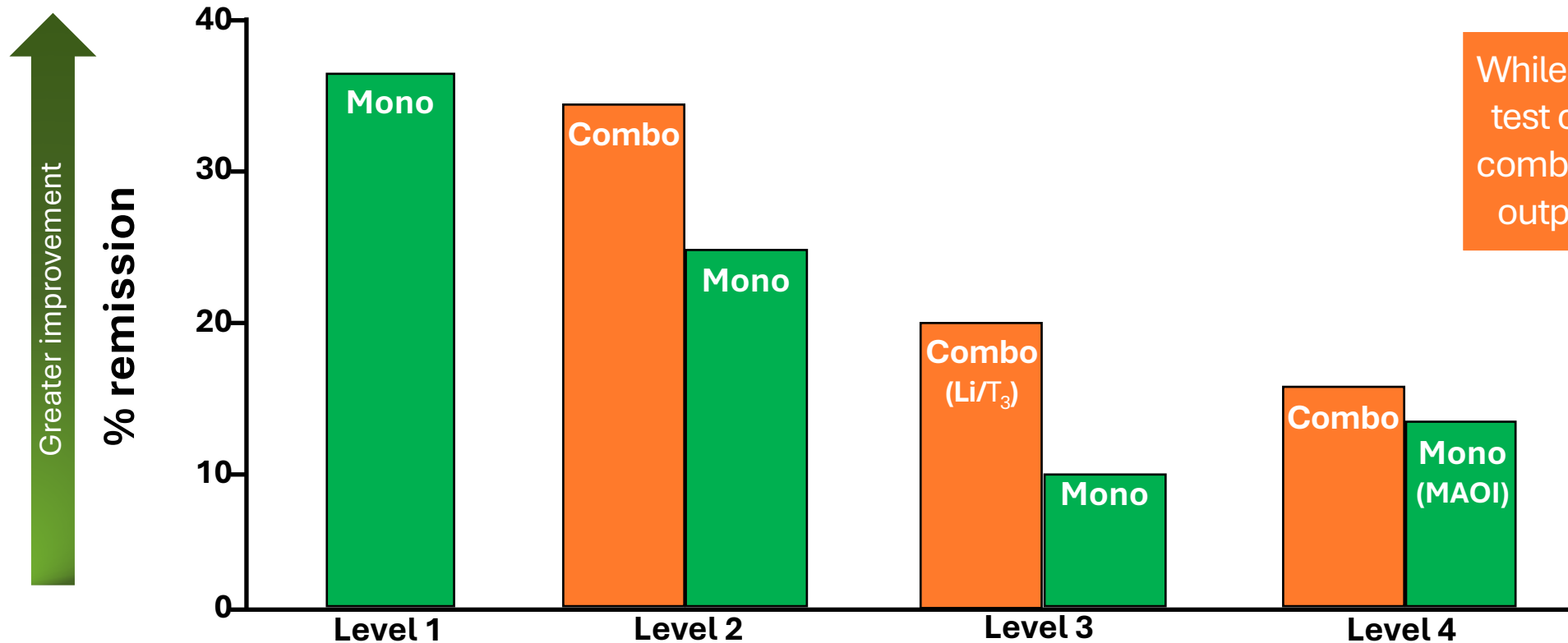
Switching Antidepressants Produces Diminishing Returns



Mono = monotherapy; Combo = combination; Li = lithium; T₃ = 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.

Switching Antidepressants Produces Diminishing Returns



While not statistically powered to test options against each other, combination options numerically outperformed monotherapies.

Mono = monotherapy; Combo = combination; Li = lithium; T₃ = 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)

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 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):980-991.

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 (e.g., 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-D2 receptor binding effects of antipsychotics may be the most important for MDD



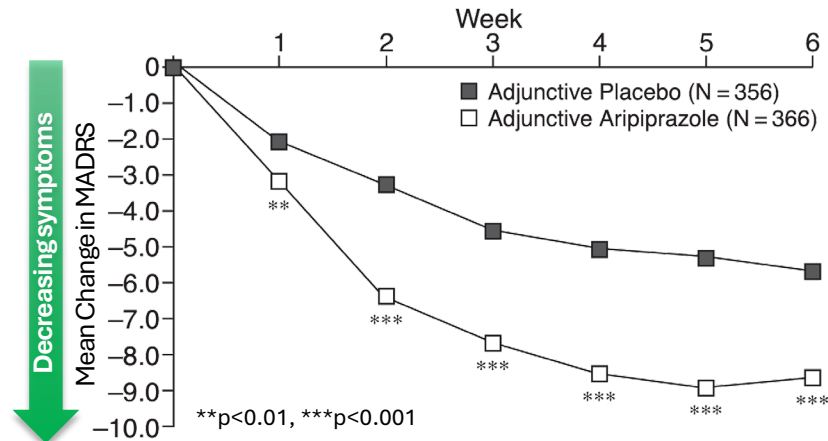
DA = dopamine; PFC = prefrontal cortex; NE = norepinephrine.

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. *Psych 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.

Aripiprazole and Quetiapine

Aripiprazole for Adjunct MDD: Pivotal Trials Summary

Adjunctive aripiprazole reduced depressive symptoms significantly more than placebo

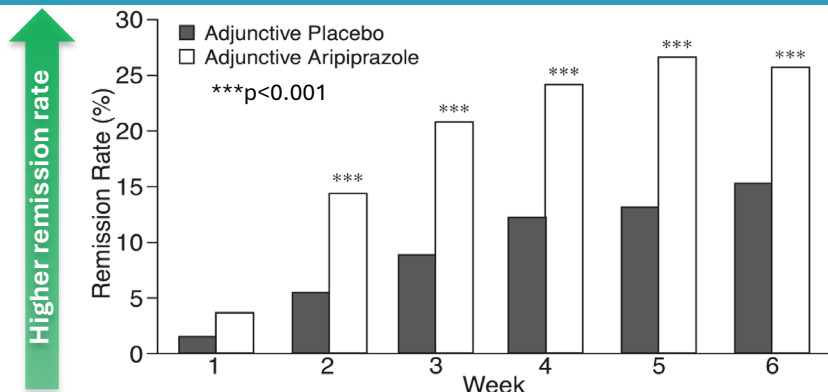


First medication with monoamine receptor partial agonism and antagonism found effective for adjunctive MDD treatment

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

AND improved remission rates



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.

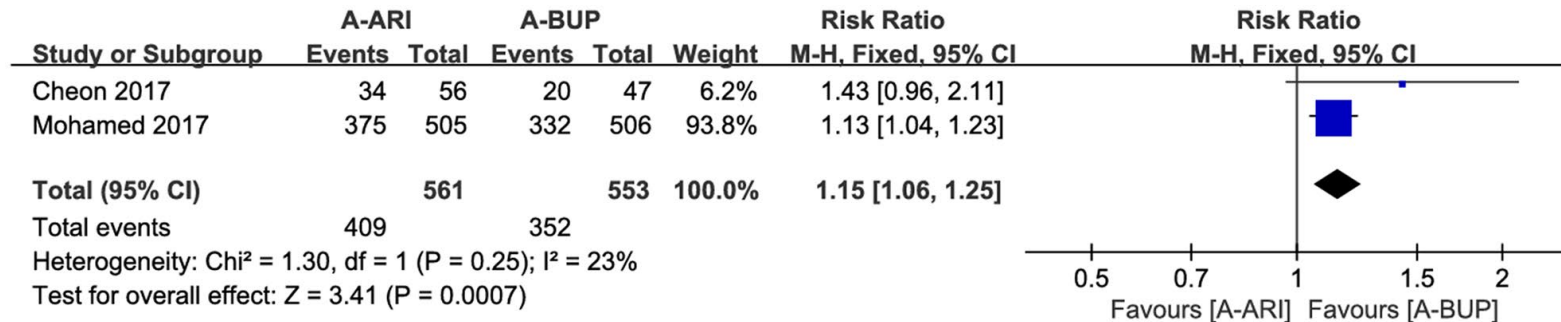
Berman RM, et al. *Neuropsychiatry Dis Treat*. 2011;7:303-312. Pae CU, et al. *CNS Drugs*. 2011;25(2):109-127. Thase ME, et al. *Prim Care Companion J Clin Psychiatry*. 2008;10(6):440-447.

Aripiprazole Augmentation Demonstrated Higher Response Rates vs Bupropion Augmentation

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)**



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

Key findings from meta-analysis

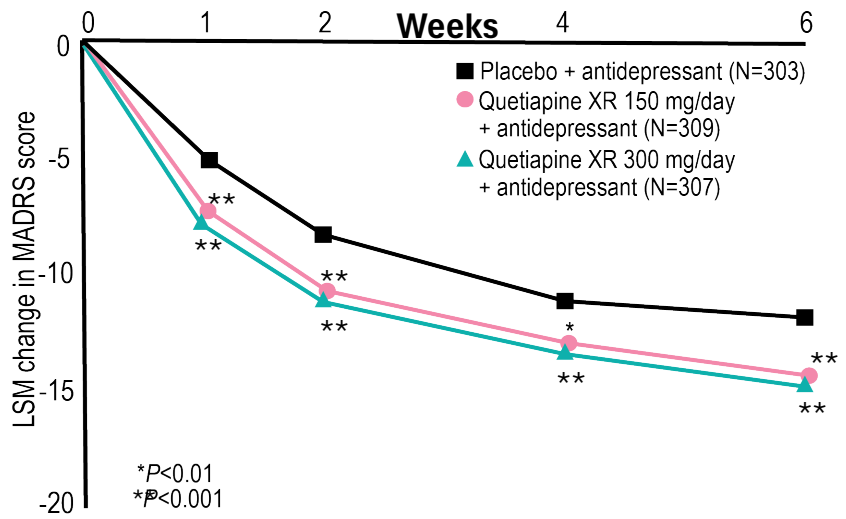
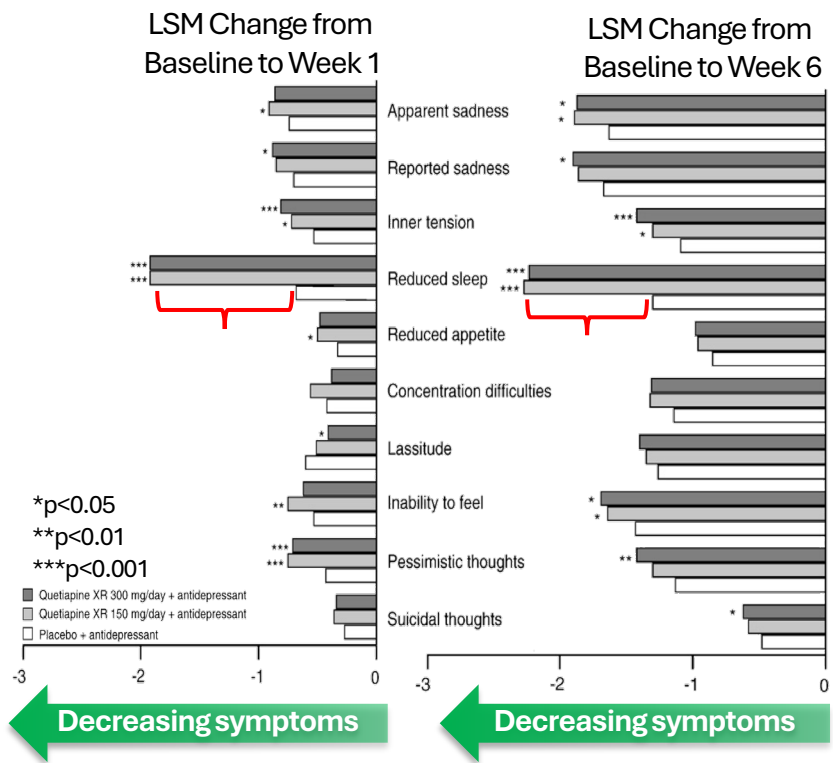
- ✓ **Aripiprazole augmentation** was associated with
 - a significantly higher response rate compared to bupropion augmentation
 - a significantly higher remission rate compared to switching to bupropion
- ✓ No significant difference in AEs or serious AEs across randomized groups

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.

Quetiapine XR for Adjunct MDD: Pivotal Trials Summary

Pooled Mean Change in MADRS from Two Pivotal Trials



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%

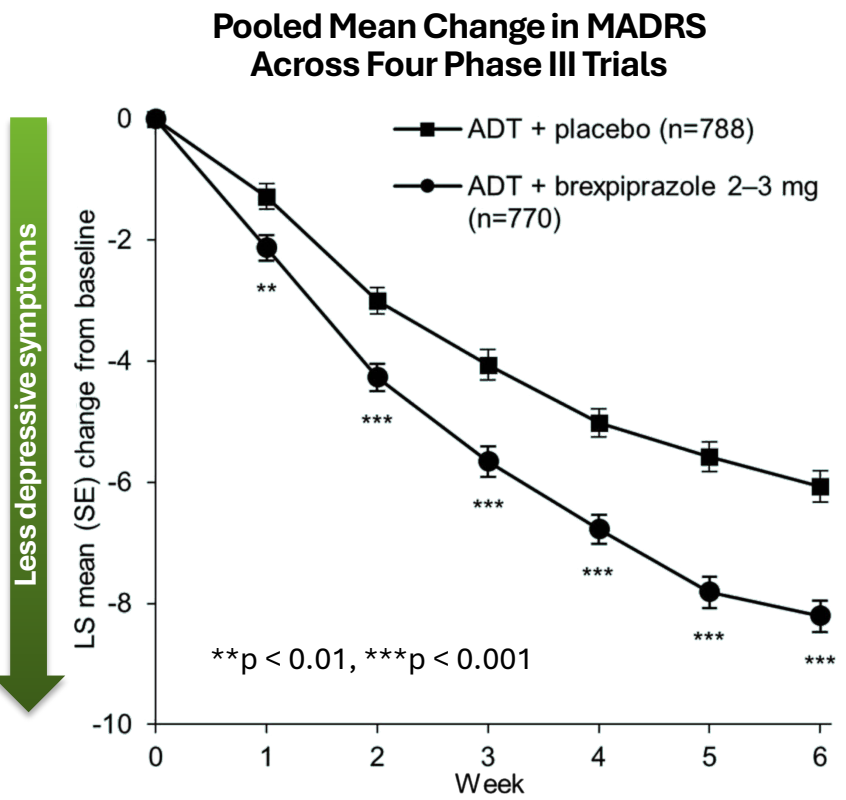
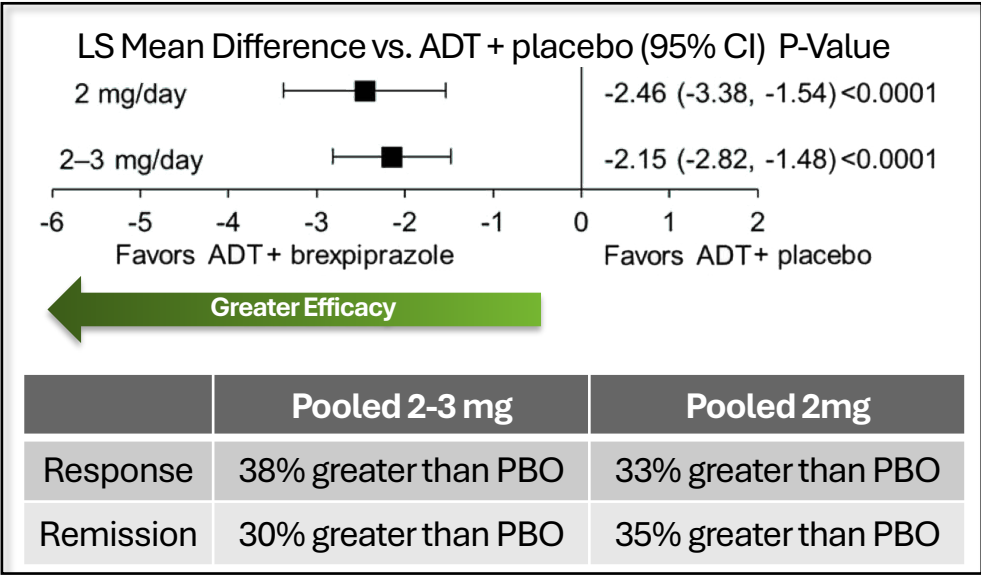
At week 6, Quetiapine XR does separate on 4 of 6 “core” MADRS items at 150 mg and 5 of 6 at 300 mg, but much of the overall separation is still driven by sleep

Long-term adverse event data unavailable for quetiapine XR



Brexpiprazole

Brexpiprazole in Adjunct MDD: Pivotal Trials Summary



Approved doses: 2 or 3 mg once daily

Titrate from 0.5 mg to 1 mg to 2 mg in weekly increments

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

Summary of Common AEs			
	2mg	3mg	PBO
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 Reduced Depressive Symptoms Even In Anxious Presentations

Pooled post-hoc analysis of three randomized placebo-controlled clinical trials

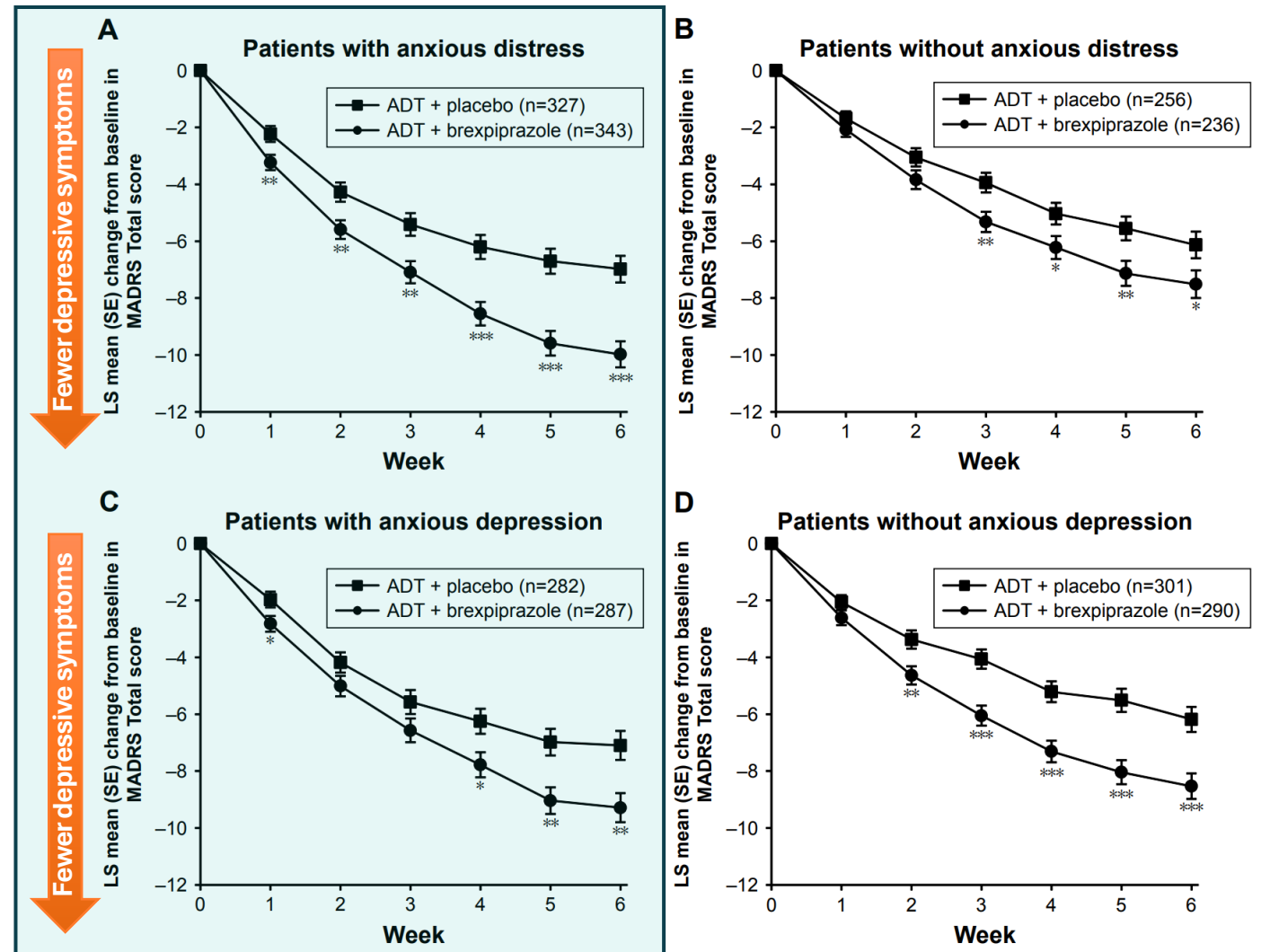
Anxiety Characterizations:

- *Anxious distress* = defined using DSM-5 features
- *Anxious depression* = defined as ≥ 7 on the HAM-D anxiety/somatization scale

Findings:

- Presence of clinically meaningful anxiety did not preclude the benefit of adjunctive brexpiprazole treatment

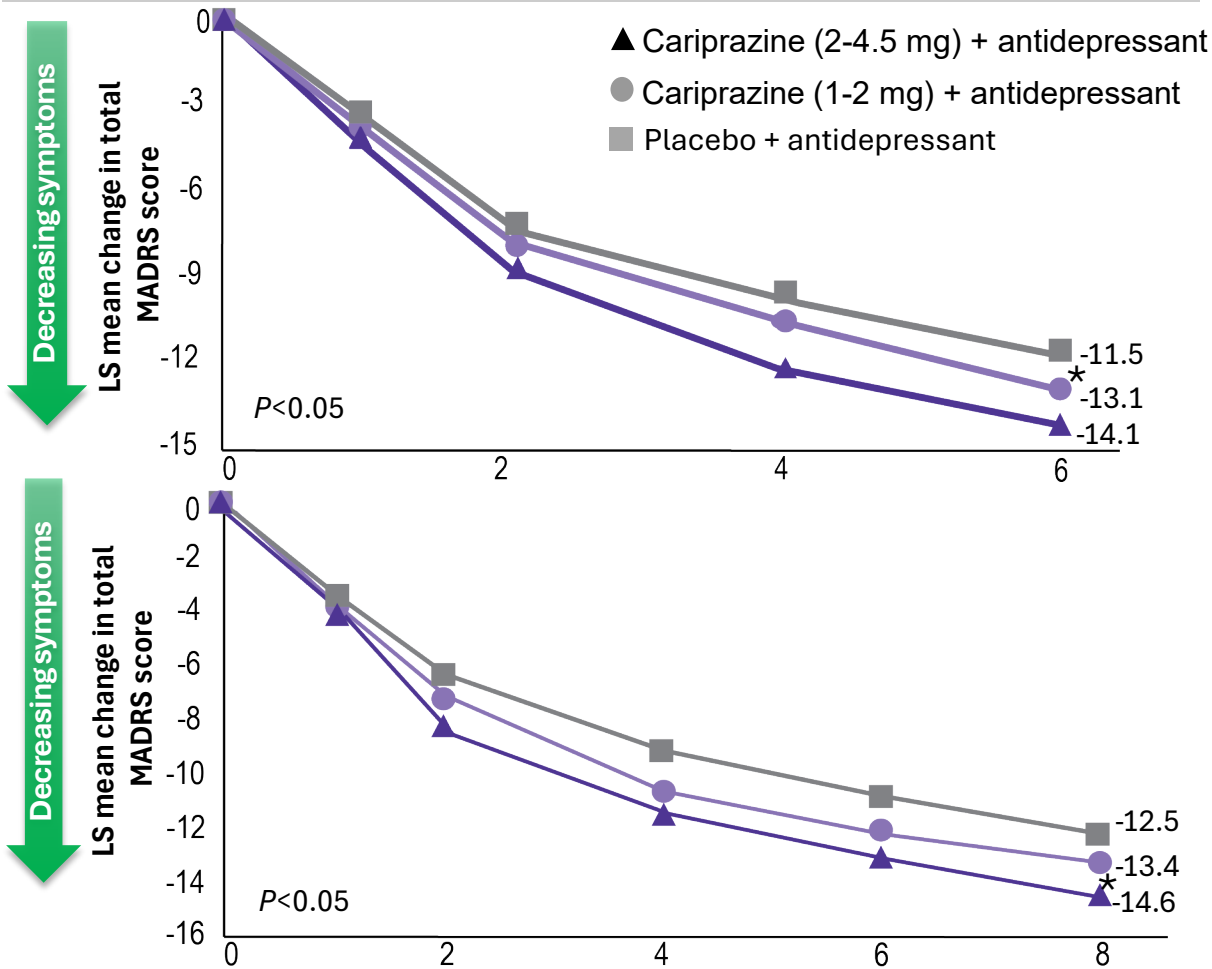
HAM-D=Hamilton Depression Rating Scale.
Thase ME, et al. Neuropsychiatr Dis Treat. 2018;15:37-45



Cariprazine

Cariprazine in Adjunct MDD: Pivotal Trials Summary

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 3A4

Adverse Events in Pivotal Trials				Adverse events in open-label extension (26 weeks, N=345)	
	1.5 mg	3 mg	Placebo		
Insomnia	9%	10%	5%	Akathisia	16%
Akathisia	7%	10%	2%	Headache	12%
Nausea	7%	6%	3%	Anxiety	10%
Somnolence	5%	7%	4%	Insomnia	10%
Weight gain	1.5lb	1.5lb	0.4lb	Restlessness	10%
Weight ≥7%	2%	2%	1%	Weight increase	10%
D/C due to AE	6% pooled		3%	Fatigue	9%
				Nasopharyngitis	9%
				Nausea	6%
				Dizziness	5%
				Sedation	5%
				D/C due to AE	14%

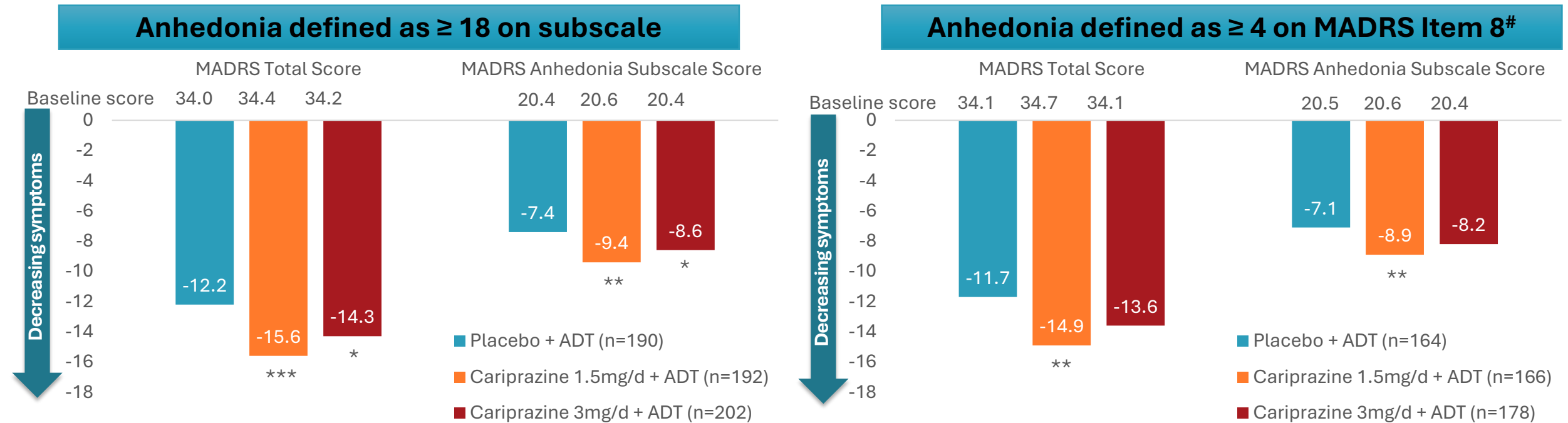
Weight gain ≥7% reported in 19%

Weight gain ≥7% reported in 19%

* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$ vs placebo for pairwise comparisons (P -values not adjusted for multiple comparisons)

LS=least squares; Durgam S, et al. J Clin Psychiatry. 2016;77(3):371-378.

Adjunctive Cariprazine Improves Anhedonia Across Subgroup Definitions



In a post-hoc analysis of individuals with moderate-to-severe baseline anhedonia, cariprazine improved MADRS total and anhedonia subscale scores, with consistent significance at 1.5 mg and dose-dependent variability at 3 mg depending on the subgroup definition.

* $p < .05$, ** $p < .01$, and *** $p < .001$ versus placebo + ADT. #Item 8=inability to feel.

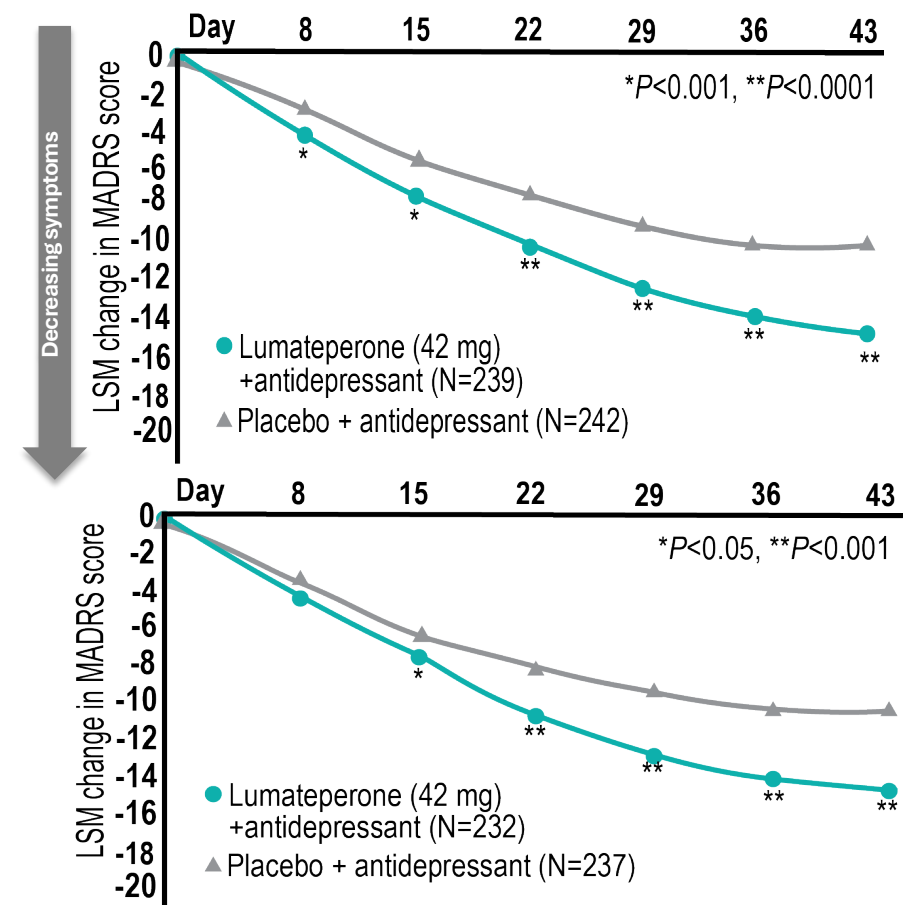
ADT = antidepressant treatment; LS = least squares

McIntyre RS, et al. J Affect Disord. 2025;385:119366.

Lumateperone

Lumateperone in Adjunct MDD: Pivotal Trials Summary

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

Pooled Results from Both Trials		
Patients, n (%)	Lumateperone 42 mg + ADT (N=483)	Placebo + ADT (N=481)
≥1 TEAE	329 (68.1)	217 (45.1)
TEAEs occurring in ~≥5% of lumateperone-treated patients and at more than twice the placebo rate		
Dizziness	80 (16.6)	24 (5.0)
Dry mouth	61 (12.6)	16 (3.3)
Somnolence	60 (12.4)	11 (2.3)
Nausea	41 (8.5)	19 (4.0)
Fatigue	37 (7.7)	8 (1.7)
Diarrhea	22 (4.6)	6 (1.2)

Most were mild-to-moderate

Low risk of clinically significant weight gain

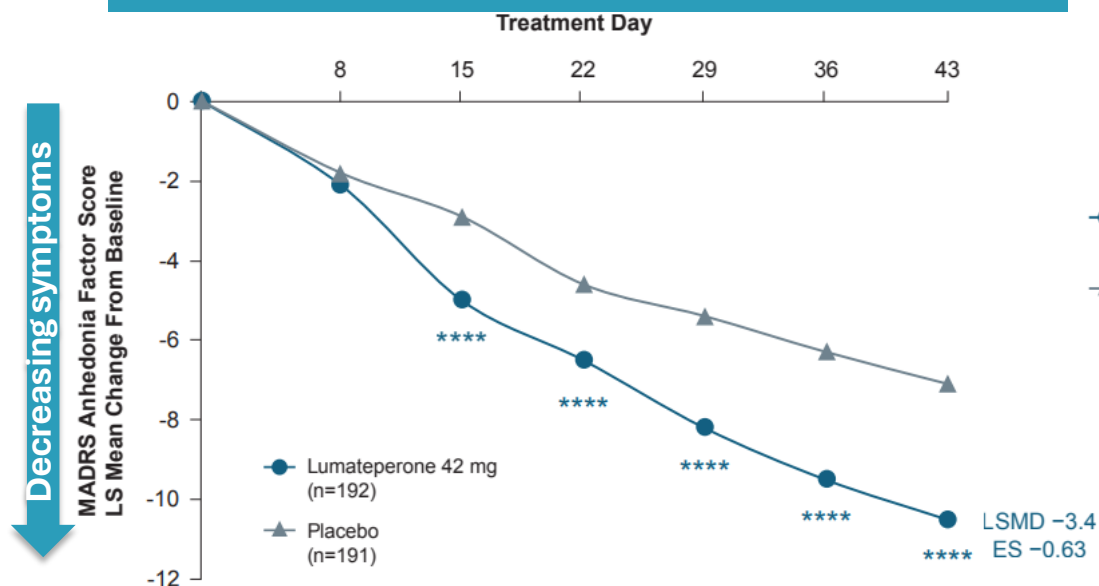
No clinically relevant increases in prolactin or cardiometabolic parameters

Approved dose: 42 mg once daily, taken orally with or without food. Dose titration not required

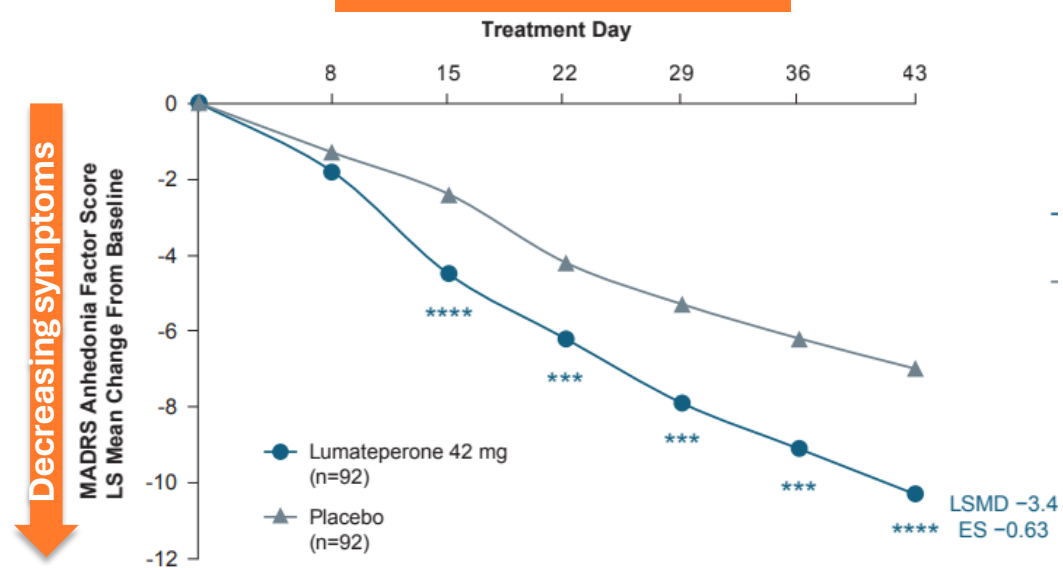


Lumateperone Monotherapy Reduced Anhedonia in MDD with Mixed Features

Combined MDD/Bipolar Depression Population



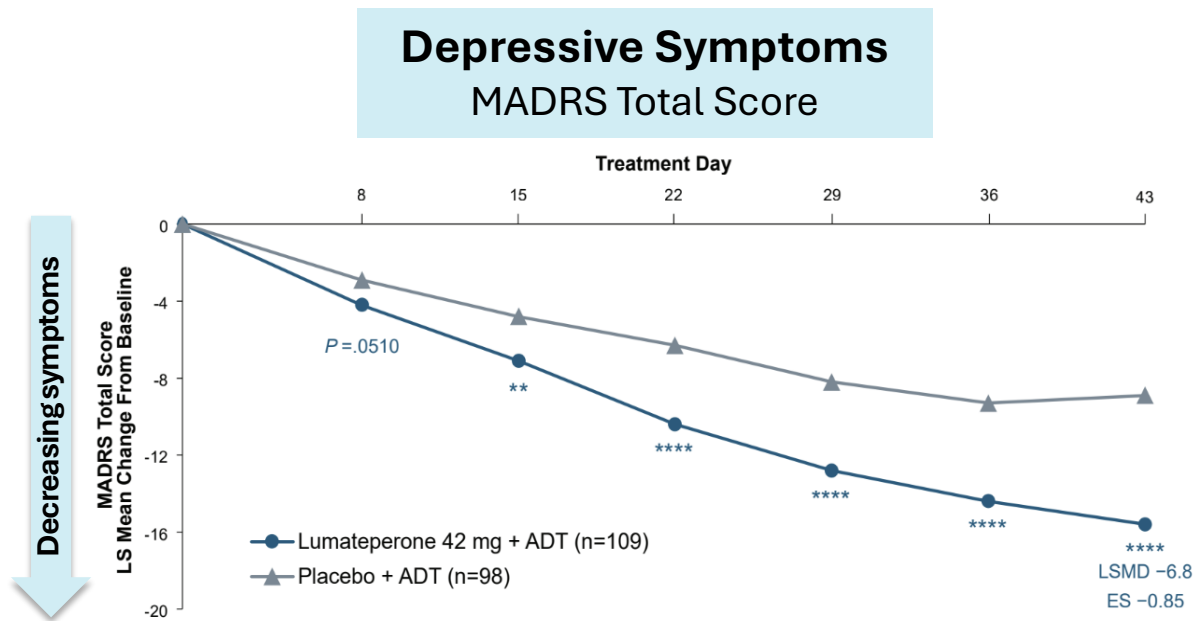
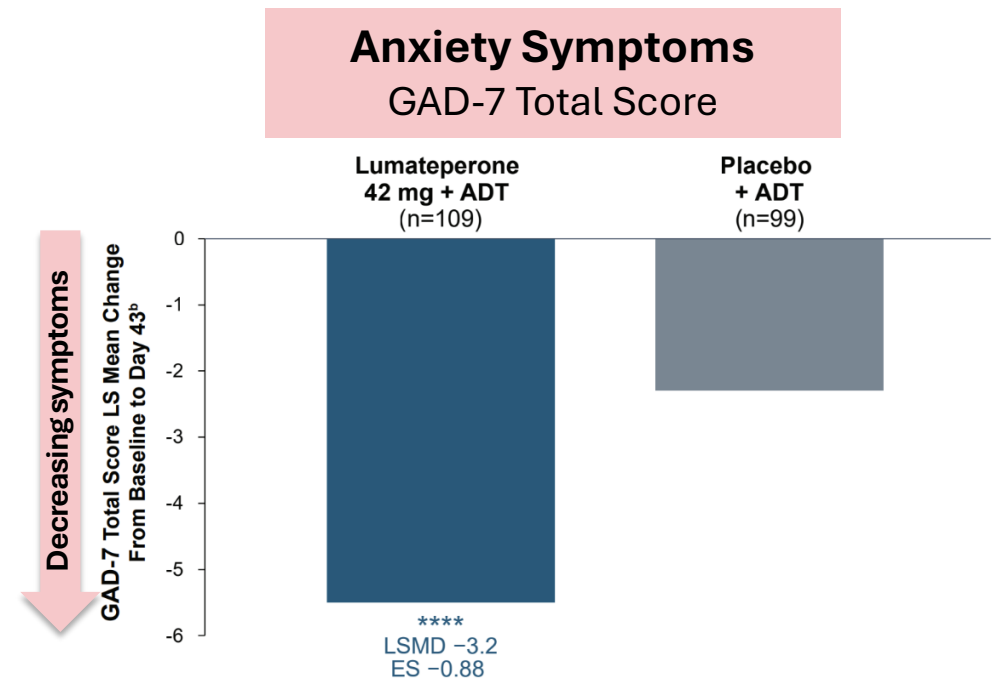
MDD Population Only



Durgam S, Kozauer SG, Earley WR, Huo J, D'Souza D, Yatham LN. Lumateperone treatment for major depressive episodes with mixed features in major depressive disorder and bipolar I or bipolar II disorder: a post hoc analysis of anhedonia. Poster presented at: International Society for Bipolar Disorders (ISBD) Annual Conference; September 17–19, 2025; Chiba, Japan.

Lumateperone Adjunct to Antidepressants Reduced Depressive and Anxiety Symptoms

A post-hoc analysis of a Phase 3 study revealed significantly improved **depressive symptoms**, **overall illness severity**, and **anxiety symptoms** in adults with MDD and DSM-5-defined anxious distress



** $P < .01$, *** $P < .001$, **** $P < .0001$

Durgam S, et al. Lumateperone as adjunctive therapy in patients with major depressive disorder and anxious distress. Poster presented at: Psych Congress Annual Meeting; September 17–21, 2025; San Diego, CA.

All of these options...

Atypical Antipsychotics Approved for Augmentation of MDD in Adults

Aripiprazole
(2007)

Quetiapine XR
(2009)

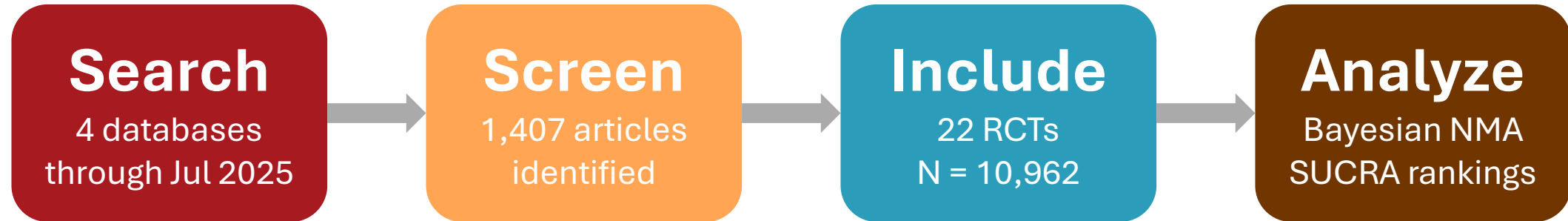
Brexipiprazole
(2015)

Cariprazine
(2022)

Lumateperone
(2025)

How do they compare?

Study Design: Systematic Review and Network Meta-Analysis



Co-Primary Outcomes

- Efficacy: **Response**, defined as $\geq 50\%$ MADRS reduction at Week 6
- Acceptability: **All-cause discontinuation rate**

Secondary Outcomes

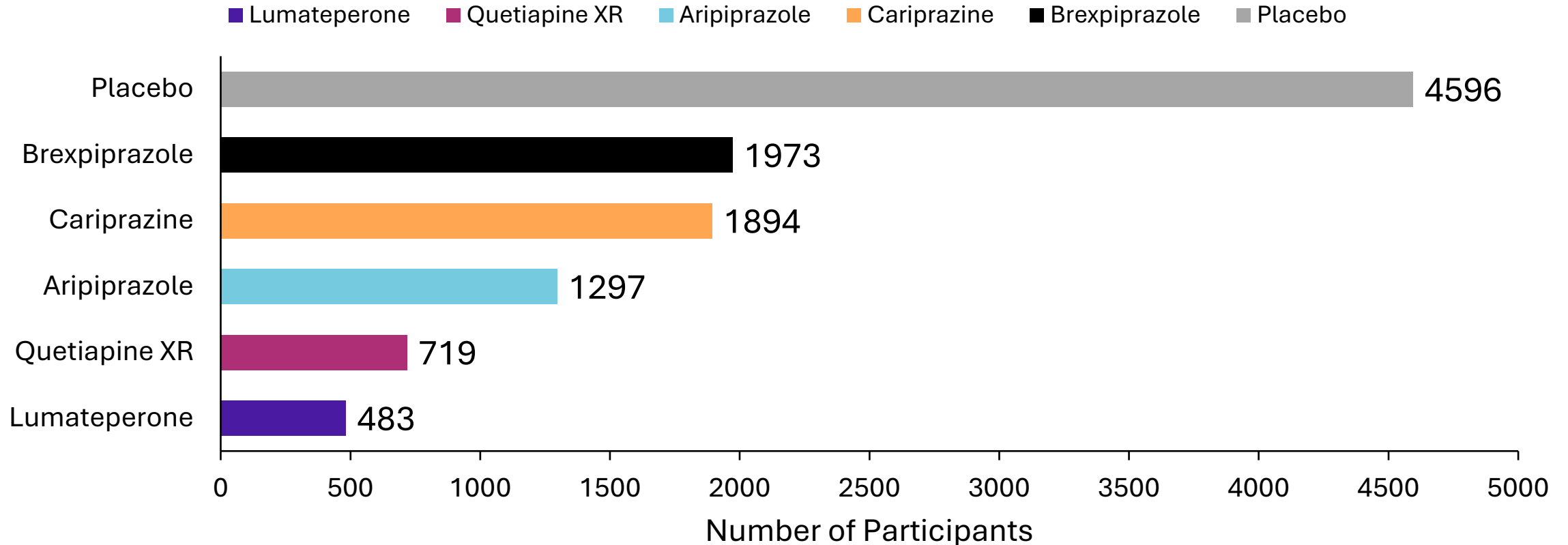
- Efficacy: **Remission**, defined as MADRS total score of ≤ 8 or ≤ 10
- Change in overall severity of symptoms
- Discontinuation due to adverse events

Statistical Approach

Bayesian NMA with random-effects models
SUCRA rankings • frequentist sensitivity analyses
6 independent raters

Study Population: 22 RCTs, N=10,962

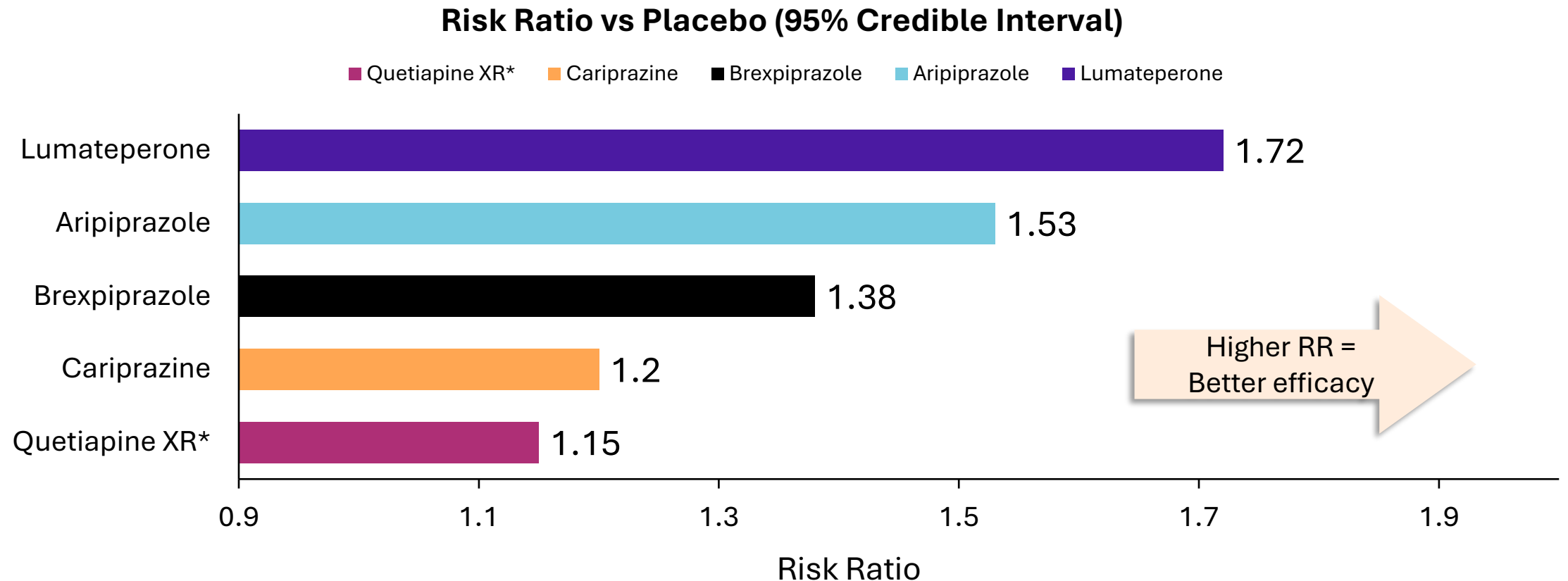
Participants (N) by Treatment Arm



Key caveat: Placebo MADRS response varied substantially across programs, substantially affecting cross-agent effect size comparisons (details on following slides).

Efficacy:

Response Rate vs Placebo at Week 6

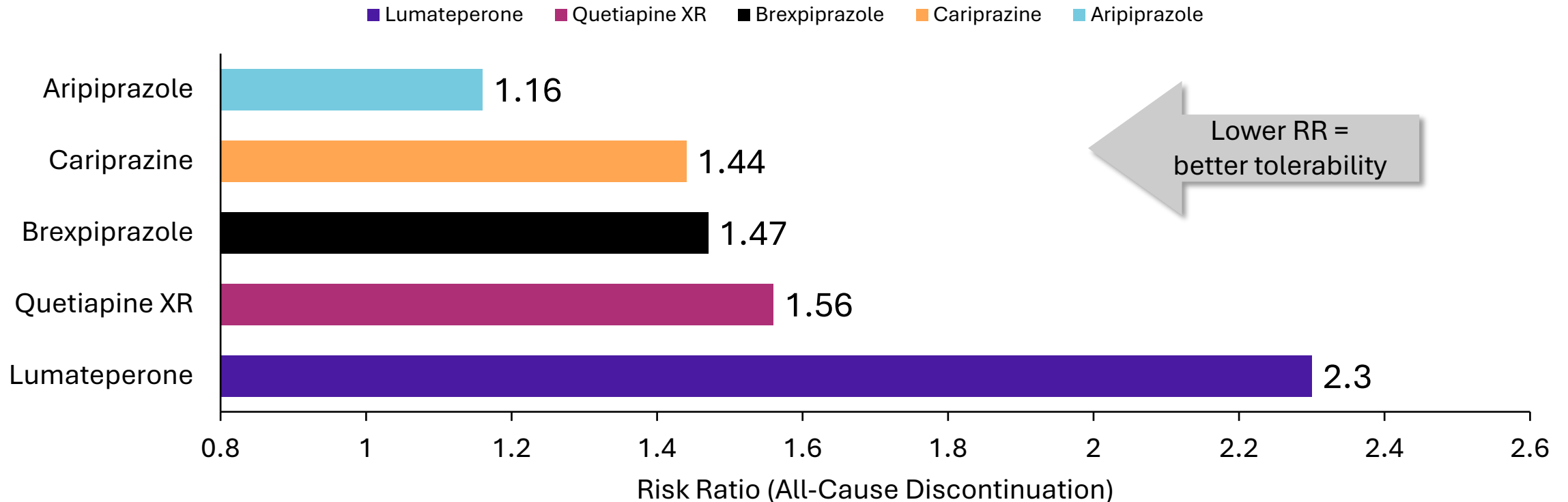


RR = risk ratio vs placebo (95% credible interval). *Quetiapine XR CrI crosses 1.0 (no statistically credible superiority over placebo). All other agents showed clinically meaningful MADRS improvement (≥ 2 pts vs placebo).

McIntyre RS, et al. *JAMA Psychiatry*. 2026:e260658. doi:10.1001/jamapsychiatry.2026.0658

Acceptability: All-Cause Discontinuation vs Placebo

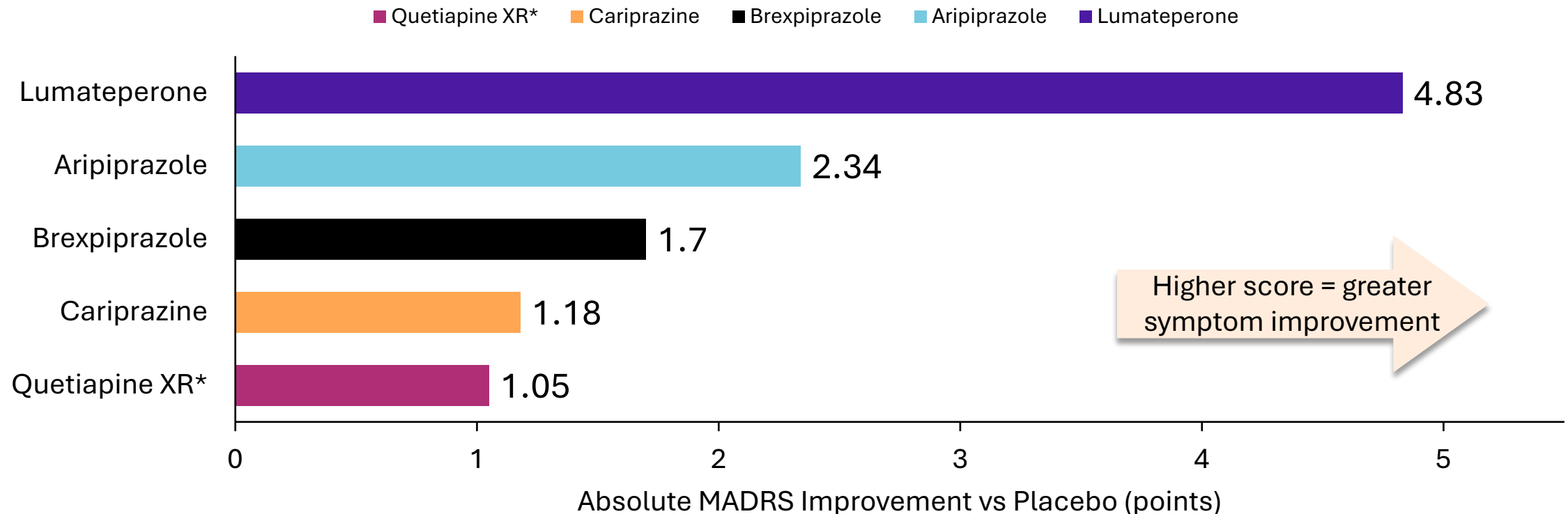
Dropout Risk Ratio vs Placebo



Key pattern: Lower RR = better acceptability (fewer dropouts). Dopamine partial agonists lead. Lumateperone's high dropout may reflect its fixed-dose design (42 mg) vs flexible dosing for all other agents.

Secondary Outcome: Depression Symptom Severity

MADRS Mean Difference vs Placebo at Week 6



*Quetiapine XR 95% CrI crosses 0. CGI-S, CGI-I, and Sheehan Disability Scale results were consistent with this hierarchy.
McIntyre RS, et al. *JAMA Psychiatry*. 2026:e260658. doi:10.1001/jamapsychiatry.2026.0658

Tolerability: Adverse Events, Weight Gain, and EPS

Drug	AE Discontinuation RR	Weight Gain Risk	Extrapyramidal Symptoms	Overall Acceptability Rank
Aripiprazole	2.21	Yes (sig.)	No sig. diff.	#1 (Best)
Cariprazine	2.82	Yes (sig.)	No sig. diff.	#2
Brexpiprazole	2.73	Yes (sig.)	No sig. diff.	#3
Quetiapine XR	6.70	Yes (sig.)	No sig. diff.	#4
Lumateperone	16.50	No (weight-neutral)	No sig. diff.	#5 (Worst)

Green = favorable **Yellow = moderate** **Red = concerning** AE RR vs placebo. No agent showed sig. EPS vs placebo.

*Lumateperone weight-neutral despite lowest acceptability rank.

Limitations



No Direct Comparisons

All comparisons are indirect network estimates; no head-to-head RCTs have been conducted for these agents in MDD.



Placebo Response Variability

Substantial variation in placebo response across trials (MADRS -5.8 to -12.5) substantially influences cross-agent effect size comparisons.



Industry-Sponsored

95.5% of trials were industry-sponsored. Definitions of 'inadequate antidepressant response' also varied across programs.



Short-Term Only (6 Weeks)

All evidence is limited to the acute treatment phase. No maintenance efficacy data exist for any adjunctive atypical in MDD.



Lumateperone Dosing Design

Fixed single dose (42 mg) vs flexible dosing for all comparators may confound its acceptability ranking.

Conclusions

Efficacy Ranking

- 1 Lumateperone
- 2 Aripiprazole
- 3 Brexpiprazole
- 4 Cariprazine
- 5 Quetiapine XR

Acceptability Ranking

- 1 Aripiprazole
- 2 Cariprazine
- 3 Brexpiprazole
- 4 Quetiapine XR
- 5 Lumateperone

No single agent dominates both dimensions.

Individualized shared decision-making must simultaneously weigh both hierarchies.
Long-term maintenance efficacy for adjunctive atypicals in MDD remains an unmet research priority.

Antipsychotic Monitoring Schedule for Adults

After Initiating or Changing Antipsychotic Medication

Parameter	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Notes
Weight/Body Mass Index	✓	✓	✓	✓	✓	—	Early metabolic signal
Waist Circumference	✓	—	—	—	—	✓	CV risk marker
Blood Pressure/Heart Rate	✓	—	—	✓	—	✓	More often if HTN risk
Glucose Screening (FPG or HbA1c)	✓	—	—	✓	—	✓	Earlier if high risk
Lipid Panel	✓	—	—	✓	—	✓	More often if higher CV risk
Tardive dyskinesia (AIMS)	✓	—	—	—	—	✓	Use AIMS earlier if high-risk for TD, annually otherwise; ideally, do before starting and repeat regularly

HTN=hypertension; EPS=Extrapyramidal symptoms; AIMS=Abnormal Involuntary Movement Scale

American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Schizophrenia*. 3rd ed. American Psychiatric Association Publishing, 2021; New York State Medicaid Prescriber Education Program (NYSMPEP). *Metabolic health as an essential consideration when using antipsychotic medications*. 2024.

Antipsychotics Are One of Multiple Adjunctive/Augmentation Strategies in MDD

FDA-Approved Adjunctive Antipsychotics

- Aripiprazole
- Brexpiprazole
- Quetiapine XR
- Cariprazine
- Olanzapine/Fluoxetine (approved for TRD)
- Lumateperone

Off-Label Pharmacologics (Non-Antipsychotic)

- Lithium
- Liothyronine (T3)
- Bupropion add-on
- Buspirone
- L-methylfolate
- Modafinil / other stimulants
- Mirtazapine
- Lamotrigine

Rapid-Acting / NMDA-Based

- Esketamine (FDA-approved for TRD)
- IV Ketamine (off-label)

Device-Based / Neuromodulation

- Transcranial magnetic stimulation (TMS) (FDA-cleared after inadequate antidepressant response)
- Electroconvulsive therapy
- Vagus nerve stimulation

KEY TAKEAWAY:

Selection should be individualized based on **symptom profile, side-effect tolerance, medical comorbidity, patient preference, and access/logistics**

TRD = Treatment-resistant depression.

Núñez NA, et al. J Affect Disord. 2022;302:385-400; Scott F, et al. J Psychopharmacol. 2023;37(3):268-278.

Key Learning Points

- There are many treatment approaches to target partial response and residual symptoms in MDD
- Multiple antipsychotic medications have efficacy in MDD with insufficient treatment response as adjunctive agents to antidepressants.
- Several post-hoc analyses indicate that certain antipsychotic medications may reduce residual symptoms, such as anxiety and anhedonia.
 - Example: lumateperone monotherapy showed significant reductions in anhedonia in individuals with bipolar or MDD with mixed features
- Augmentation of an antidepressant with an atypical antipsychotic medication has a unique side effect profile that requires ongoing metabolic and physical examination monitoring



Panel Discussion: Faculty and Patient Advocate

How do we best assess and address partial response in MDD?

What is the potential impact of specific residual symptoms?

How can we best navigate and overcome roadblocks in atypical antipsychotic augmentation strategies in MDD?

Identifying Partial Response and Assessing the Impact of Specific Residual Symptoms

What did partial response feel like to you?

Did you know it was partial response, and were you afraid of adding another medicine to what you were already taking?

Navigating and Overcoming Roadblocks in AAP Augmentation in MDD

*What were some of the roadblocks you experienced
in your own treatment?*

Practical Take-Aways



Prioritize full symptom remission and target functional recovery by systematically identifying and treating residual symptoms, including anxiety and anhedonia.



If antidepressant monotherapy is insufficient, consider an augmentation strategy tailored to the patient's symptom profile, comorbidities, and preferences.



When using adjunctive antipsychotics, balance efficacy with adverse effects, including proactive metabolic and movement disorder monitoring to ensure safe, long-term care.



Q&A