

Practical Updates in Primary Care

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

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Disclosures

- **Rakesh Jain, MD, MPH:** Advisory Board – Adamas, Alkermes, Corium, Eisai, Indivior, Intra-Cellular Therapies, Ironshore Pharmaceuticals, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Supernus, Takeda, Teva, Tris Pharmaceuticals; Advisory Board (spouse) – Otsuka; Consultant – AbbVie (Allergan), Acadia, Adamas, Alfasigma USA, Axsome, Cingulate Therapeutics, Corium, Eisai, Evidera, Impel NeuroPharma, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Osmotica, Otsuka, Pamlab, Pfizer, Sage Therapeutics, Shire, Sunovion, Supernus, Takeda, Teva; Consultant (spouse) – Lilly, Otsuka, Pamlab, Sunovion; Grant/Research Support – AbbVie (Allergan), Lilly, Lundbeck, Otsuka, Pfizer, Shire, Takeda; Speakers Bureau – AbbVie (Allergan), Alkermes, Axsome, Corium, Eisai, Indivior, Intra-Cellular Therapies, Ironshore Pharmaceuticals, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Takeda, Teva, Tris Pharmaceuticals; Speakers Bureau (spouse) – Lilly

- **Wendy Wright, DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP:** Consultant – Otsuka Pharmaceutical Development & Commercialization; Speakers Bureau – Otsuka Pharmaceutical Development & Commercialization

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 (eg, atypical antipsychotics) for patients with partial response in MDD, including their efficacy for specific residual symptoms

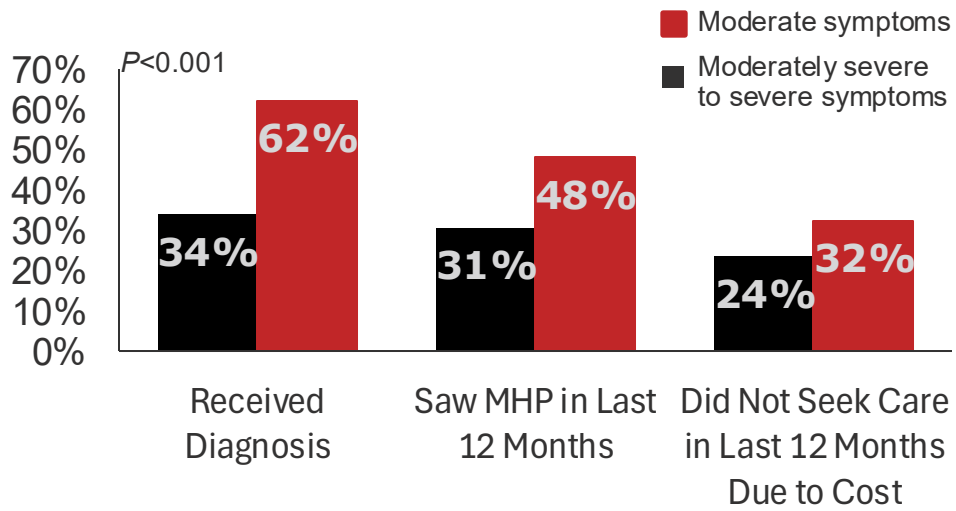
- Implement evidence-based and patient-centered adjunctive treatment strategies to address residual symptoms and improve outcomes for patients with partial response in MDD

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 Healthcare Specialist in the Last Year



- Half of US adults live in a MHP shortage area
- Over the last 20 years
  - US 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 provider.

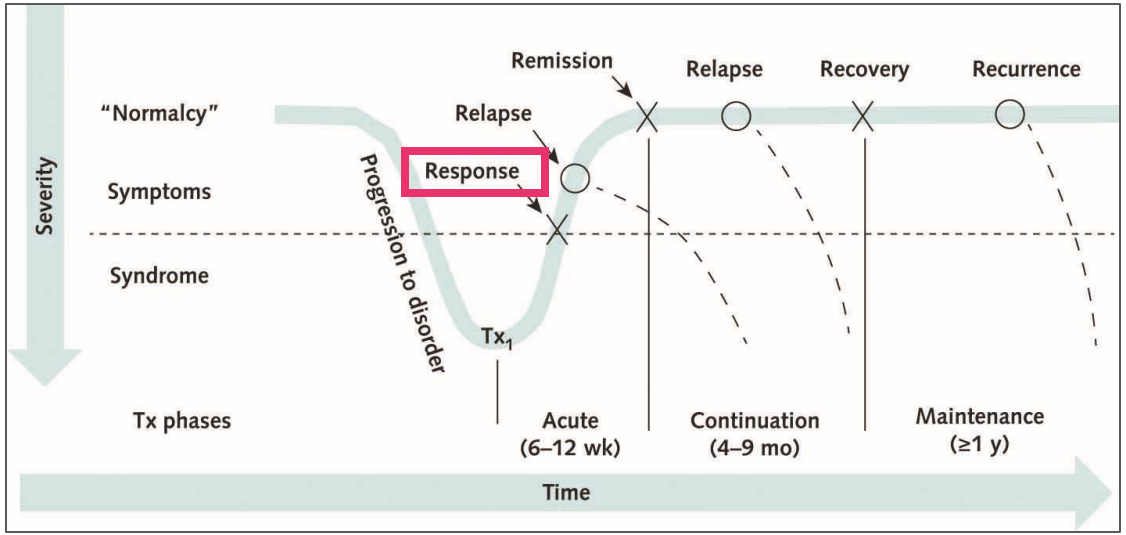
Brenner AM, et al. *Acad Psychiatry*. 2017;41(2):202-206. Goodwin RD, et al. *Am J Prevent Med*. 2022;63(5):726-733. Health Resources and Services Administration (HRSA). December 31, 2025. Accessed March 24, 2026. https://data.hrsa.gov/Default/GenerateHPSAQuarterlyReport. National Institute of Mental Health (NIMH). Updated July 2023. Accessed March 24, 2026. https://www.nimh.nih.gov/health/statistics/major-depression.

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Understanding Partial Response and Inadequate Treatment Response in MDD

What Is Partial Response in MDD?

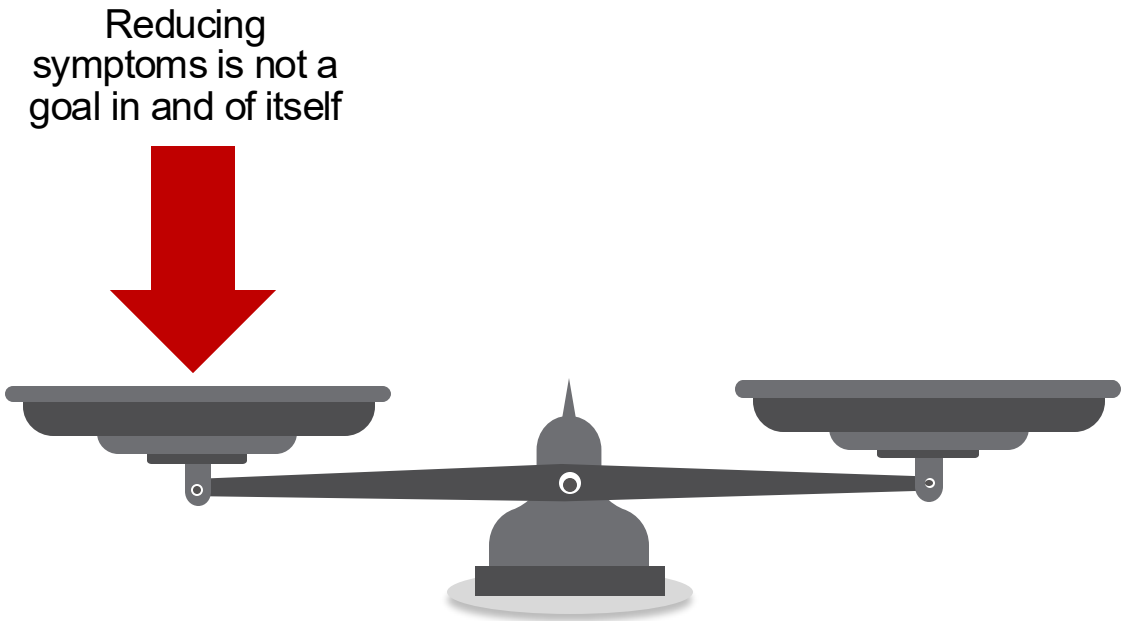


Response	Typical Definition
Partial Response	Meaningful improvement in symptoms but <50%
Response	≥50% improvement in symptoms
Remission	Mild or no symptoms

Qaseem A, et al. *Ann Intern Med*. 2023;176(2):239-252.

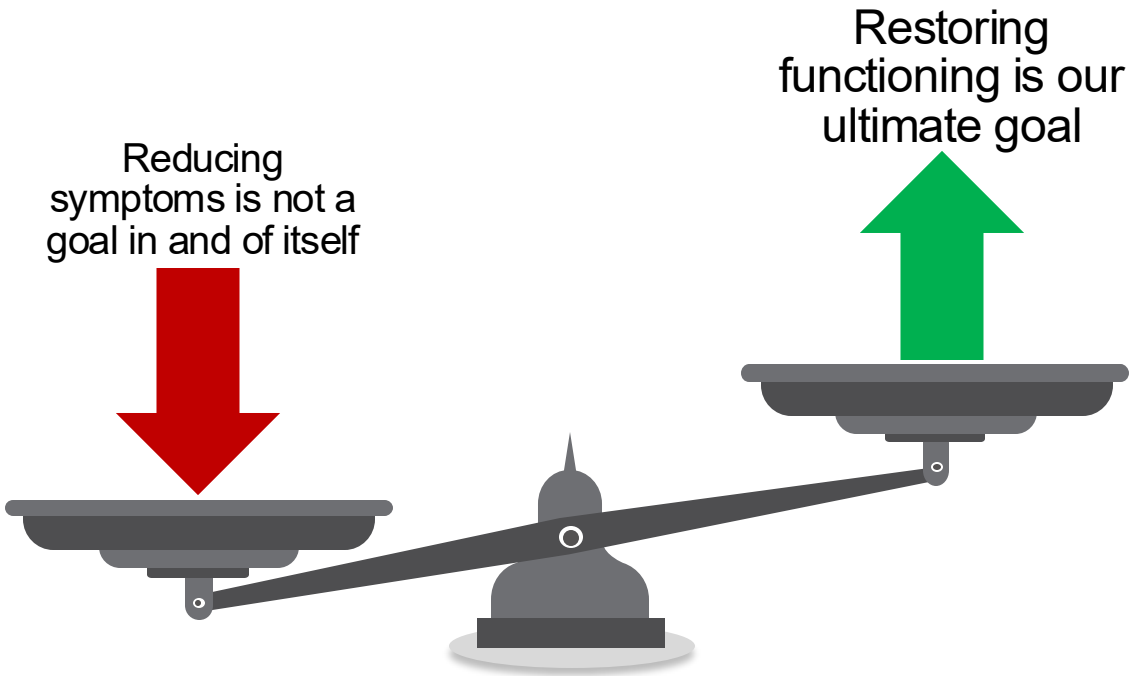
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The Goal of Treating Major Depressive Disorder Is Not Simply to Reduce Symptoms



Papakostas GI. *J Clin Psychiatry*. 2016;77(8):e1009. Trivedi MH, et al. *Int Clin Psychopharmacol*. 2009;24(3):133-138. Working Group on Major Depressive Disorder. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd ed. APA Press; 2010.

The Goal of Treating MDD Is to Restore Function



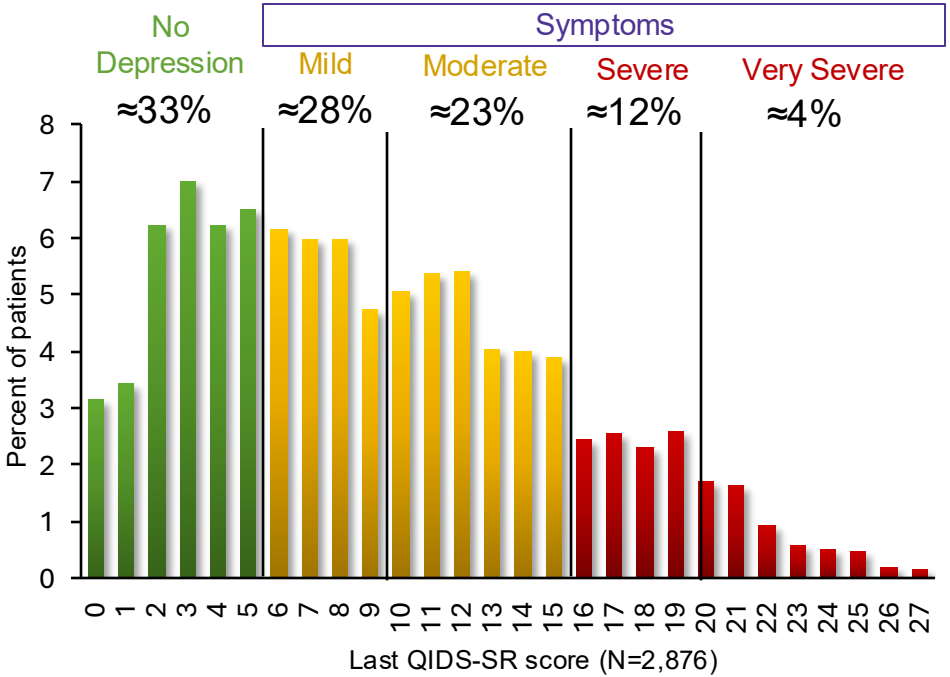
Papakostas GI. *J Clin Psychiatry*. 2016;77(8):e1009. Trivedi MH, et al. *Int Clin Psychopharmacol*. 2009;24(3):133-138. Working Group on Major Depressive Disorder. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd ed. APA Press; 2010.

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



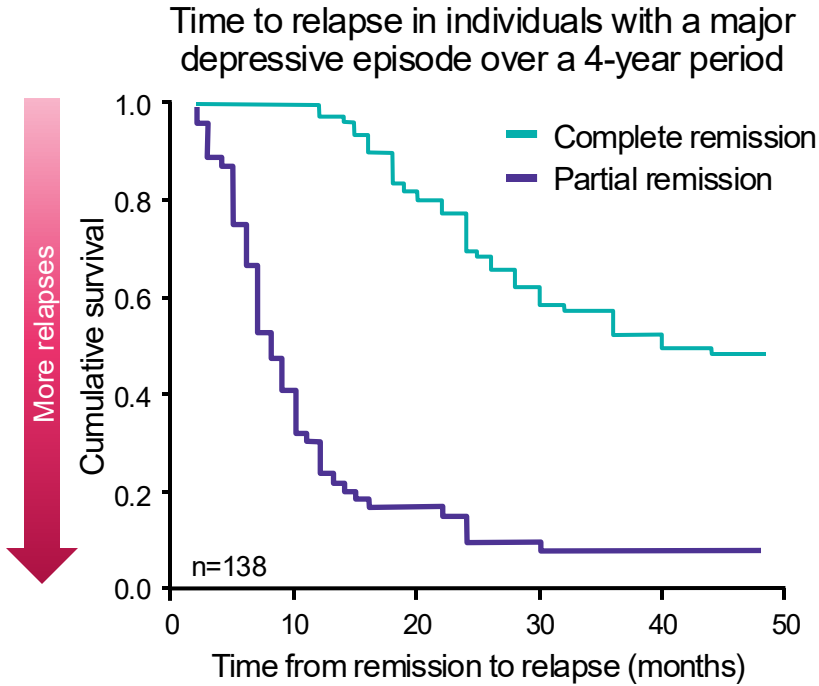
STAR*D = Sequenced Treatment Alternatives to Relieve Depression; QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report.

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

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Settling for Partial Response Worsens Outcomes

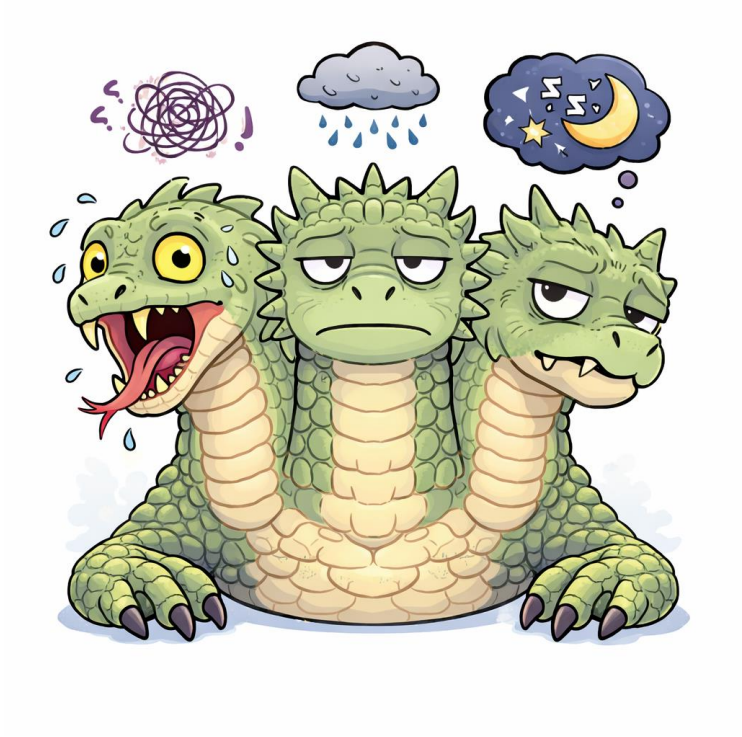
- Increases risk of relapse
- Increases the number of depressive episodes
- Increases frequency of depressive episodes
- Continues impairment in work and relationships
- Associated with increased all-cause mortality risk



Judd 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, et al. *World Psychiatry*. 2017;16(2):219-220. van Dooren FEP, et al. *PLoS One*. 2013;8(3):e57058. de Groot M, et al. *Psychosom Med*. 2001;63(4):619-630. Pence BW, et al. *JAMA Psychiatry*. 2018;75(4):379-385. Ickovics JR, et al. *JAMA*. 2001;285(11):1466-1474. Pintor L, et al. *J Affect Disord*. 2004;82(2):291-296.

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Co-Morbidities of MDD – A Three-Headed Challenge



Prognosis and treatment decisions are heavily impacted by the co-occurrence of any one of these three co-morbidities:

- Anxiety
- Anhedonia
- Insomnia

Serretti A. *Clin Psychopharmacol Neurosci*. 2023;21(3):401-409. Gillissie ES, et al. *J Psychiatr Res*. 2023;158:209-215.

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First Things First – Defining Anhedonia

Patients with anhedonia have a reduced ability to experience pleasure or interest in things previously enjoyable

"Without"

Anhedonia

"pleasure"

Anhedonia has both consummatory and anticipatory elements

Consummatory

Inability to feel pleasure during current events

Reduced joy or interest in interpersonal or social interactions and natural rewards, including eating and sexual behavior

Anticipatory

Inability to predict future experience of pleasure

↓

Lower reward responsiveness and reduced motivation to act towards future pleasure

Gillissie ES, et al. *J Psychiatr Res*. 2023;158:209-215.

Dimensions of Anhedonia

Anticipatory vs Consummatory Anhedonia

Anticipatory Pleasure: "Wanting"





Consummatory Pleasure: "Liking"

	Anticipatory Anhedonia	Consummatory Anhedonia
Definition	Reduced ability to experience pleasure in anticipation of rewarding events	Reduced ability to experience pleasure during enjoyable activities
Example	A person may no longer anticipate / look forward to activities previously enjoyed, such as playing a sport or going on a vacation	A person may not feel joy while doing something they typically find pleasurable, such as eating their favorite meal or watching a show
Consequences	Reduced motivation, difficulty planning and initiating activities, lack of excitement about future events	Reduced pleasure from social and recreational activities, reduced frequency of engaging in pleasurable activities

Serretti A. *Clin Psychopharmacol Neurosci*. 2023;21(3):401-409. Gillissie ES, et al. *J Psychiatr Res*. 2023;158:209-215.

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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**

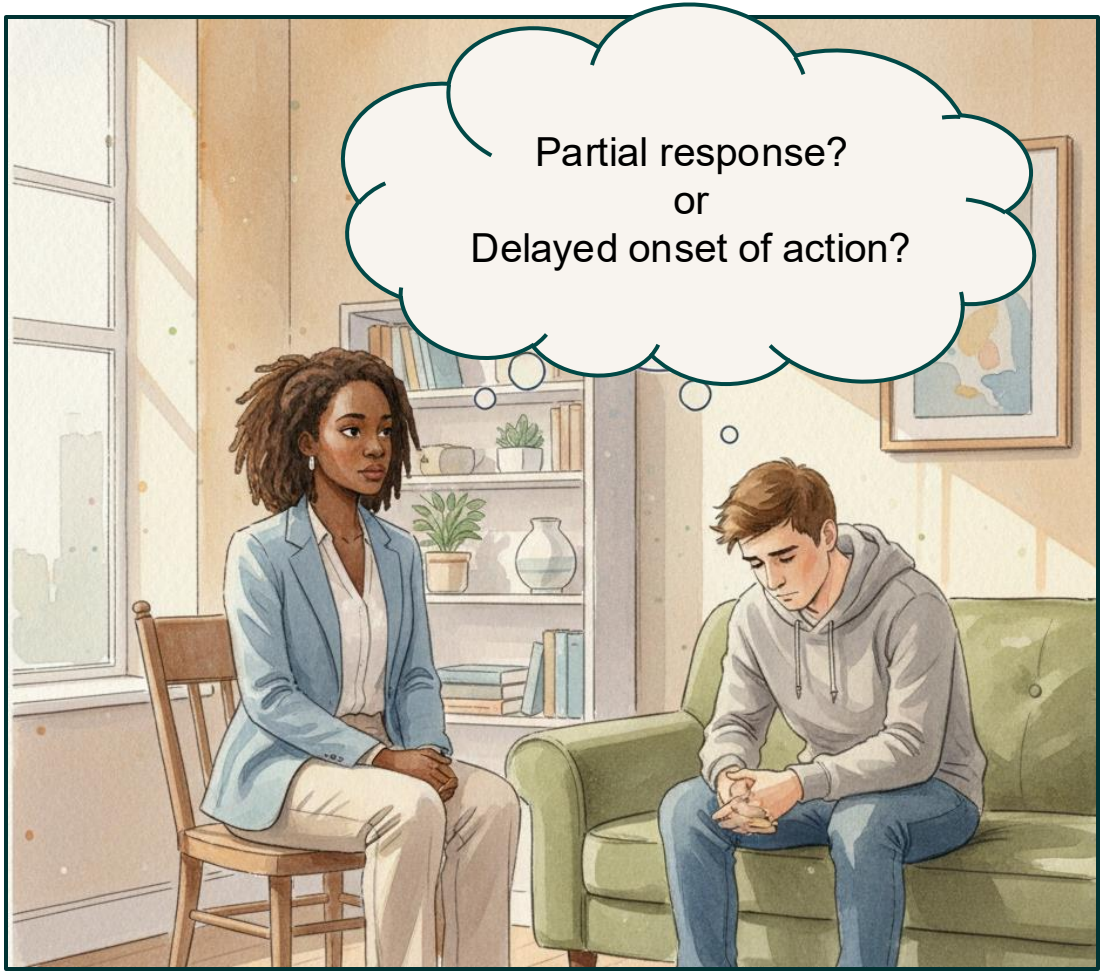
- The three common co-morbidities of MDD (anxiety, anhedonia, insomnia) should be kept in mind in order to restore function and quality of life; symptom reduction is not enough



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Detection and Evaluation of Partial Response in MDD

An Important Question to Ask When Encountering a Patient 3-4 Weeks after Starting an Antidepressant



Practical Tools for Detecting and Monitoring Specific Residual Symptoms of MDD

- Residual symptoms, such as insomnia, anhedonia, and/or anxiety, often persist despite treatment

- Utilizing standardized tools like the **Patient Health Questionnaire-9 (PHQ-9)** or the **GAD-7** allows clinicians to objectively track progress

- Targeted monitoring helps distinguish between a true partial response and lingering subclinical symptoms

GAD = general anxiety disorder.

Kroenke K, et al. *J Gen Intern Med*. 2001;16(9):606-613. Zimmerman M, et al. *J Clin Psychiatry*. 2012;73(6):790-795.

Two Wonderful Scales to Use in All Care Settings

Patient Health Questionnaire (PHQ-9)

Name: _____ Date: _____

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

For office coding: Total Score _____ = _____ + _____ + _____

Total Score

Guide for Interpreting PHQ-9 Scores		
Score	Depression Severity	Action
0 - 4	None-minimal	Patient may not need depression treatment.
5 - 9	Mild	Use clinical judgment about treatment, based on patient's duration of symptoms and functional impairment.
10 - 14	Moderate	Use clinical judgment about treatment, based on patient's duration of symptoms and functional impairment.
15 - 19	Moderately severe	Treat using antidepressants, psychotherapy or a combination of treatment.
20 - 27	Severe	Treat using antidepressants with or without psychotherapy.

GAD-7

Over the *last 2 weeks*, how often have you been bothered by any of the following problems? (circle the best answer)	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

GAD-7 Score and Anxiety Severity

GAD-7	Anxiety Severity
0-4	Minimal
5-9	Mild
10-14	Moderate
15-21	Severe

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Validated Anhedonia Rating Scales

SHAPS

14-item self-reported scale assessing consummatory anhedonia

A higher score indicates higher levels of anhedonia

Question
1. I would enjoy my favorite television or radio program
2. I would enjoy being with my family or close friends*
3. I would find pleasure in my hobbies and pastimes
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

DARS

17-item self-reported scale assessing anticipatory and consummatory anhedonia in 4 domains

A higher score indicates higher levels of anhedonia

List at least 2:
A. List at least 2 of your favorite pastimes/hobbies that are NOT primarily social:
1. I would enjoy these activities
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:
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

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.

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A Successful Pathway to Assessment for Anhedonia

Open-Ended Questions:

Create a dialogue. For instance, “Tell me about what you like to do for fun? What are you looking forward to?”

Frequency and Duration:

Follow up with specific questions about the frequency and duration of these symptoms. “How often do you feel this way?” and “How long has it been since you felt pleasure in [specific activities]?”

Impact Assessment:

Gauge how these symptoms affect the patient’s daily life by asking, “How has your lack of interest or enjoyment affected your daily routine or responsibilities?”

Behavioral Observations:

Note any behavioral cues or body language that indicate lack of interest or enthusiasm during the conversation.

Normalize the Discussion:

Reassure the patient that their experiences are common and valid, which helps to reduce any stigma associated with their feelings.

Additional Symptoms:

Inquire about related symptoms that may accompany anhedonia, such as social withdrawal, fatigue, sleep disturbances, or changes in appetite.

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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 – PHQ-9
- Treatment adherence
- Persistent or poorly tolerated side effects
- Inadequate dose of medication
- Pharmacokinetic/pharmacodynamic factors affecting medication action
- Poor therapeutic alliance

Working Group on Major Depressive Disorder. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd ed. APA Press; 2010.

Strategies for Discussing and Addressing Adherence Issues

- Partial adherence is a significant barrier in treating major depressive disorder (MDD)
- Research indicates that roughly **50%** of patients with chronic conditions, including depression, fail to take medications as prescribed
- Inconsistency often leads to sub-therapeutic outcomes, mimicking a “partial response” or “delayed onset”

Brown MT, Bussell JK. *Mayo Clin Proc*. 2011;86(4):304-314. Sansone RA, Sansone LA. *Innov Clin Neurosci*. 2012;9(5-6):41-46.

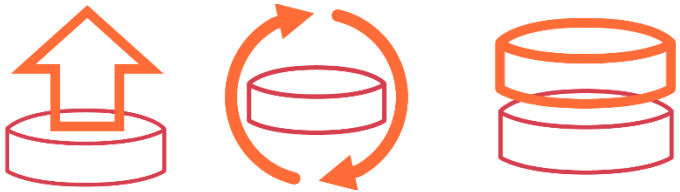


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Managing Partial Response in MDD

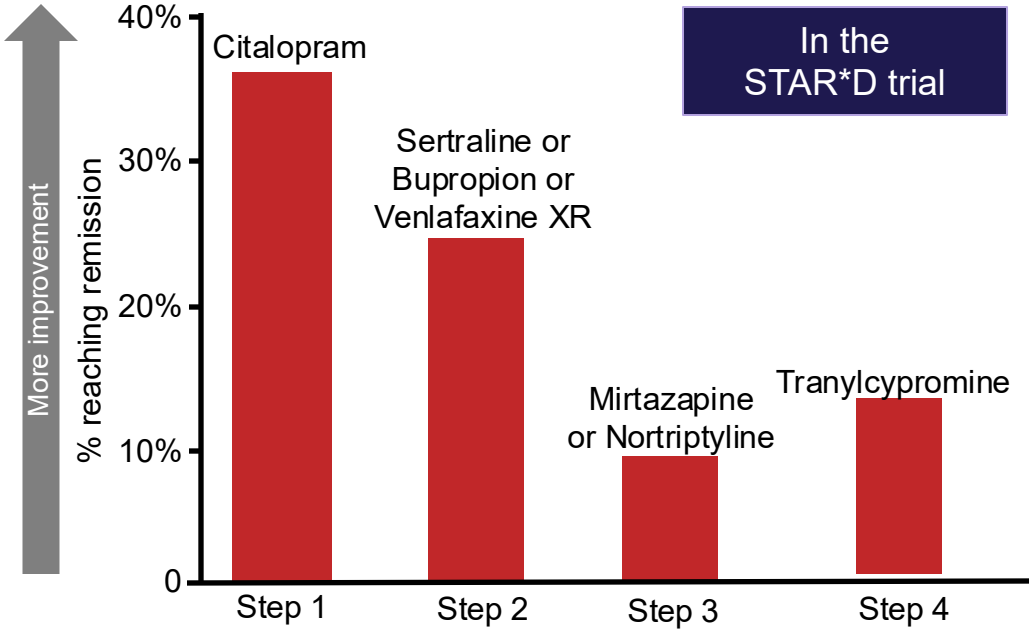
To Switch or Add? … That Is the Question





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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

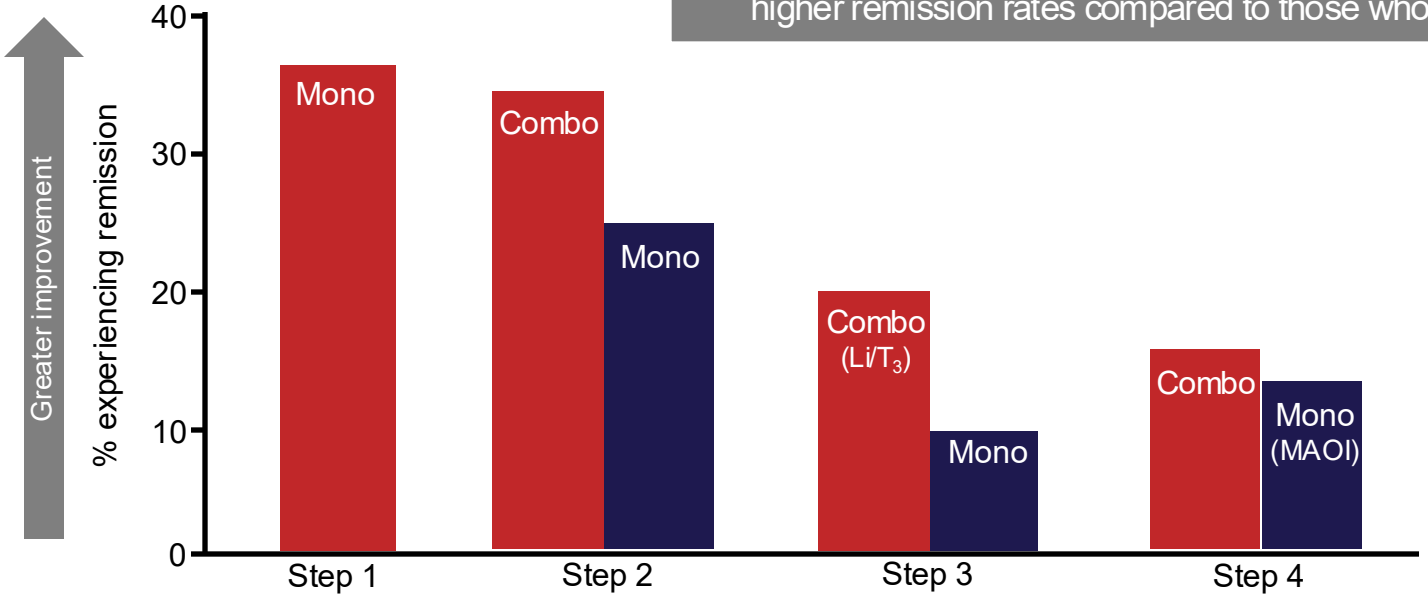
Similar results are seen, whether switching between medicines in
- Different classes (eg, citalopram to bupropion)
- The same class (eg, citalopram to sertraline)

Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40. Trivedi MH, et al. *N Engl J Med*. 2006;354(12):1243-1252. 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.

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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.

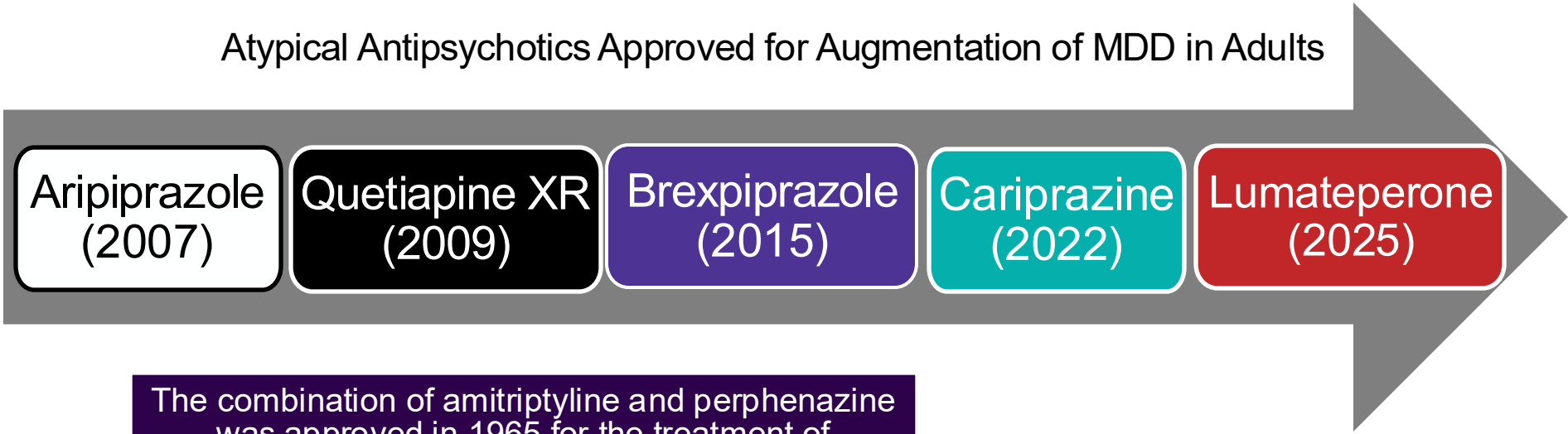
Clinical Scenarios that Warrant Treatment Augmentation

- Presence of significant anxiety, insomnia, and/or anhedonia are SIGNALs to consider augmentation
- These symptoms do not tend to resolve spontaneously on SSRIs or SNRIs, especially if patient has already been on them for 6+ weeks
- Presence of psychosocial impairment, fatigue, and amotivation – secondary to anxiety or anhedonia – are all clues for urgent action
- It's equally important to not just "throw something" at the patient – but rather, we should use evidence-based, risk/benefit-assessed, FDA-approved treatment options when considering an augmentation treatment

SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors.

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

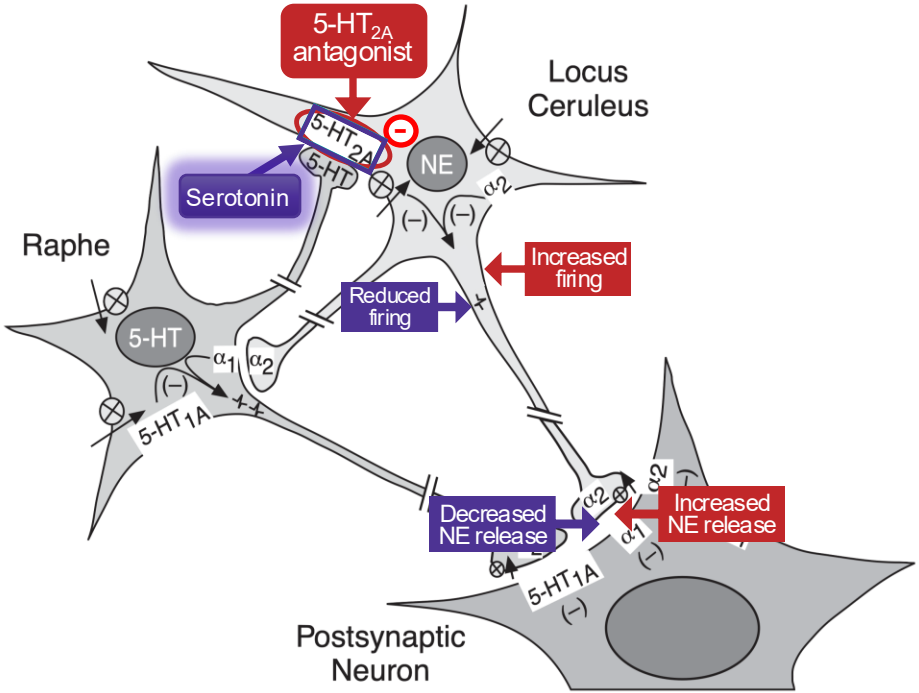
The description of this combination in its PI was:
"A broad-spectrum psychotherapeutic agent"

PI = prescribing information; XR = extended release.

FDA. Accessed March 24, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/071443s028lbl.pdf.
Nelson JC, et al. *Am J Psychiatry*. 2009;166(9):980-991.

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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.

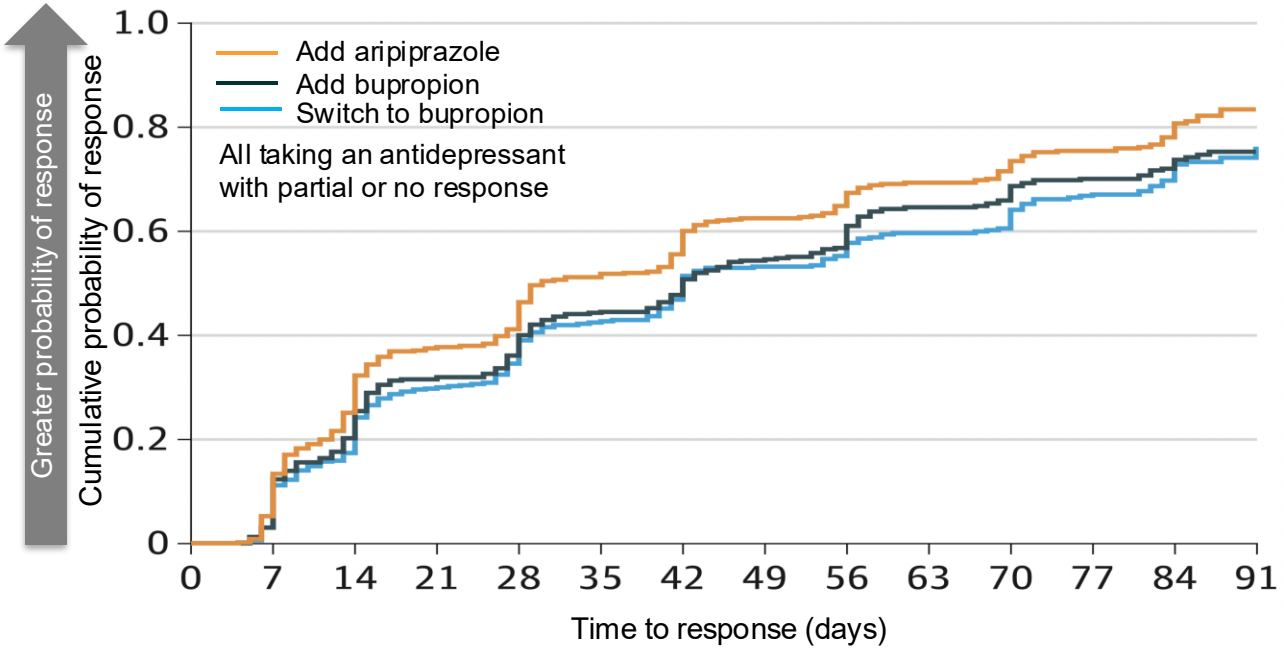
Blier P, Szabo ST. *J Clin Psychiatry*. 2005;66(Suppl 8):30-40. Blier P, Blondeau C. *J Affect Disord*. 2011;128(Suppl 1):S3-S10. Szabo ST, et al. *J Pharmacol Exp Ther*. 2002;302(3):983-991.

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Overview of Common Augmentation Options

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

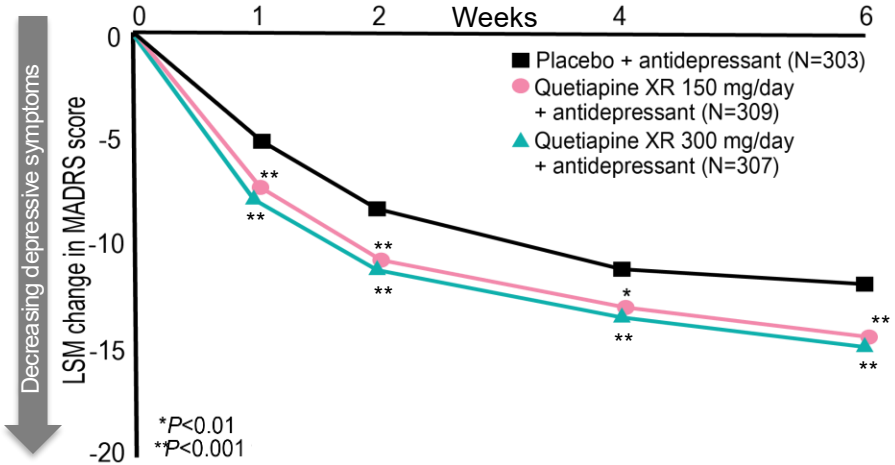
Dropout rates were lowest with aripiprazole augmentation

VA = Veterans Affairs; AE = adverse event.

Mohamed S, et al. *JAMA*. 2017;318(2):132-145.

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

	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

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

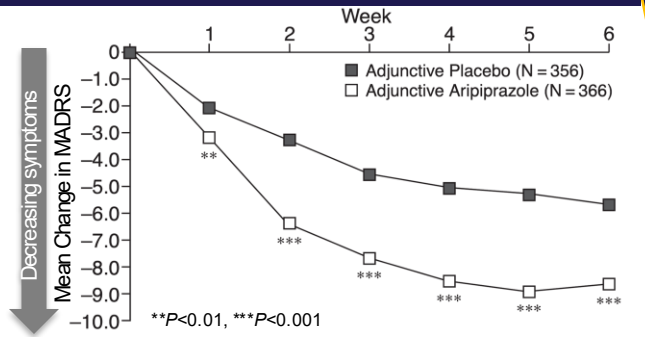
MADRS = Montgomery-Åsberg Depression Rating Scale; D/C = discontinued; LSM = least squares mean.

Bauer M, et al. *J Affect Disord*. 2010;127(1-3):19-30. Rummel-Kluge C, et al. *Schizophr Bull*. 2012;38(1):167-177. Citrome L, et al. *J Clin Psychiatry*. 2023;84(2):22r14631. FDA. Accessed March 24, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022047s048lbl.pdf.

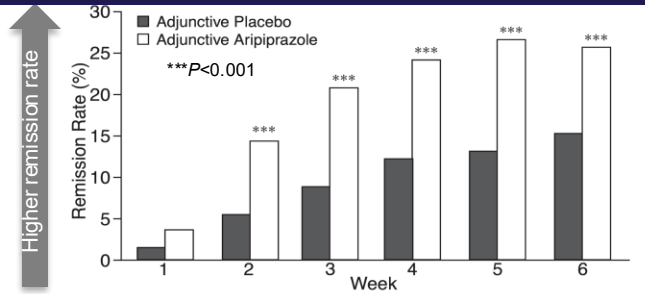
Practical Updates in Primary Care

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%

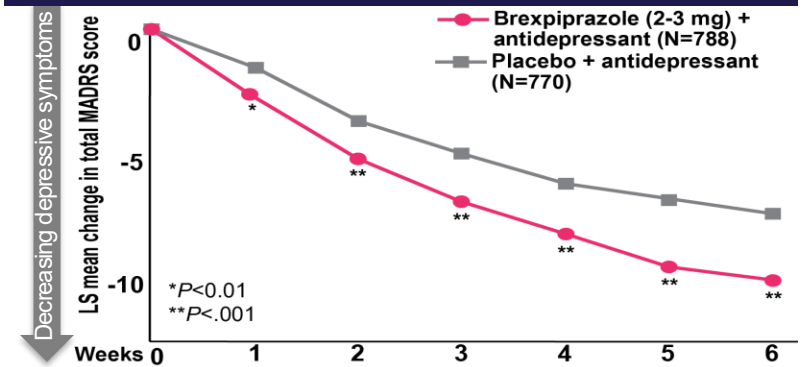
URI = upper respiratory infection.

FDA. Accessed March 24, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021436s046s050lbl.pdf.
Berman RM, et al. *Neuropsychiatry Dis Treat*. 2011;7:303-312. Pae C-U, et al. *CNS Drugs*. 2011;25(2):109-127.
Thase ME, et al. *Prim Care Companion J Clin Psychiatry*. 2008;10(6):440-447.

Practical Updates in Primary Care

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	3.3 lb	3.3 lb	0.7 lb
Weight ≥7%	5%	2%	2%
D/C due to AE	3% pooled		1%

Adverse Events in Open-Label Extension (52 weeks, N=2,994)

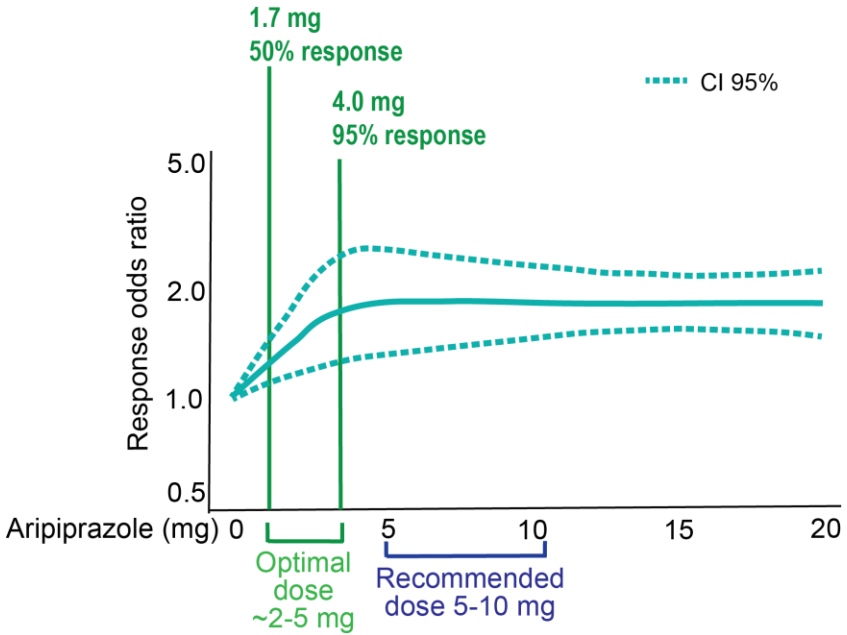
Weight increase	18%
Somnolence	8%
Headache	7%
Akathisia	7%
Increased appetite	6%
Insomnia	6%
Fatigue	6%
Viral URI	5%
Anxiety	5%
D/C due to AE	9%

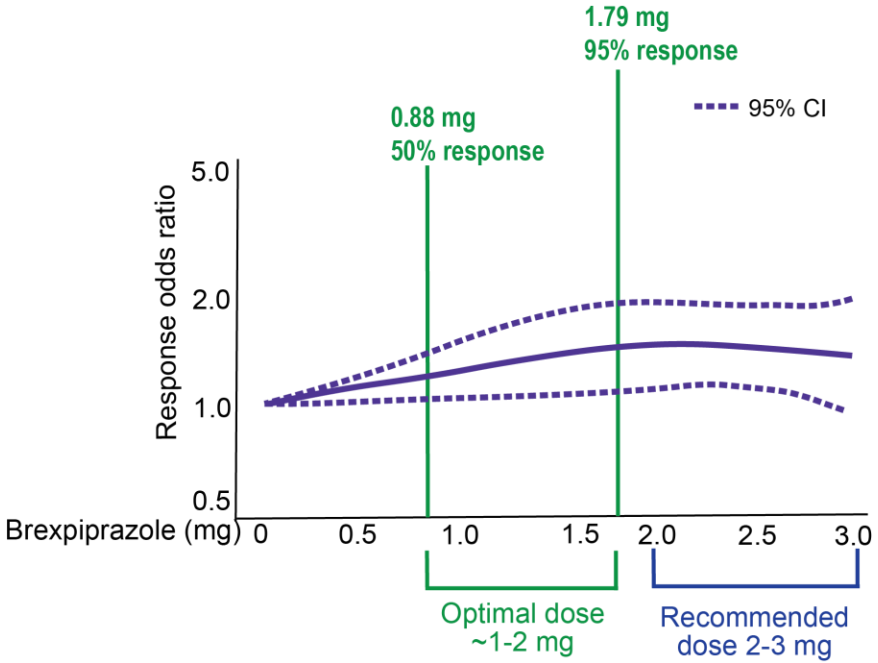
Weight gain ≥7% reported in 26%

PBO = placebo.

FDA. Accessed March 24, 2026. 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 Opin Pharmacother*. 2019;20(15):1907-1916.

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

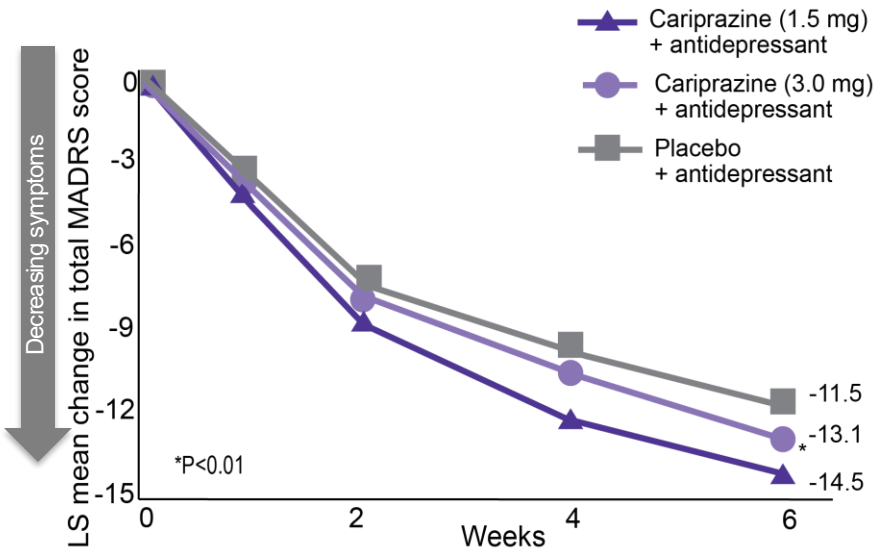
CI = confidence interval.

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

Practical Updates in Primary Care

Pivotal Trials of Adjunctive Cariprazine for MDD

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- to 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	1.5 lb	1.5 lb	0.4 lb
Weight ≥7%	2%	2%	1%
D/C due to AE	6% pooled		3%

Adverse Events in Open-Label Extension (26 weeks, N=345)

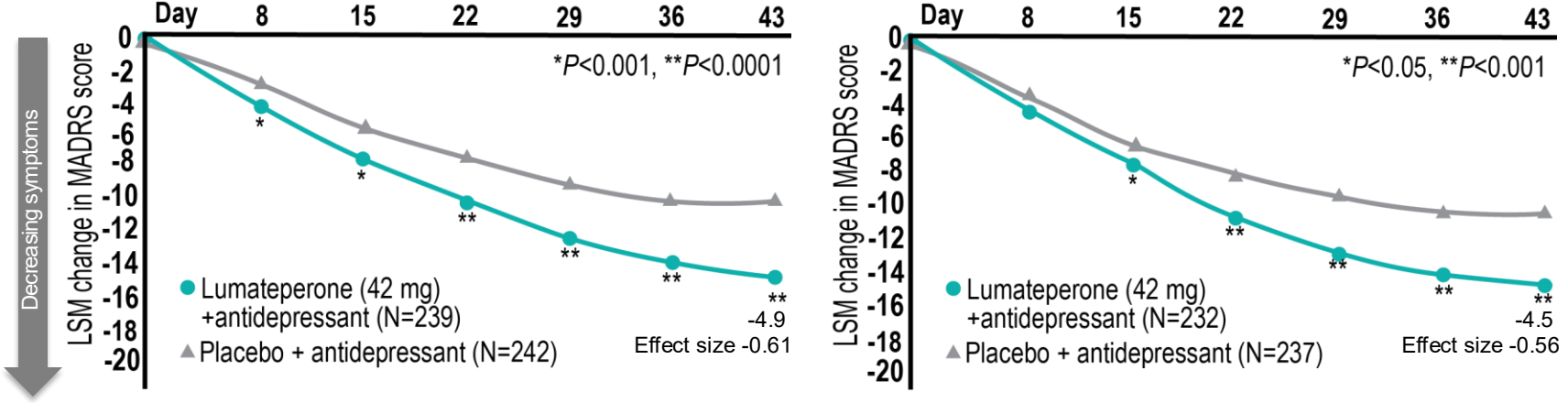
Akathisia	16%
Headache	12%
Anxiety	10%
Insomnia	10%
Restlessness	10%
Weight increase	10%
Fatigue	9%
Nasopharyngitis	9%
Nausea	6%
Dizziness	5%
Sedation	5%
D/C due to AE	14%

Weight gain ≥7% reported in 19%

FDA. Accessed March 24, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204370s014s015s016s017lbl.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. ClinicalTrials.gov. Accessed March 24, 2026. https://clinicaltrials.gov/ct2/show/NCT03739203.

Pivotal Trials of Adjunctive Lumateperone for MDD

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, et al. Presented at: Psych Congress Annual Meeting; October 29-November 2, 2024; Boston, MA.

Practical Updates in Primary Care

Adverse Events of Adjunctive Lumateperone for 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, et al. Presented at: Psych Congress Annual Meeting; October 29-November 2, 2024; Boston, MA. ClinicalTrials.gov. Accessed March 24, 2026. https://clinicaltrials.gov/study/NCT05061706; https://clinicaltrials.gov/study/NCT04985942.

Practical Updates in Primary Care

Each Dopamine Partial Agonist Has Distinct Pharmacodynamics

All atypical antipsychotics are not equal!

They differ in pharmacologic profiles and receptor binding

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-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

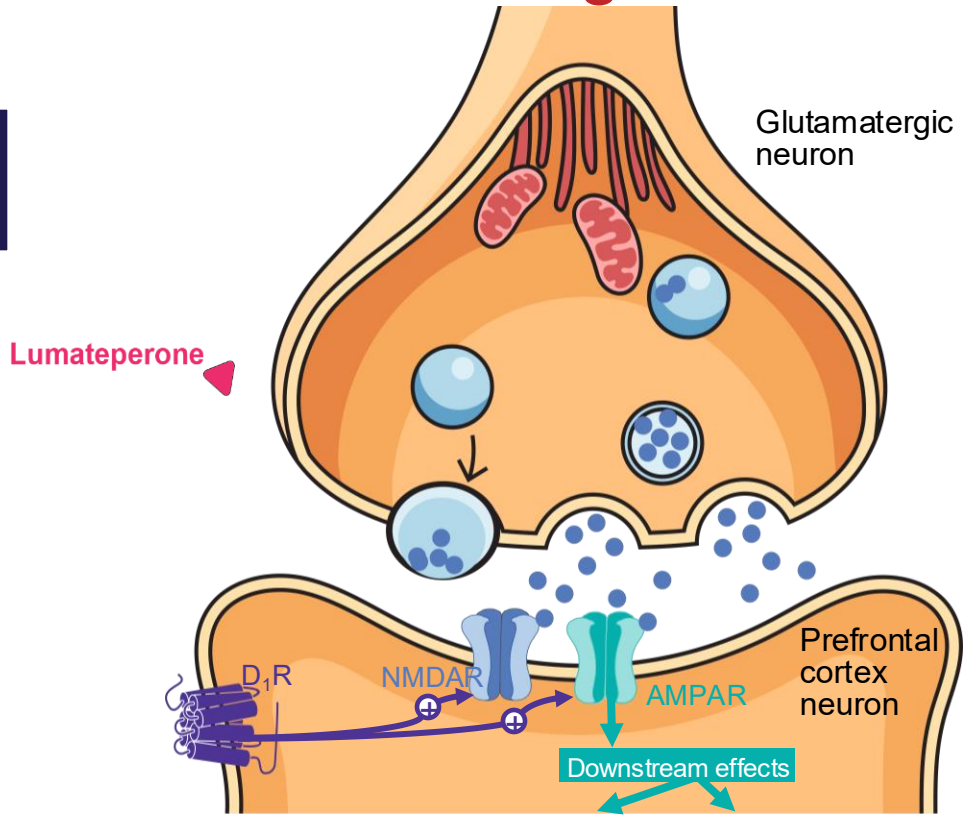
Citrome L. *Int J Clin Pract*. 2015;69(11):1211-1220. Kiss B, et al. *Drug Des Devel Ther*. 2019;13:3229-3248.

Practical Updates in Primary Care

Lumateperone's Effects on D1 May Indirectly Modulate Glutamate Functioning

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

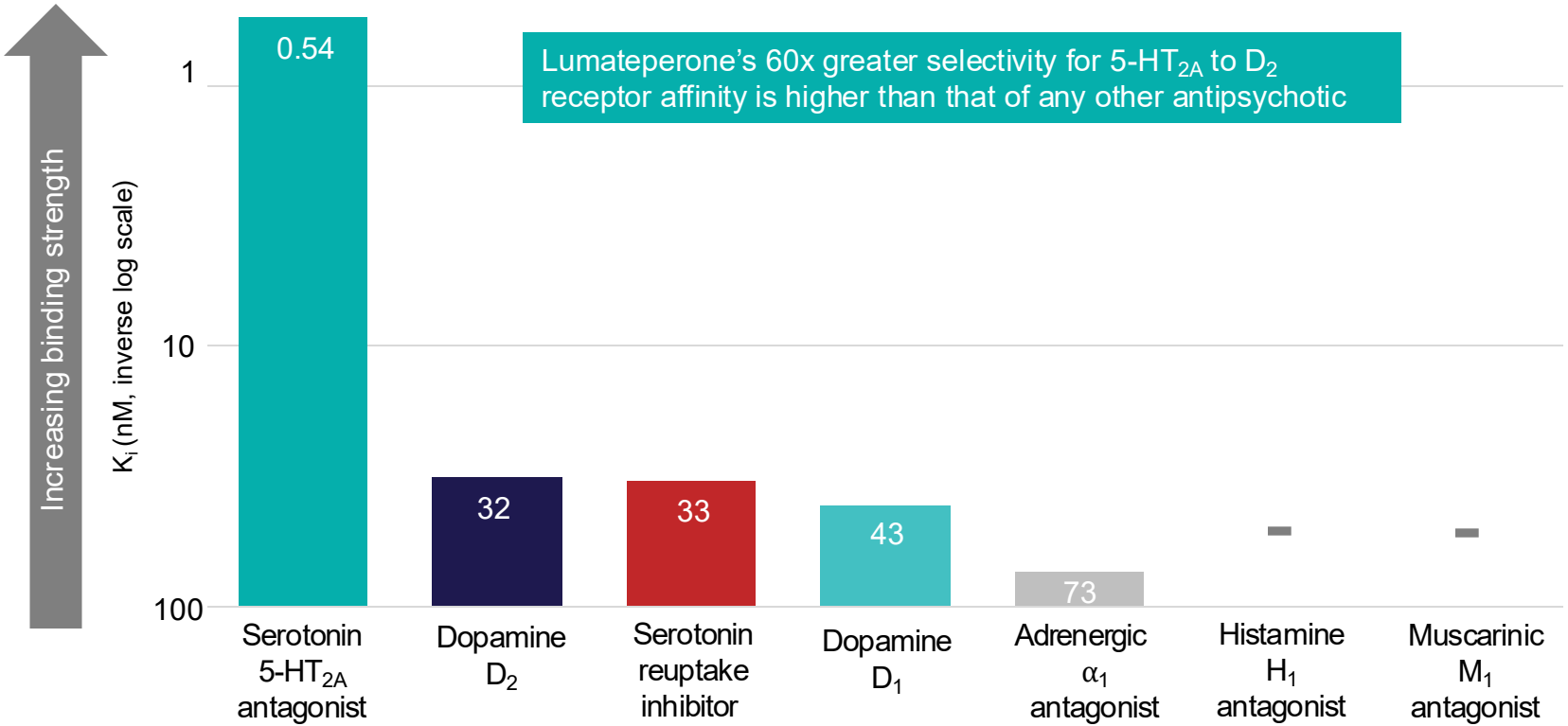
1. Lumateperone binds the D_1R receptor
2. Activation of the D_1R receptor strengthens AMPA and NMDA glutamate signaling
3. The AMPA receptor activates multiple downstream processes that are important for learning, memory, and recovery



AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor; D_1R = D_1 dopamine receptor; NMDAR = N-methyl-D-aspartate glutamate receptor.

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

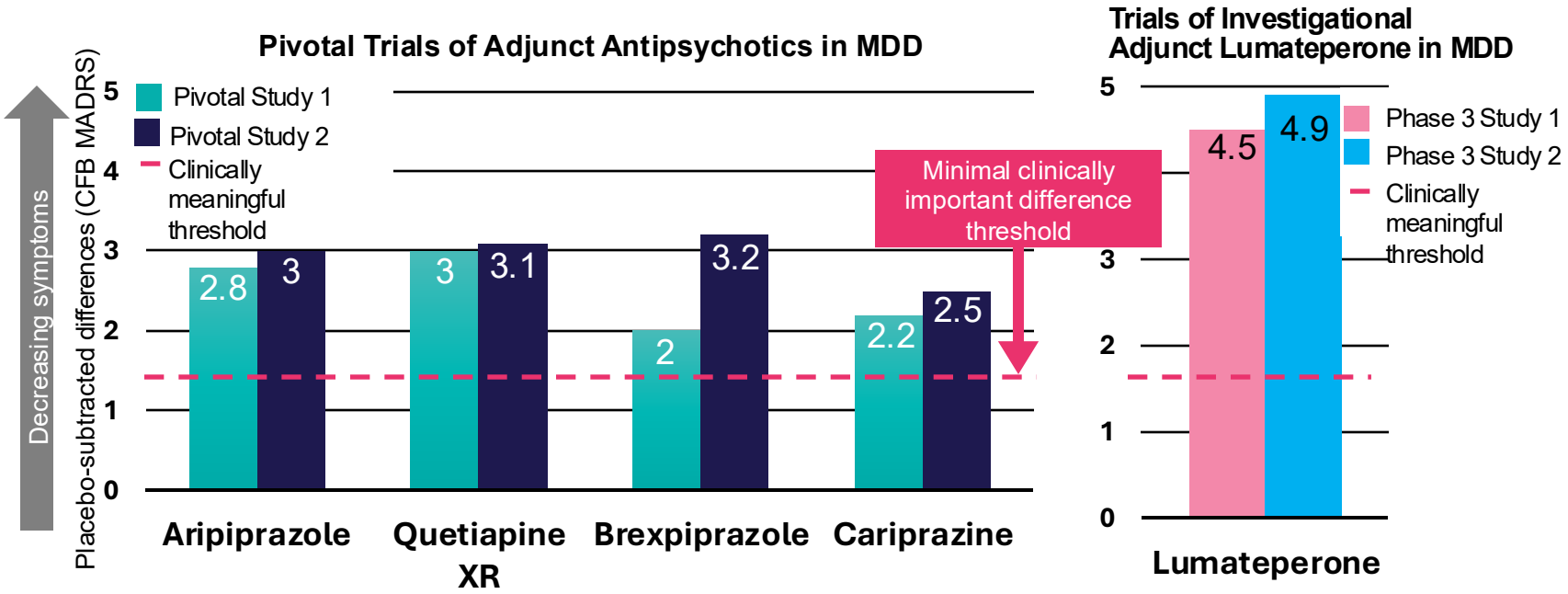
Lumateperone Pharmacology



FDA. Accessed March 25, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/209500s016lbl.pdf.
Li P, et al. *J Med Chem*. 2014;57(6):2670-2682. Kantrowitz JT. *CNS Drugs*. 2020;34(9):947-959.

Practical Updates in Primary Care

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

CFB = change from baseline.

FDA. Accessed March 25, 2026. www.accessdata.fda.gov/scripts/cder/daf/. Durgam S, et al. Presented at: Psych Congress Annual Meeting; October 29-November 2, 2024; Boston, MA.

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