



Across Mood Episodes and Throughout
the Lifespan: **Atypical Antipsychotic
Strategies for MDD and Bipolar Disorder**

MasterClass

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Faculty Disclosures

- **Greg Mattingly, MD:** Consultant – AbbVie, Acadia, Akilli, Alkermes, Angelini, Axsome, Aytu, Biogen, BMS, Boehringer Ingelheim, Cerevel, Corium, Eisai, GH Research, Intracellular, Ironshore, Johnson & Johnson, Liva Nova, Lumos Labs, Lundbeck, Neurocrine, Noven, Otsuka, Redax, Relmada, Revibe, Roche, Sage, Sirona, Sky Therapeutics, Sunovion, Supernus, Takeda, Teva, Tris Pharma; Research – AbbVie, Acadia, Aitu, Alkermes, Akilli, Alto Therapeutics, Avanir, Axsome, BMS, Boehringer Ingelheim, Cingulate, Click Therapeutics, Croium, Emalex, Idorsia, Intracellular, Johnson & Johnson, Karuna, Lumos Labs, Medgenics, Neurocrine, NLS Pharma, Redax, Relmada, Roche, Sage, Sirtsei, Sumitomo, Sunovion, Supernus, Takeda, Teva, Transcend; Speakers Bureau – AbbVie, Alkermes, Angelini, Axsome, BMS, Corium, Intracellular, Ironshore, Johnson & Johnson, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Takeda, Teva, Tris Pharma
- **Desiree Matthews, PMHNP-BC** is CEO of Different MHP, a telepsychiatry practice based in Charlotte, NC. Consultant/Advisor: AbbVie, Alkermes, Biogen, Boehringer Ingelheim, BristolMyers Squibb, Definium, Johnson & Johnson, Neurocrine Biosciences, Otsuka, SageTherapeutics, Teva Pharmaceuticals Speakers Bureau: AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Johnson & Johnson, Lundbeck, Neurocrine Biosciences, Otsuka Precision, Otsuka Pharmaceuticals, Teva Pharmaceuticals

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Learning Objectives



Differentiate the clinical presentations of MDD, bipolar depression, and bipolar mania/mixed episodes (including mixed features/anxious distress) that directly influence AAP selection and risk management



Evaluate the evidence base for the use of select AAPs (eg, aripiprazole, quetiapine, cariprazine, and lumateperone), interpreting key efficacy/safety findings across mood states and associated clinical implications



Describe practical strategies to improve persistence and outcomes by proactively addressing nonadherence, addressing patient expectations, and managing high-impact AEs (eg, akathisia and somnolence/sedation)



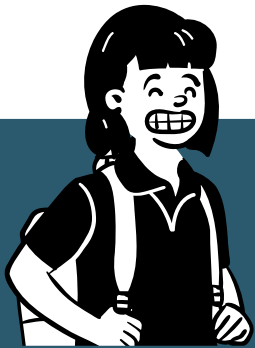
Assess real-world case scenarios to optimize the use of AAPs in mood disorders

Framing the Issue

Efficacy Priorities and Tolerability Considerations

Change Throughout the Lifespan

Adolescence

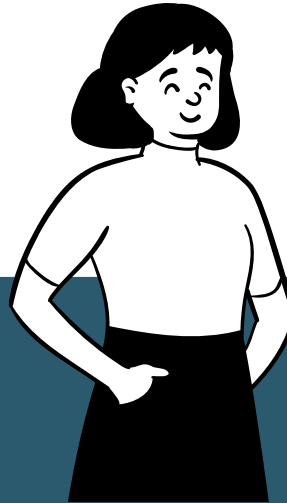


Priority: Control mania/mixed symptoms; prevent disruption

Considerations: Weight/metabolic effects, akathisia, school functioning, family-supported adherence



Adulthood



Priority: Polarity-specific control and relapse prevention

Considerations: Sexual/reproductive concerns, stigma, activation, persistence



Older Adulthood

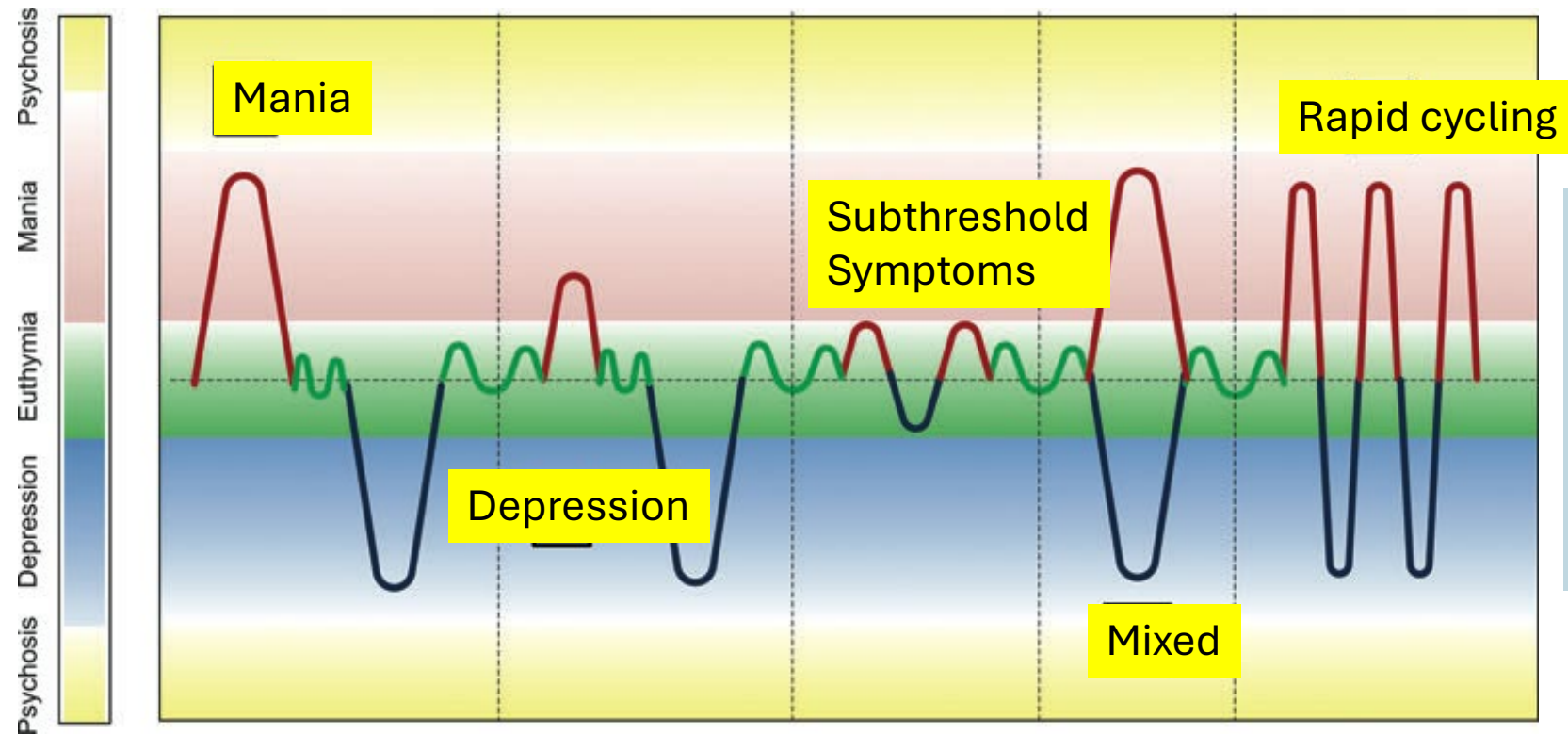


Priority: Avoid relapse while preserving function

Considerations: Falls, cognition, orthostasis, sedation, medical comorbidities, slower titration



Bipolar Disorder Is Variable



Patients spend 3x more time in depressive episodes compared to manic or hypomanic episodes

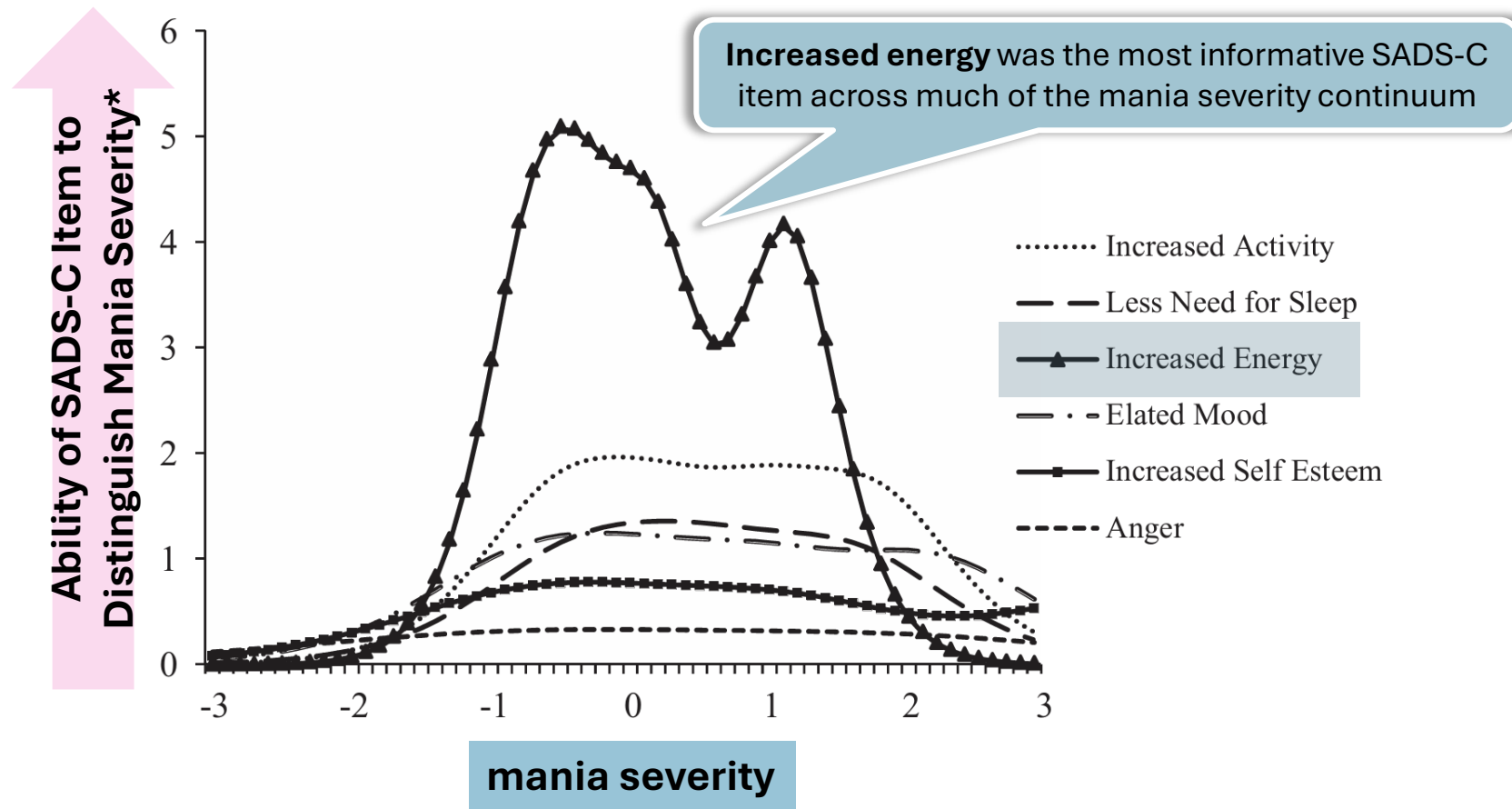
The Core Patterns of BD

i = bipolar I disorder; ii = bipolar II disorder; iii = subsyndromal bipolar symptoms;
iv = mixed states; v = rapid cycling; **red = hypo-mania; blue = depression; green = euthymia.**

BD = bipolar disorder.

Malhi GS, et al. *Bipolar Disord.* 2012;14 Suppl 2:66-89. Forte A, et al. *J Affect Disord.* 2015;178:71-78.

Increased Energy/Activity May Be More Central to Mania Than Mood Change

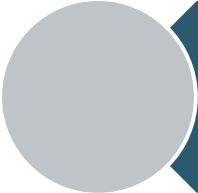


*how precisely/usefully each SADS-C item distinguishes among patients around that particular level of mania severity.

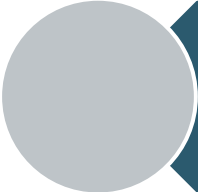
SADS-C =

Cheniaux E, et al. *J Affect Disord.* 2014;152-154:256-261.

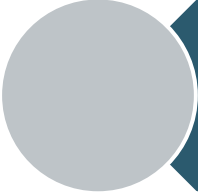
The Consequences of Missed Diagnosis Highlight The Importance of Early Detection of Bipolar Disorder



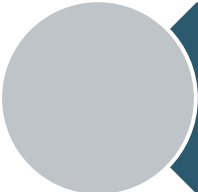
Average of **5-10 years'** delay from initial symptom onset to accurate diagnosis of bipolar disorder



Delayed treatment associated with poorer psychosocial functioning, **7-fold increased risk** for suicide attempts, more hospitalizations



Use of traditional antidepressants may be less effective to improve outcomes than mood stabilizers and atypical antipsychotics



Some medications (eg, lithium) may be less effective if begun after the passage of multiple episodes

Consequences of Inadequately Treated MDD

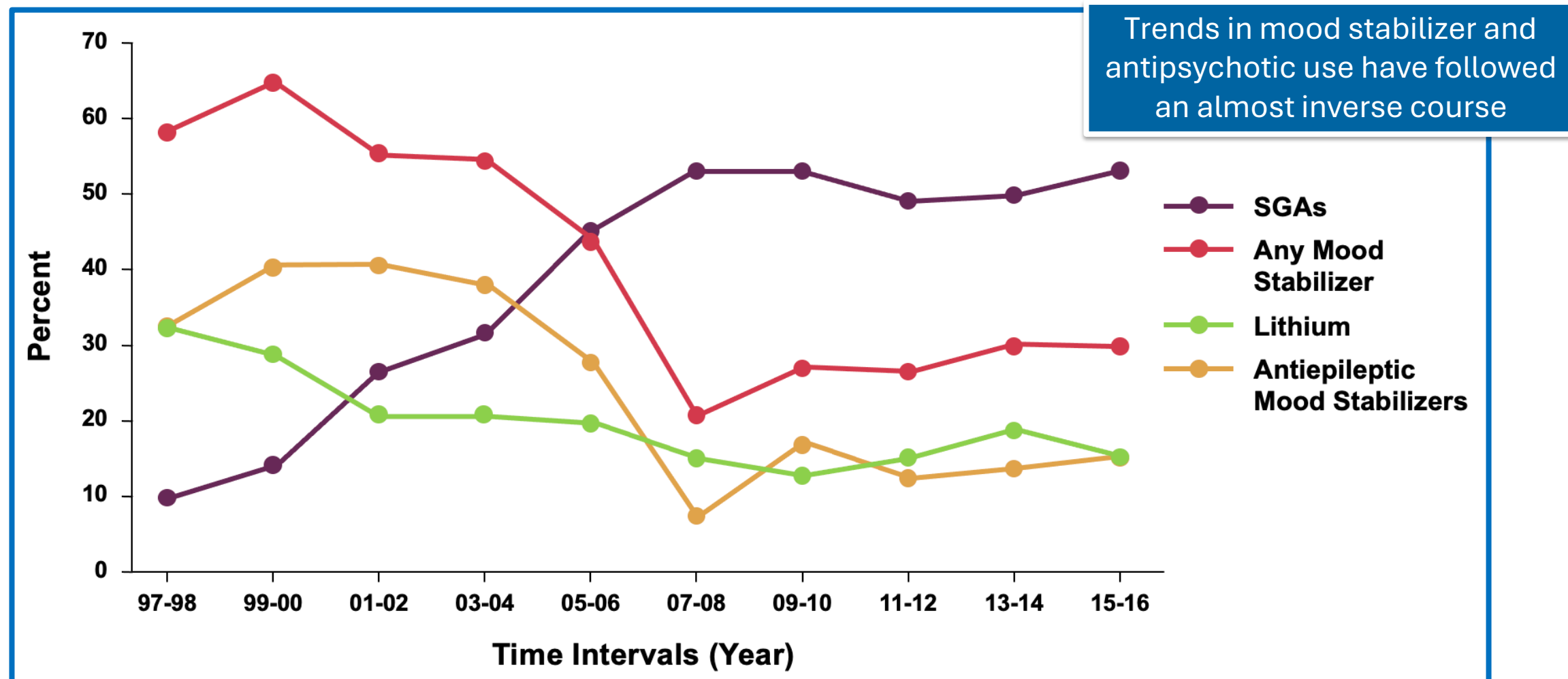
- 2 out of 3 patients on antidepressant therapy had unresolved symptoms.
- Residual symptoms of depression can lead to
 - Increase risk of relapse
 - Reduced time to next depressive episode
 - Higher risks of heart attack and strokes
 - Impaired psychosocial functioning
 - Increase risk for death by suicide

Key Learning Points

- Treatment priorities and tolerability can change across the lifespan— medication choices may need to evolve with age, functioning, and adverse-effect burden.
- Delays in diagnosing bipolar disorder are associated with poorer outcomes.
- Residual MDD symptoms worsen disease prognosis and reduce functional outcomes

Mood Polarity & Treatment Targeting Across the Lifespan

20-Year Trends in Outpatient Bipolar Disorder Treatment: *Mood Stabilizers and SGAs*

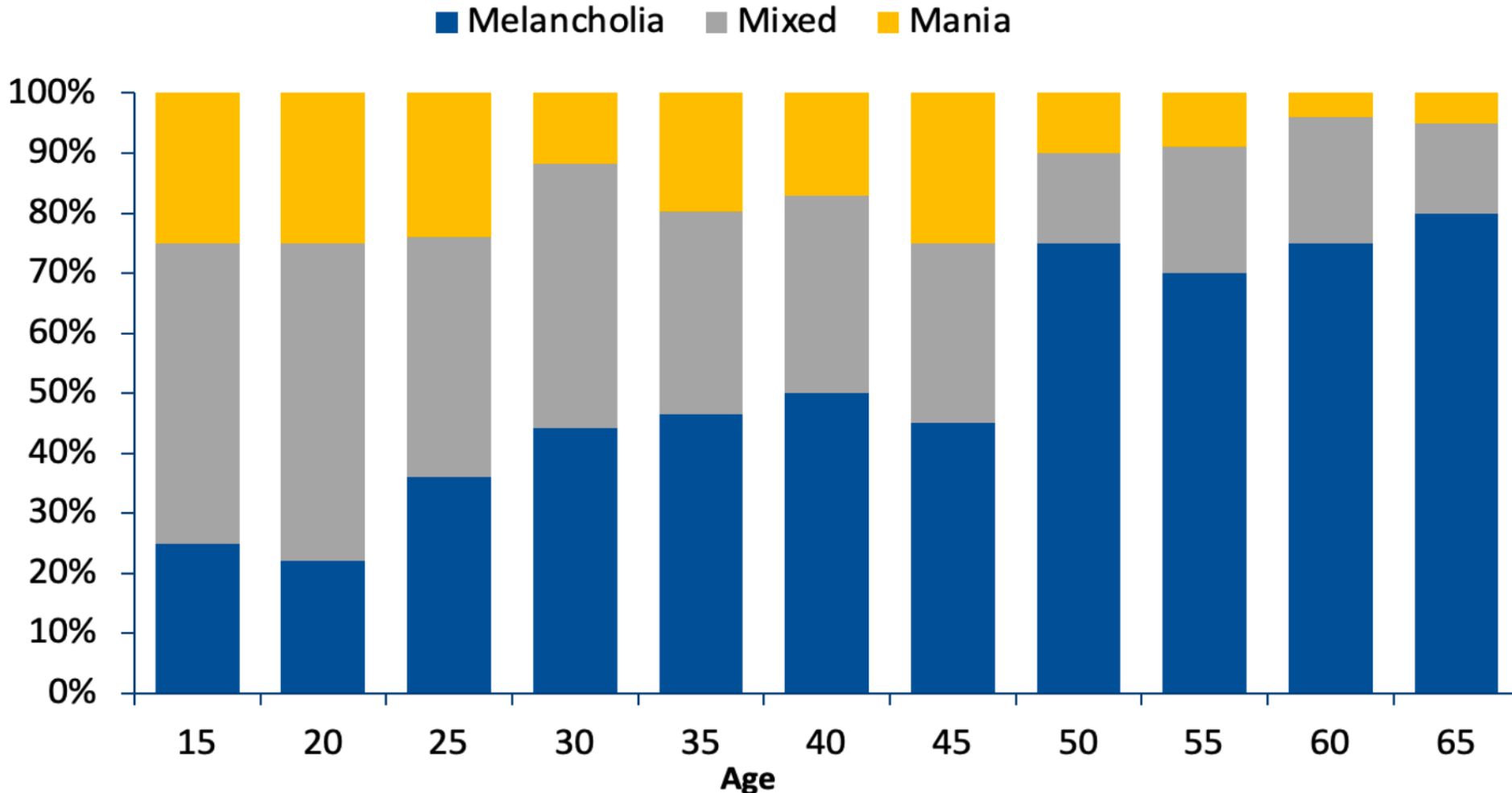


SGA = second-generation anti-psychotics
Gerhard T, et al. J Clin Psychiatry. 2014;75(5):490-497.

Increasing Your Index of Suspicion for Bipolar

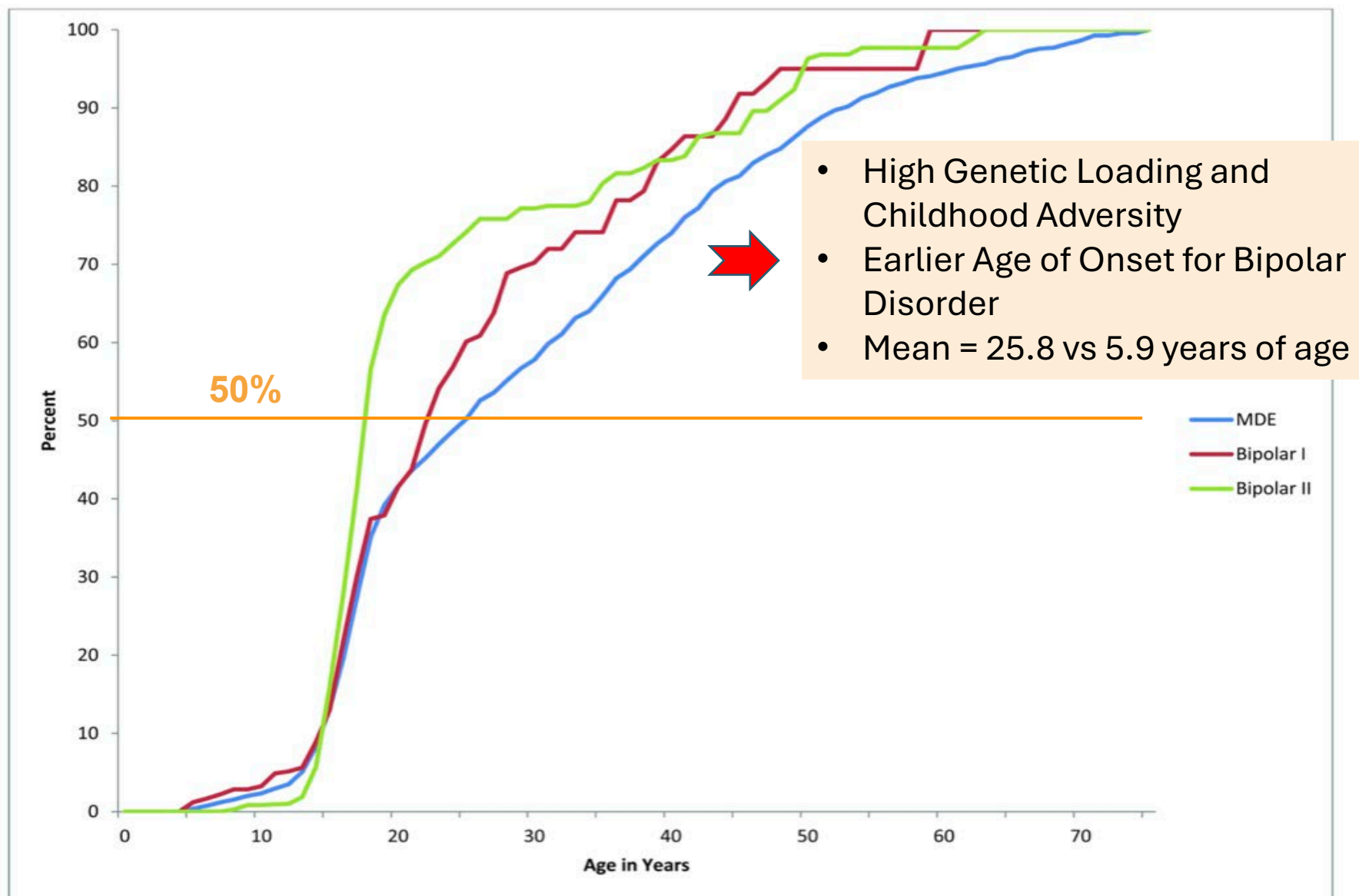
- 1) onset $\leq$ 25 years
 - 2) bipolar family history
 - 3) loaded pedigree
 - 4) precipitation by childbirth
 - 5) hypersomnic-retarded phenomenology
 - 6) pharmacologically-mobilized hypomania
- specificity of any 3 of these variables combined was 98%

Predominance of Mixed States in Early Onset Bipolar Disorder



Kraepelin E. *Manic-Depressive Insanity and Paranoia*. Edinburgh, Scotland: E & S Livingstone; 1921:169.

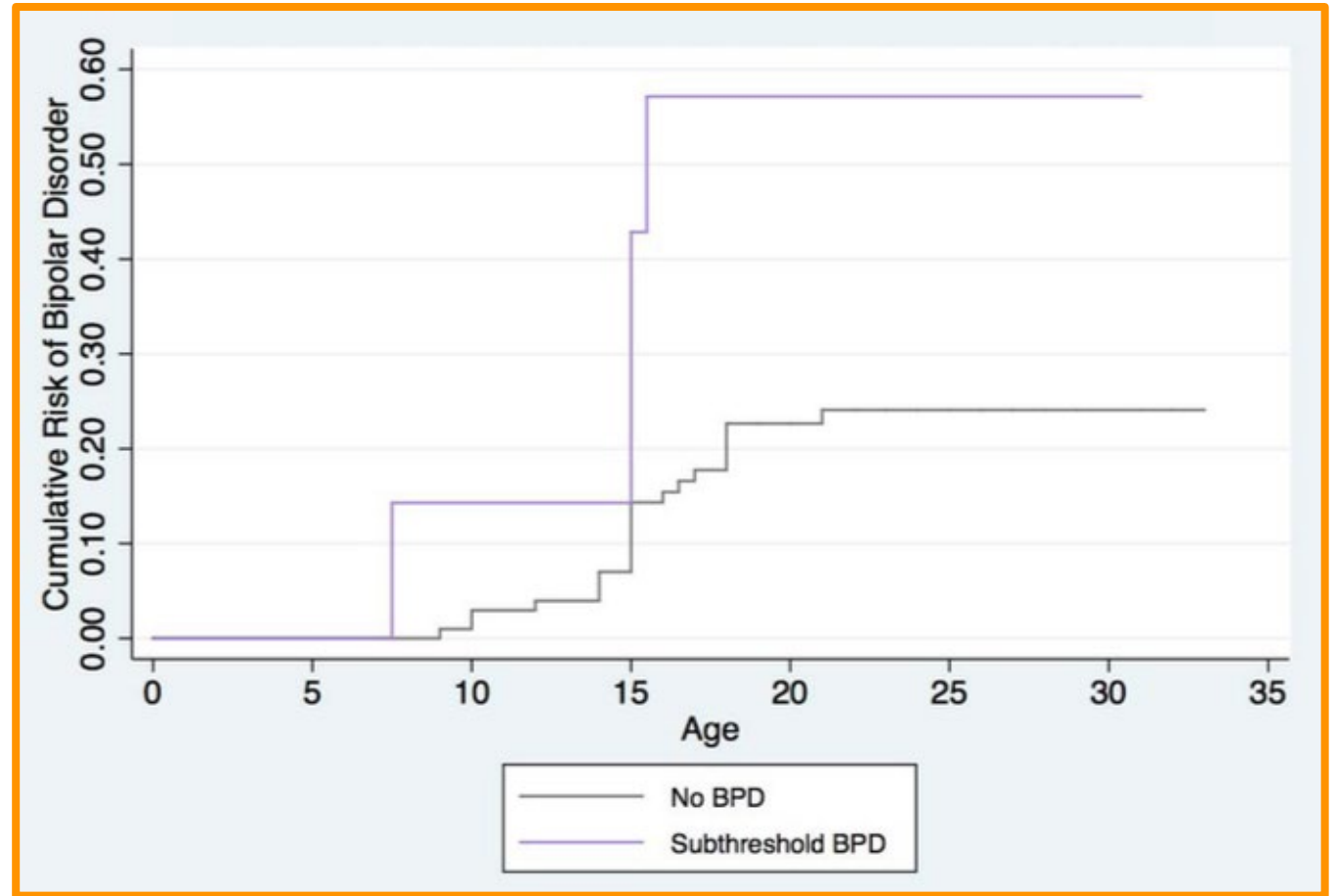
Age of Onset for MDD vs Bipolar



Childhood Depression Comorbid with ADHD

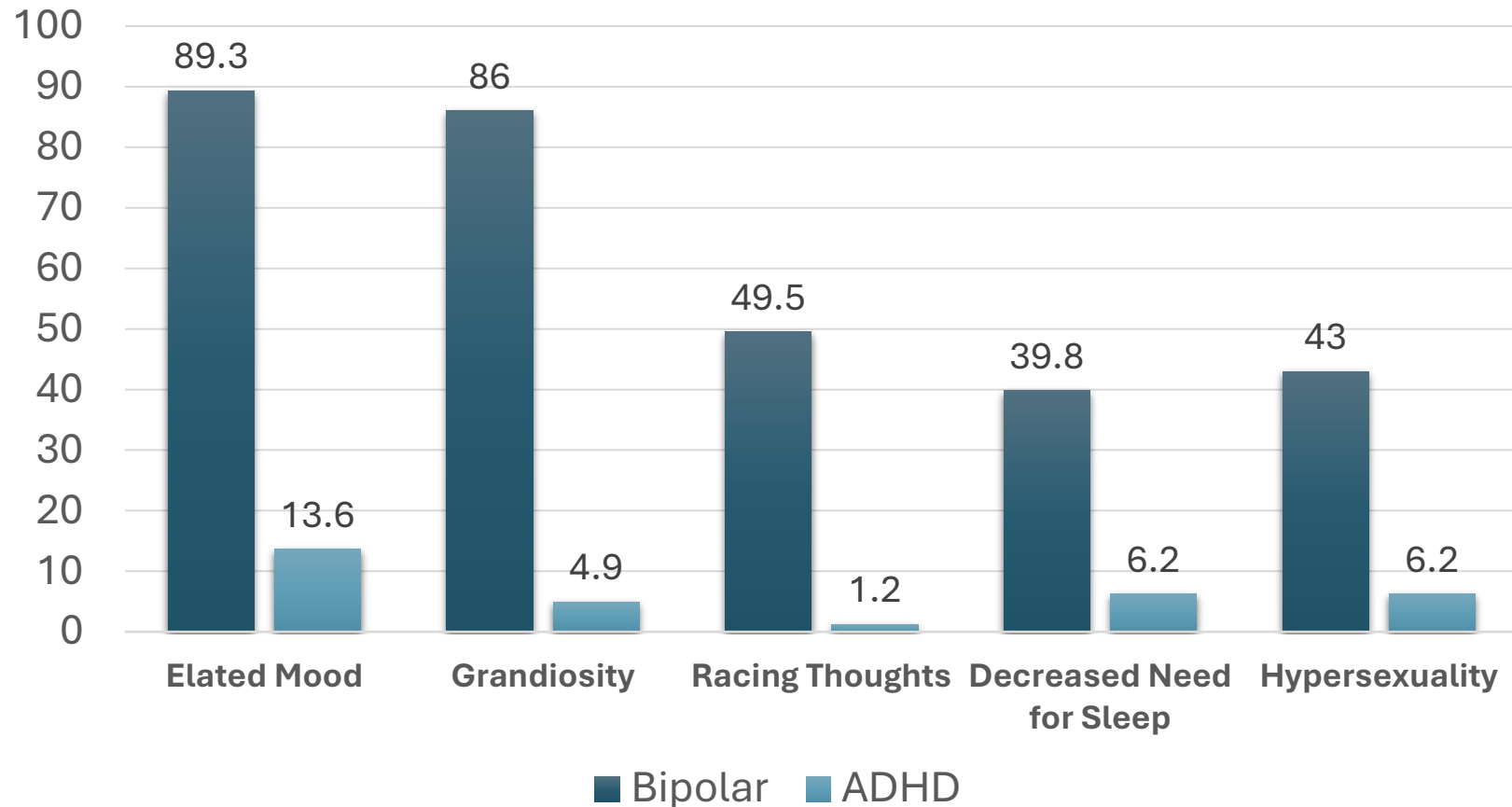
How often does ADHD with Depression convert to Bipolar?

- **25%** or 28 of 110 ADHD comorbid MDD pediatric patients
- **57%** or 4 of 7 patients with sub-clinical BP at baseline



Prepubertal/Early Adolescent Bipolar vs ADHD: 5 Key Differences

- Children ages 7-16 yr
- N = 93 with bipolar disorder
 - 87.1% rapid cyclers
 - 77.4% ultradian
- N = 81 with ADHD
- In contrast, symptoms of irritability, accelerated speech, distractibility, and increased energy overlapped considerably



What About Depression With Mixed Features?

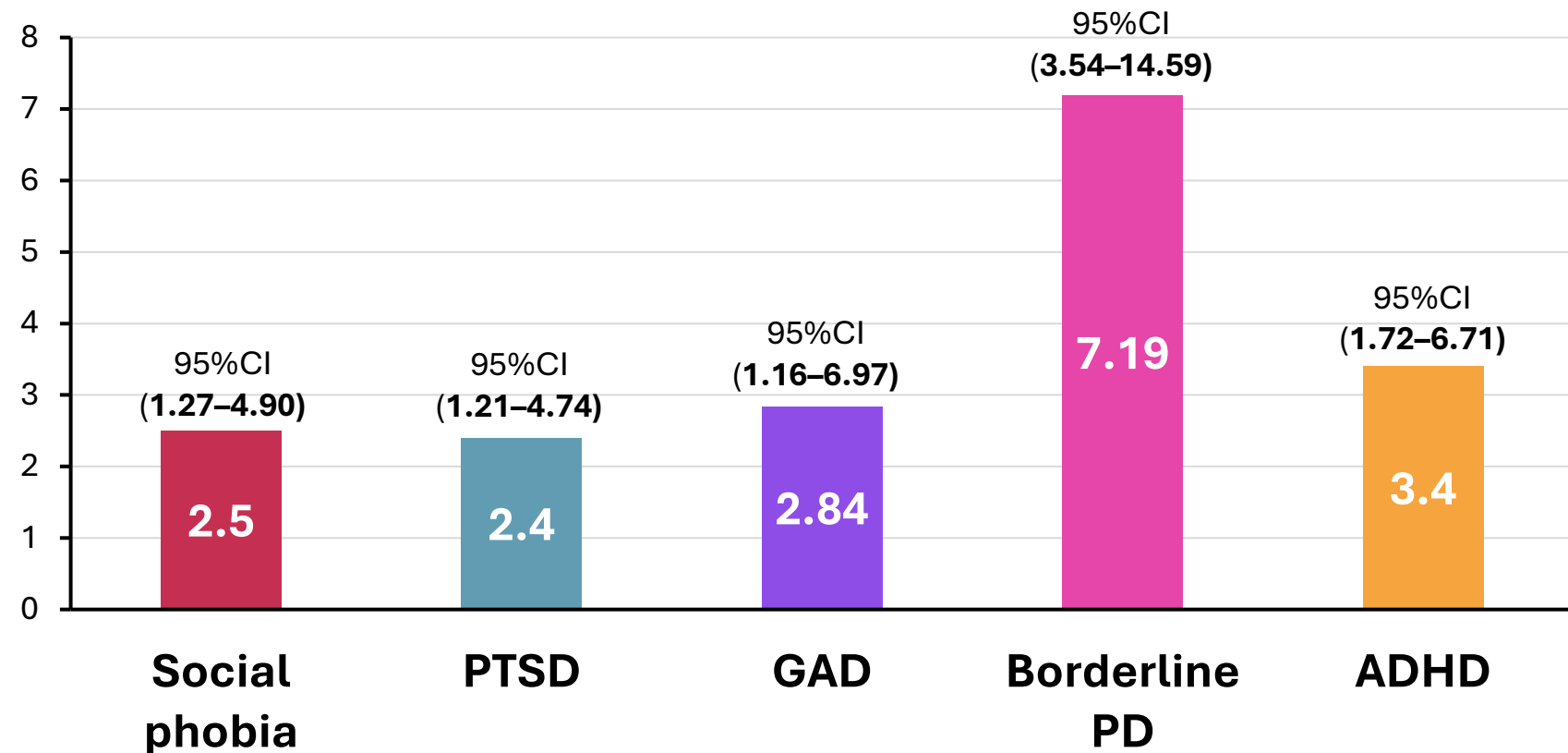
- **Depression with ≥ 3 manic/hypomanic symptoms**
 - ✓ Elevated, expansive mood
 - ✓ Inflated self-esteem, grandiosity
 - ✓ More talkative, pressured speech
 - ✓ Racing thoughts, flight of ideas
 - ✓ Increased energy/goal-directed activity
 - ✓ Excess involvement in pleasurable activities, or activities with high potential for painful consequences
 - ✓ Decreased need for sleep

Comorbidities in Depression With Mixed Features

N=459 psychiatric patients in a depressive episode were interviewed using DSM-5 Mixed Features Specifier Interview. Patients with mixed features were:

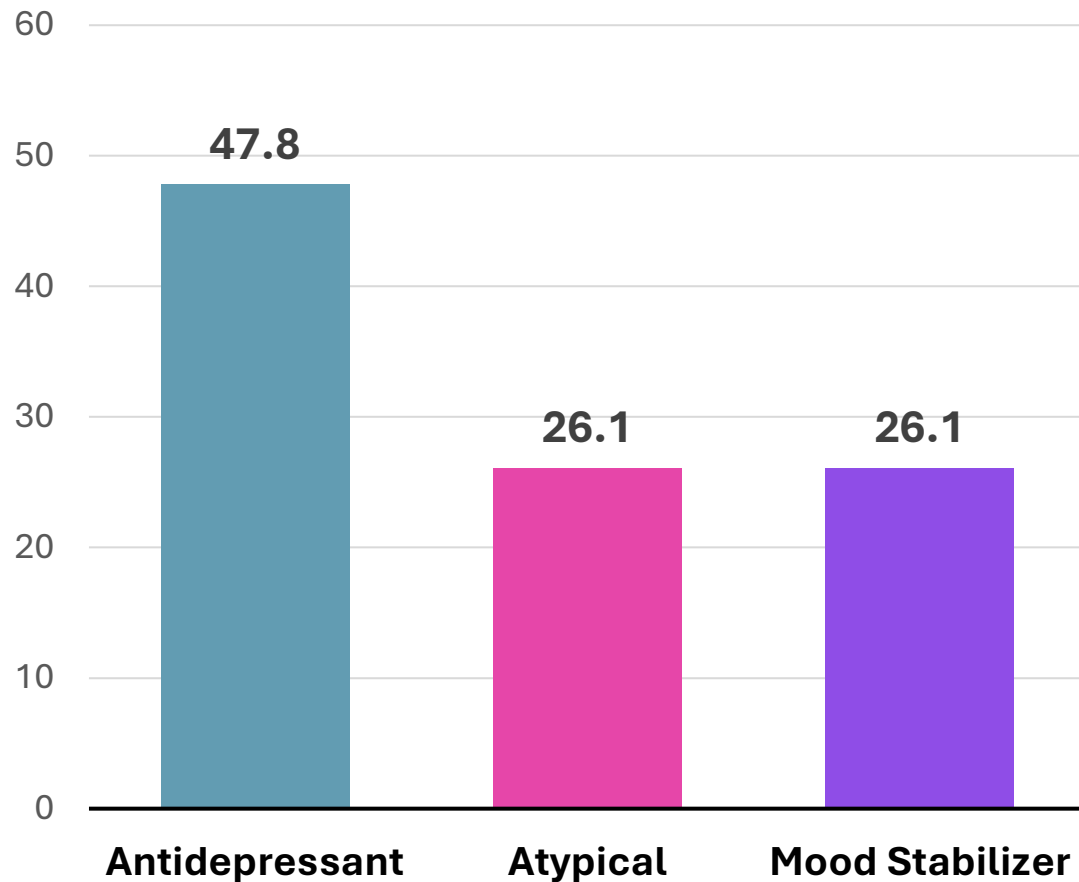
- **More severely depressed**
- **Anxious and irritable**
- **More frequently attempted suicide**

Odds Ratio of Comorbid Diagnosis (DSM-IV) in Patients with MDD and Mixed Features vs Without

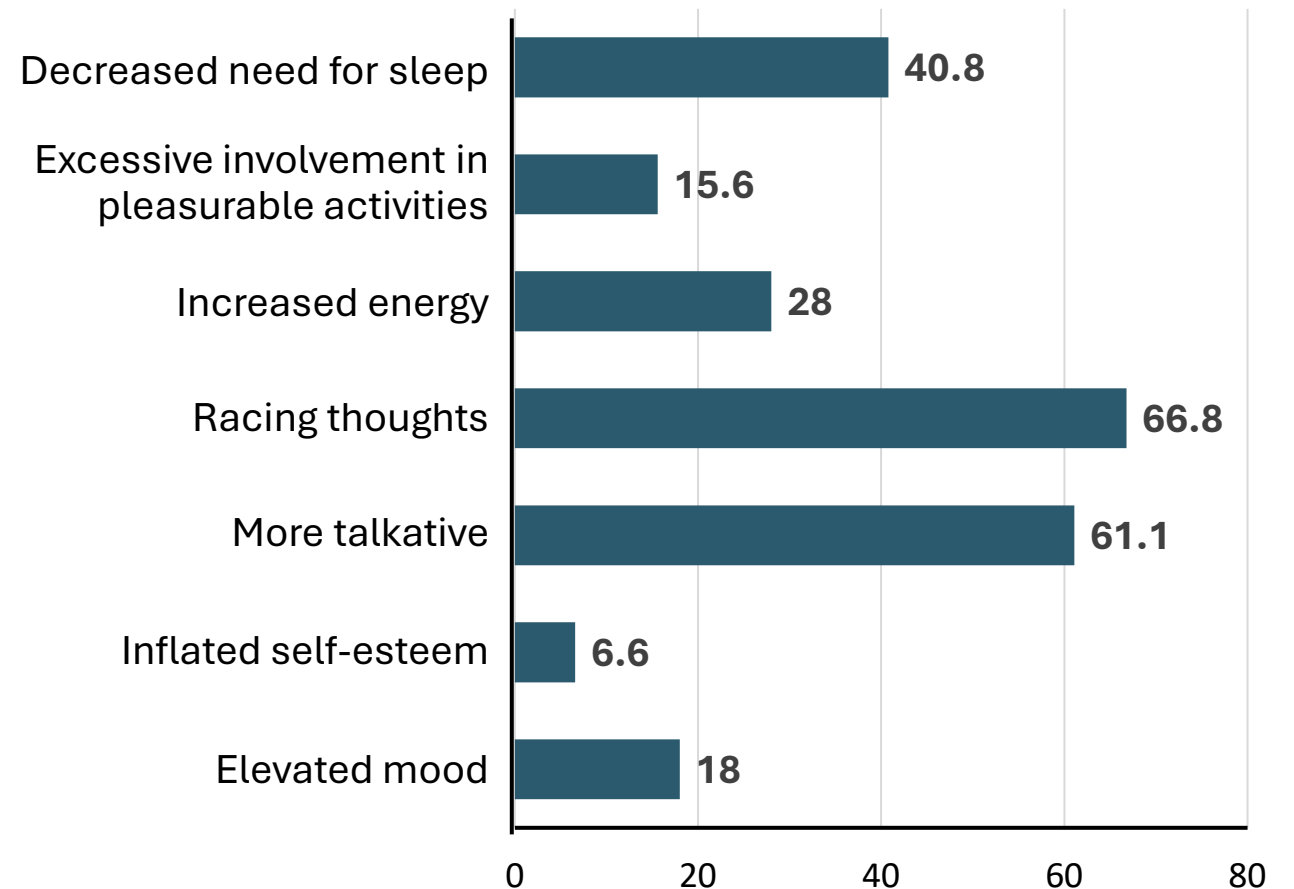


MDD with Mixed Features

Least Tolerated Treatment (%)



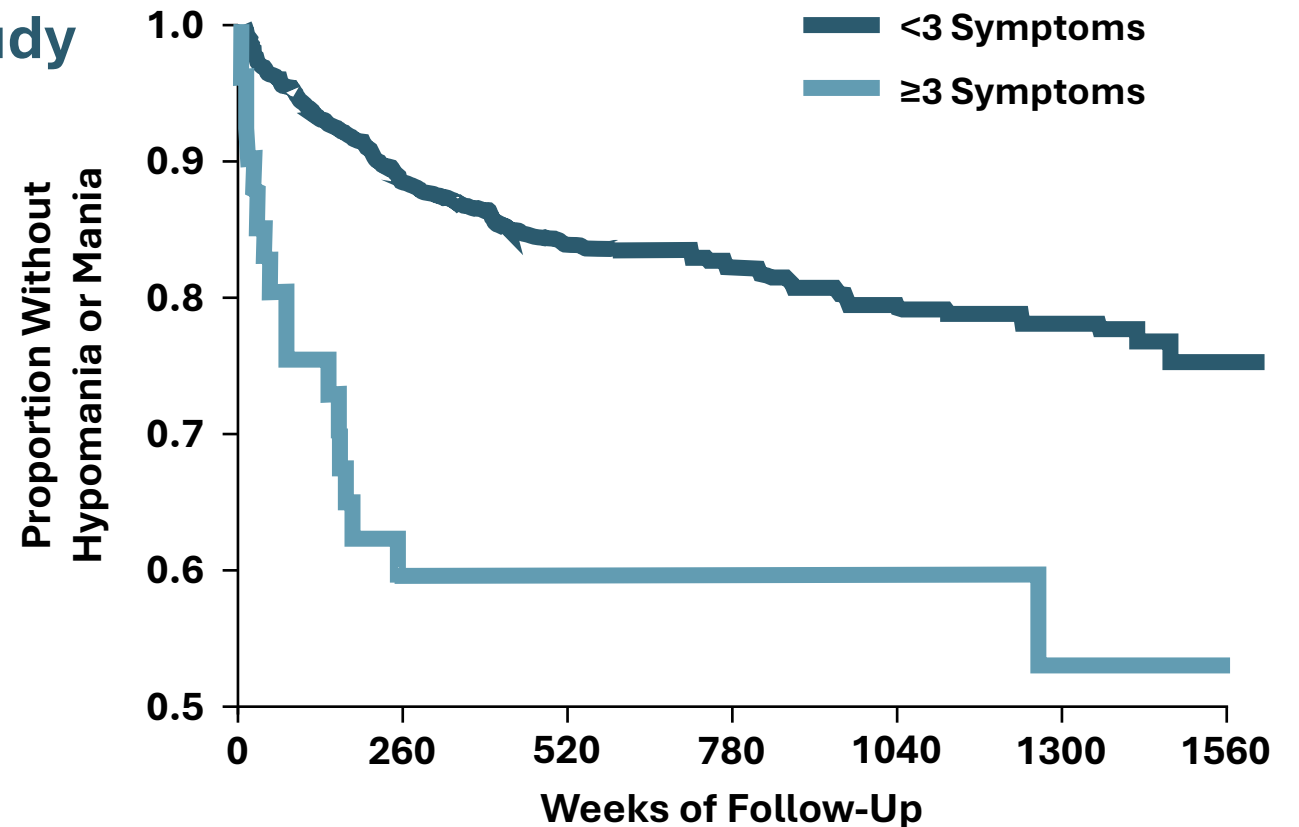
Frequency of Mixed Symptoms (%)



Mixed Features Increase the Chance of Switch

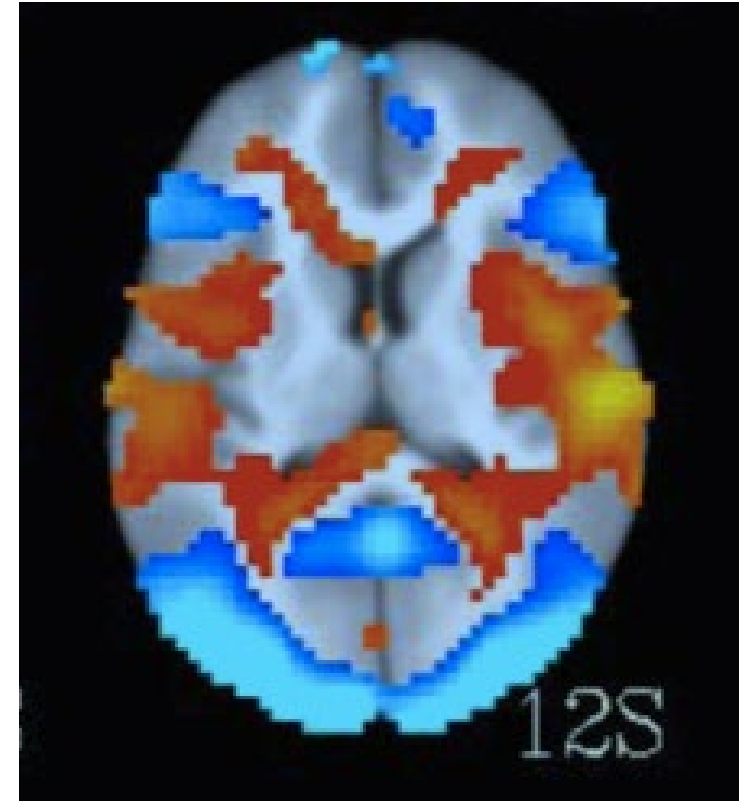
NIMH Collaborative Depression Study

- 550 patients with MDD followed for 17.5 years
- 19.6% (N=108) experienced hypomania or mania
- Number of subthreshold hypomanic symptoms, presence of psychosis, and age at illness onset predicted progression to bipolar disorder
 - Decreased need for sleep, unusually high energy, and increased goal-directed activity specifically implicated



Different Diagnoses, Similar Brains

- Regional brain activation on fMRI during depressive episode
 - Performed an attentional task incorporating emotional pictures during scan
 - Visual cues: 70% colored squares, 10% colored circles, 10% emotionally neutral, 10% emotionally unpleasant
- Participants with bipolar I disorder (n = 25), MDD (n = 25), healthy controls (n = 25)
- No differences in cortico-limbic regions found between bipolar and MDD groups



Which Scale is "BEST"?



- MADRS ??
- Hamilton ??
- BDI ??
- CUDOS ??
- PHQ9 ??
- MDQ ??
- RMS ??
- YMRS ??
- CGI-S ??

Screening for Bipolar Disorder:

The Mood Disorder Questionnaire

Has there ever been a period of time where you were not your usual self and you... (Yes/No)	
Felt so good or hyper that others thought you were not your normal self or you got into trouble?	Were so easily distracted by things around you that you had trouble concentrating/staying on track?
Were so irritable that you shouted at people or started fights/arguments?	Were much more social/outgoing than usual (eg, phoned your friends in middle of night)?
Felt much more self-confident than usual?	Had more energy than usual?
Slept much less than usual and didn't really miss it?	Were much more interested in sex than usual?
Were more talkative or spoke much faster than usual?	Were much more active/did many more things than usual?
Couldn't slow your mind down/thoughts raced through your head?	Did things that were unusual for you or that others might think were excessive, foolish, or risky?
Spent money that got you/your family in trouble?	

Rapid Mood Screener

Rapid Mood Screener (RMS): 6-item self-report measure; scores ≥ 4 = suspected case

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

Screening Tool	Concordance Index	Sensitivity	Specificity	PPV	NPV	Accuracy
RMS	0.87	0.88	0.80	0.80	0.88	83.61
MDQ	0.82	0.86	0.78	0.78	0.86	81.97

Risk of Treatment Emergent Mania (TEM)

*N=10,098 BD patients
over 51 studies*

**TEM was 18.8% across all
studies and 11.8% in 20 RCTs**

Predictors of TEM were:

- family history of mood disorders
- lifetime psychosis in BD
- psychiatric hospitalization
- rapid cycling
- polarity of index episode of BD
- substance misuse
- early age of onset

TEM = treatment-emergent mania

Fornaro M et al. *Bipolar Dis.* 2018;20:195-227.

Factors That Influence Candidacy for Antidepressant Use in Bipolar Disorder



 Favors Antidepressant Use	 Discourages Antidepressant Use	Why?
BP II	BP I	BP I: No (+) placebo-controlled trials; higher risk for TEAS
Pure depressed episodes	Mixed features	Higher risk for TEAS
No rapid cycling	Past year rapid cycling	Higher risk for more recurrences
No recent mania/hypomania	Recent mania/hypomania	Antecedent mania increases risk for TEAS

Key Take Away: Antidepressants are not good with BP1, Mixed Sx, Rapid Cycling

Leverich G et al., 2006. *Am J Psychiatry* 163: 232-239; Goldberg JF et al. 2007; *Am J Psychiatry* 164: 1348-1355; Frye MA et al. 2009. *Am J Psychiatry* 2009; 166: 164-172; Ghaemi SN et al. 2015. *J Affect Disord* 184; 318-321; MacQueen G et al 2002. *Acta Psychiatr Scand* 105: 414-418.

FDA-Approved Atypical Antipsychotics and Mood Disorder Indications in Adults

	Adjunctive MDD	BP-I Depression	BP-I Manic/Mixed
Cariprazine	●	●	●
Quetiapine XR	●	●	●
Aripiprazole	●		●
Brexipiprazole	●		
Lumateperone	●	●	
Lurasidone		●	
Olanzapine/Fluoxetine		●	
Olanzapine			●
Asenapine			●
Olanzapine/Samidorphan			●
Risperidone			●
Ziprasidone			●

Different atypical antipsychotics have distinct FDA-approved roles across major depression and bipolar depression and mixed/manic.

Adult indications shown. Products are not interchangeable; consult current FDA-approved prescribing information for complete indications, dosing, safety, and administration.

Second-Generation Antipsychotics in Bipolar Disorder:

Strengths and Limitations

Agent	Strengths	Limitations
Aripiprazole	Acute mania and maintenance efficacy; LAI	No efficacy for bipolar depression
Asenapine	Acute mania and 26-week maintenance efficacy	No established efficacy from dedicated bipolar-depression trials
Brexipiprazole	No positive data	2 (-) trials in acute mania
Cariprazine	Bimodal efficacy, large effect	(-) maintenance data
Lumateperone	Robust efficacy in bipolar I and II depression; <i>Phase 3 acute mania data at Psych Congress 2026</i>	No established maintenance efficacy
Lurasidone	Efficacy in bipolar depression alone or with lithium or divalproex	(-) maintenance data; no established efficacy in acute mania
Olanzapine	Acute mania and maintenance efficacy	Sedation, metabolic/weight liability
Quetiapine	Bimodal efficacy; maintenance efficacy	Sedation, metabolic/weight liability
Risperidone	Acute mania and maintenance efficacy; LAI	No efficacy for bipolar depression
Ziprasidone	Acute mania and maintenance efficacy	2 (-) trials in acute bipolar depression

LAI = long-acting injectable.

Goldberg JF, et al. *Practical Psychopharmacology*. Cambridge University Press; 2021; Kishi T, et al. *Mol Psychiatry*. 2021;26(8):4146-4157.

Key Learning Points



- Bipolar disorder often presents with depression; age at onset, family history, mixed features, and comorbidities can help distinguish it from MDD across the lifespan
- Validated screening tools can support recognition of bipolar disorder, but results must be interpreted alongside a thorough clinical history
- Treatment should be matched to mood polarity, with careful consideration of treatment-emergent mania risk and the relative strengths and limitations of available therapies
 - **To prevent treatment-emergent affective switches, antidepressant use is generally favored in bipolar II disorder without recent mania/hypomania or mixed features**

Comparative Evidence Across Atypical Antipsychotics

Aripiprazole

Aripiprazole:

Dopamine-Serotonin Partial Agonist Pharmacology

Dopamine partial-agonist profile

High affinity for D₂ and D₃ receptors

D₂
PARTIAL AGONIST

D₃
HIGH AFFINITY

5-HT_{1A}
PARTIAL AGONIST

5-HT_{2A}
ANTAGONIST

Lower-affinity secondary targets

5-HT_{2C} • 5-HT₇ • α_1 -adrenergic
• H₁, Minimal muscarinic affinity

What makes the profile clinically distinctive?

D₂ partial agonism

Can reduce D₂ signaling in settings of high dopaminergic tone while retaining intrinsic agonist activity

5-HT_{1A} partial agonism

Adds 5-HT_{2A} antagonist activity to the D₂ partial-agonist profile.

5-HT_{2A} antagonism

Complements D₂ activity and is characteristic of atypical antipsychotic pharmacology.

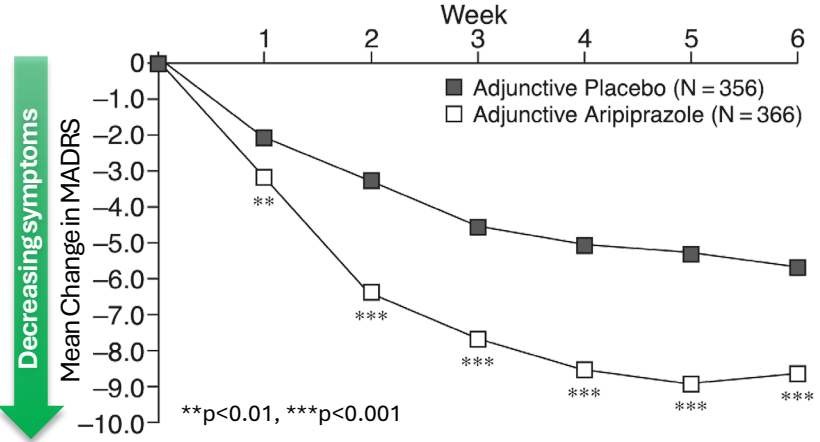
Long pharmacokinetic tail

Parent t_{1/2} ≈ 75 h; active dehydro-aripiprazole t_{1/2} ≈ 94 h. Metabolism is primarily CYP2D6 + CYP3A4.

Key concept: receptor function, not affinity alone, defines aripiprazole's pharmacology.

Aripiprazole for Adjunct MDD: Pivotal Trials Summary

Adjunctive aripiprazole reduced depressive symptoms significantly more than placebo

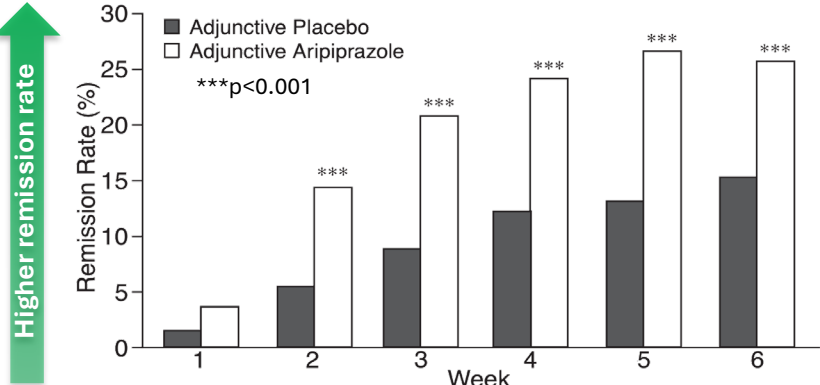


First medication with monoamine receptor partial agonism and antagonism found effective for adjunctive MDD treatment

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%

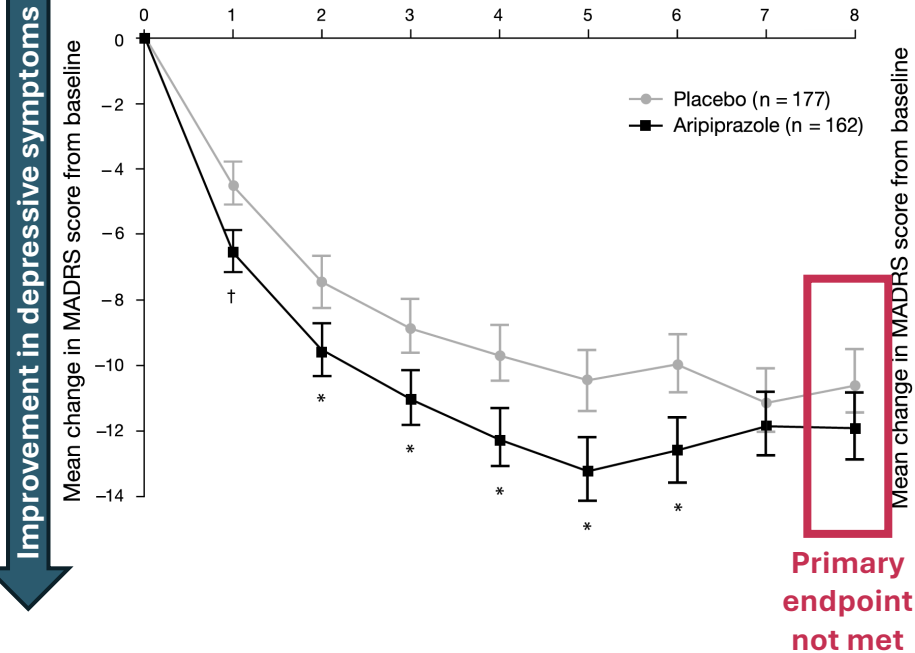
D/C = discontinuation; URI = upper respiratory infection.
Aripiprazole Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed August 10, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021436s046s050lbl.pdf.
Berman RM, et al. *Neuropsychiatry Dis Treat*. 2011;7:303-312. Pae 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 for Bipolar Depression: Pivotal Trials Summary

In two RCTs, aripiprazole monotherapy (5-30 mg/d) was not significantly more effective than placebo at the primary end point (Week 8)

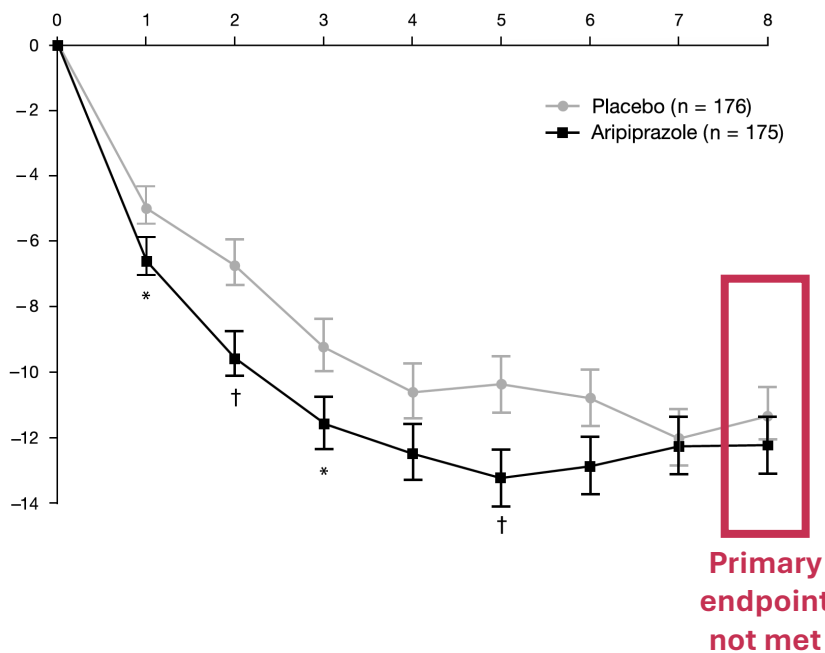
Study 1

Week of treatment



Study 2

Week of treatment



Early improvement was not sustained through Week 8

Discontinuation: 41%-47% with aripiprazole vs 30%-35% with placebo

Akathisia: 21%-28% vs 3%-5%

Other common AEs: insomnia (16%-19%), nausea (14%-15%), and fatigue (11%-13%)

Weight/metabolic effects and mania-switch rates were comparable with placebo

Aripiprazole: Depression & Bipolar Disorder

FDA-approved oral indications, dosing, and commonly observed adverse reactions

Major Depressive Disorder (Adults)

INDICATION

Adjunctive treatment to antidepressant therapy — not approved as monotherapy for MDD.

DOSING

Initial: 2–5 mg once daily • Recommended: 5–10 mg/day • Maximum: 15 mg/day

TITRATION

Dose adjustments up to 5 mg/day should occur gradually, at intervals of ≥ 1 week.

COMMON ADVERSE REACTIONS

Akathisia 25% vs 4% placebo; restlessness 12% vs 2%; insomnia 8% vs 2%; fatigue 8% vs 4%; blurred vision 6% vs 1%; constipation 5% vs 2%.

Bipolar I Manic/Mixed- 10 yo - adults

INDICATION

Acute treatment of manic and mixed episodes — monotherapy or adjunct to lithium/valproate. Oral aripiprazole also has evidence/labeling for maintenance treatment in Bipolar I formulations.

ADULT DOSING

Monotherapy: 15 mg once daily. Adjunct to lithium/valproate: 10–15 mg/day; recommended 15 mg/day. Maximum: 30 mg/day.

PEDIATRIC DOSING (10–17 yr)

Start 2 mg/day → 5 mg/day after 2 days → target 10 mg/day after 2 additional days. Maximum: 30 mg/day.

COMMON ADVERSE REACTIONS — ADULT MANIA

Monotherapy: akathisia 13% vs 4%; sedation 8% vs 3%; tremor 6% vs 3%; restlessness 6% vs 3%; extrapyramidal disorder 5% vs 2%. Adjunctive: akathisia, insomnia, extrapyramidal disorder.

Aripiprazole: Depression & Bipolar Disorder

FDA-approved oral indications, dosing, and commonly observed adverse reactions

- **The First FDA Approved D2 Partial Agonist**
- **Not Approved for Bipolar Depression**
- **Akathisia 25% in MDD and 13% in BP1**

mg/day • Maximum: 15 mg/day

TITRATION

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Quetiapine

Quetiapine: Parent Drug + Active Metabolite

Create a Multimodal Profile

QUETIAPINE: parent drug

5-HT_{2A}
ANTAGONIST

H₁
ANTAGONIST

α_{1B}
ANTAGONIST

D₂
ANTAGONIST

D₁
AFFINITY

NET
MINIMAL

Quetiapine's substantially higher affinity for H₁ and α_{1B} than D₂ receptors may contribute to its differing pharmacologic effects across the clinical dose range.

Higher affinity for 5-HT_{2A} than D₂ receptors

NORQUETIAPINE: active metabolite

5-HT_{2A}
HIGH AFFINITY

H₁
HIGH AFFINITY

M₁
ANTAGONIST

NET
INHIBITION

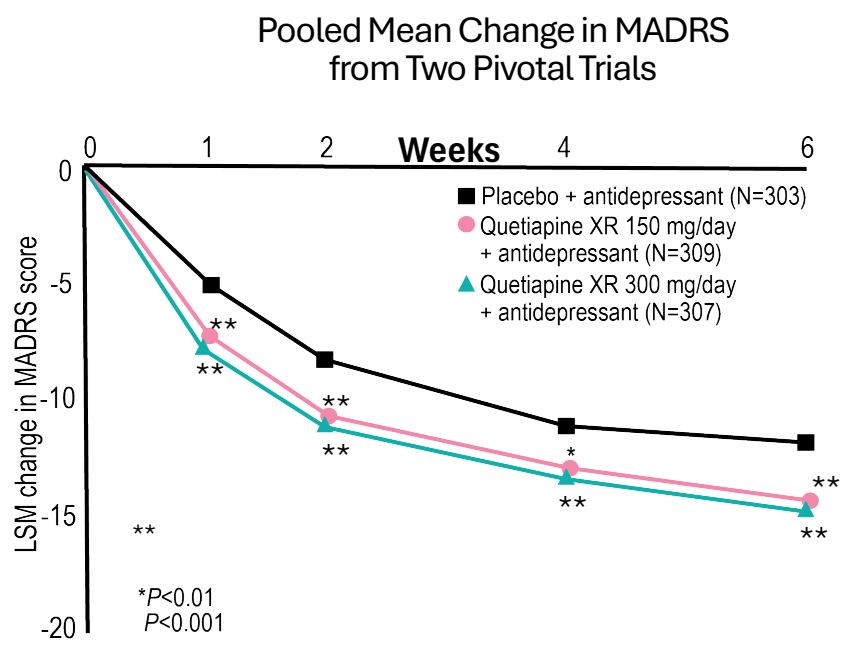
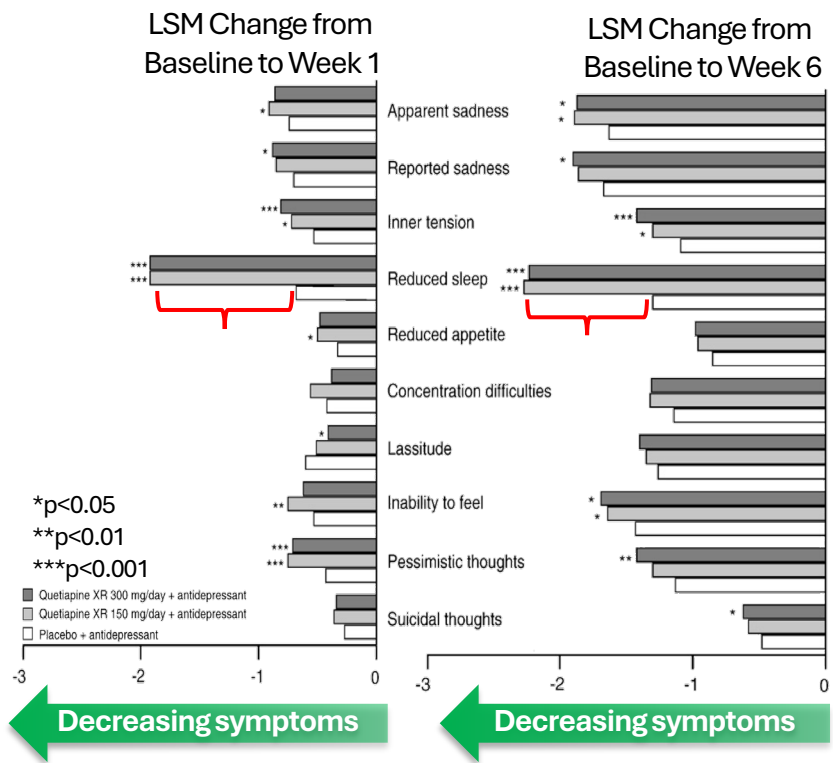
5-HT_{1A}
AGONIST†

D₂
ANTAGONIST

Norquetiapine adds noradrenergic and serotonergic activity that may contribute to quetiapine's antidepressant effects.

NET inhibition + 5-HT_{1A} agonism

Quetiapine XR for Adjunct MDD: Pivotal Trials Summary



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%

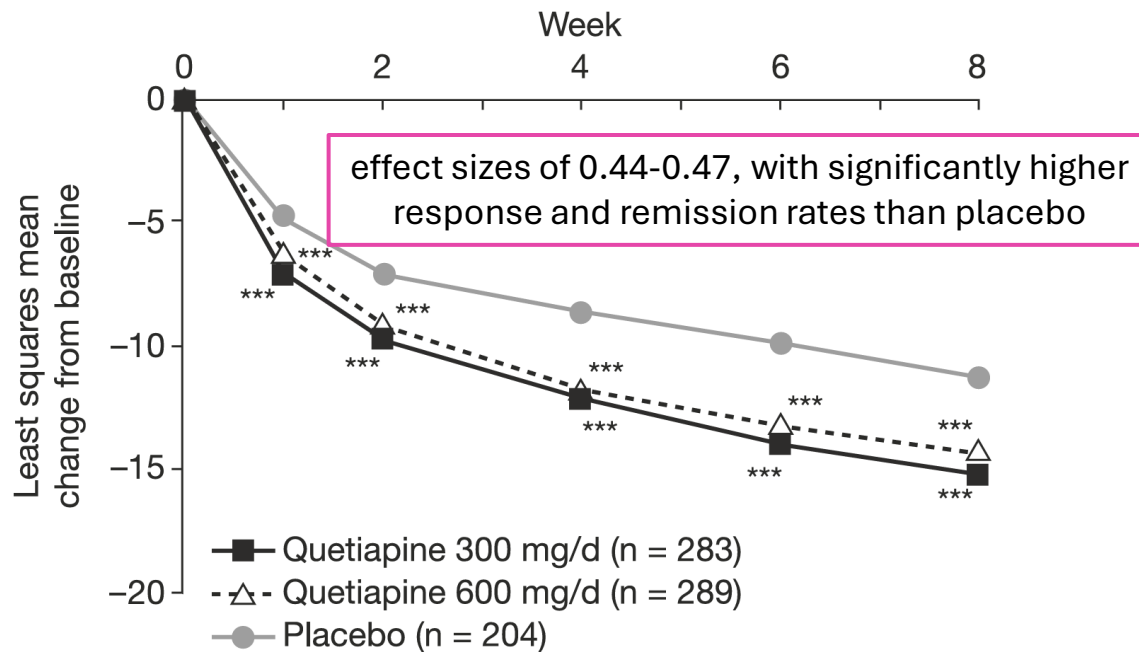
At week 6, Quetiapine XR does separate on 4 of 6 “core” MADRS items at 150 mg and 5 of 6 at 300 mg, but much of the overall separation is still driven by sleep

Long-term adverse event data unavailable for quetiapine XR

Quetiapine for Bipolar: Pivotal Trials Summary

Bipolar Depression

Pooled LSM from Four RCTs

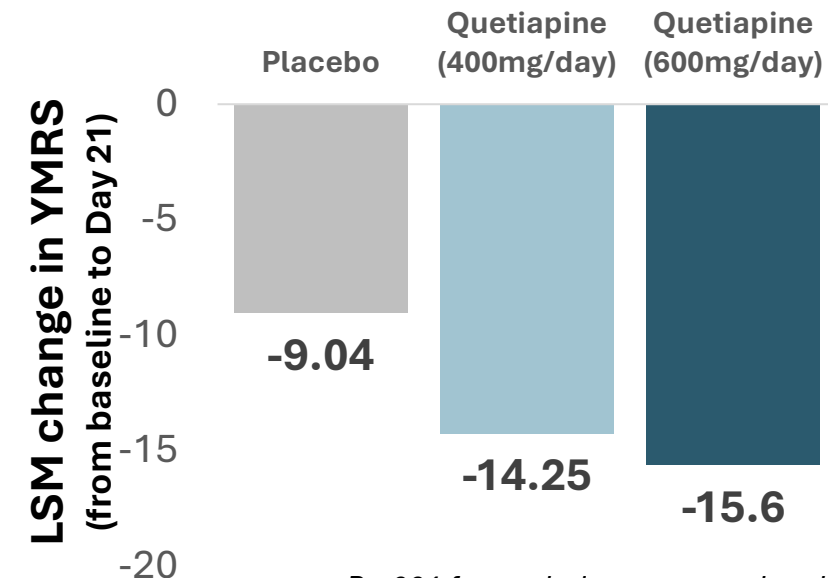


AEs with quetiapine (both doses) included dry mouth, somnolence, sedation, dizziness, and headache

Bipolar Mania

In adults with bipolar I mania, quetiapine monotherapy reduced YMRS scores by 12.3-14.6 points vs 6.7-8.3 points with placebo across two 12-week trials

In children/adolescents (10-17yo) with bipolar I mania, significantly reduced manic symptoms. Somnolence/sedation was common, and clinically relevant weight gain occurred within 3 weeks



$P < .001$ for each dose versus placebo

Quetiapine ER: Depression & Bipolar Disorder

FDA-approved oral indications, once-daily dosing, and common adverse reactions

Major Depressive Disorder (Adults)

INDICATION

Adjunctive therapy to antidepressants for MDD in patients with inadequate antidepressant response. Not approved as monotherapy.

DOSING

Day 1: 50 mg qPM • Day 2: 150 mg qPM • Day 3: 150 mg qPM.
Recommended: 150–300 mg/day.
Maximum: 300 mg/day.

COMMON ADVERSE REACTIONS

Somnolence/sedation 37–43% vs 9% placebo; dry mouth 27–40% vs 8%; fatigue 11–14% vs 4%; constipation up to 11%; weight increased up to 5%.

Bipolar Depression (Adults)

INDICATION

Acute treatment of depressive

mg/day.

COMMON ADVERSE REACTIONS

Somnolence/sedation 52% vs 13% placebo; dry mouth 37% vs 7%; increased appetite 12% vs 6%; weight gain 7% vs 1%; dyspepsia 7% vs 1%; fatigue 6% vs 2%.

Bipolar I Disorder: Mania & Maintenance

ACUTE MANIC OR MIXED EPISODES

Adults: monotherapy or adjunct to lithium/divalproex. Day 1: 300 mg • Day 2: 600 mg • Day 3: 400–800 mg.
Recommended: 400–800 mg/day.
Maximum: 800 mg/day.

18–65: acute manic episodes, monotherapy; target 400–600 mg/day; 600 mg/day.

MAINTENANCE

Adults: adjunct to lithium/divalproex; 400–800 mg/day.

COMMON ADVERSE REACTIONS — MANIA

Somnolence 50%, dry mouth 34%, dizziness/constipation 10%, dyspepsia/fatigue/weight gain/EPS 7%.

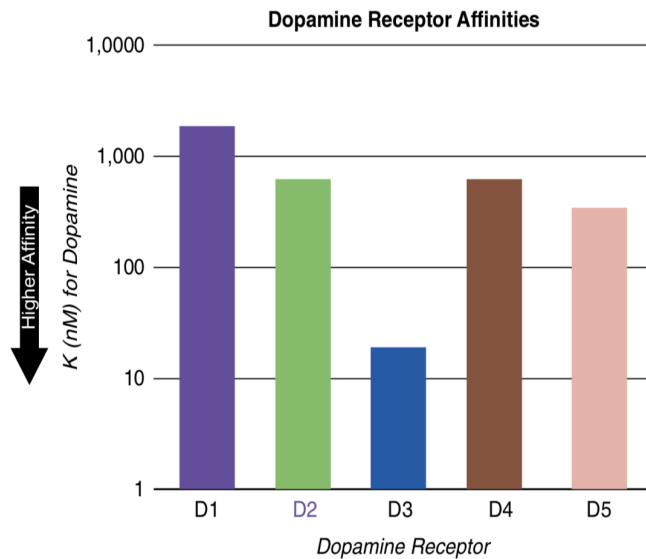
Do You Have To BE Sedating?

Cariprazine

Cariprazine Pharmacokinetics and D₃ Pharmacology

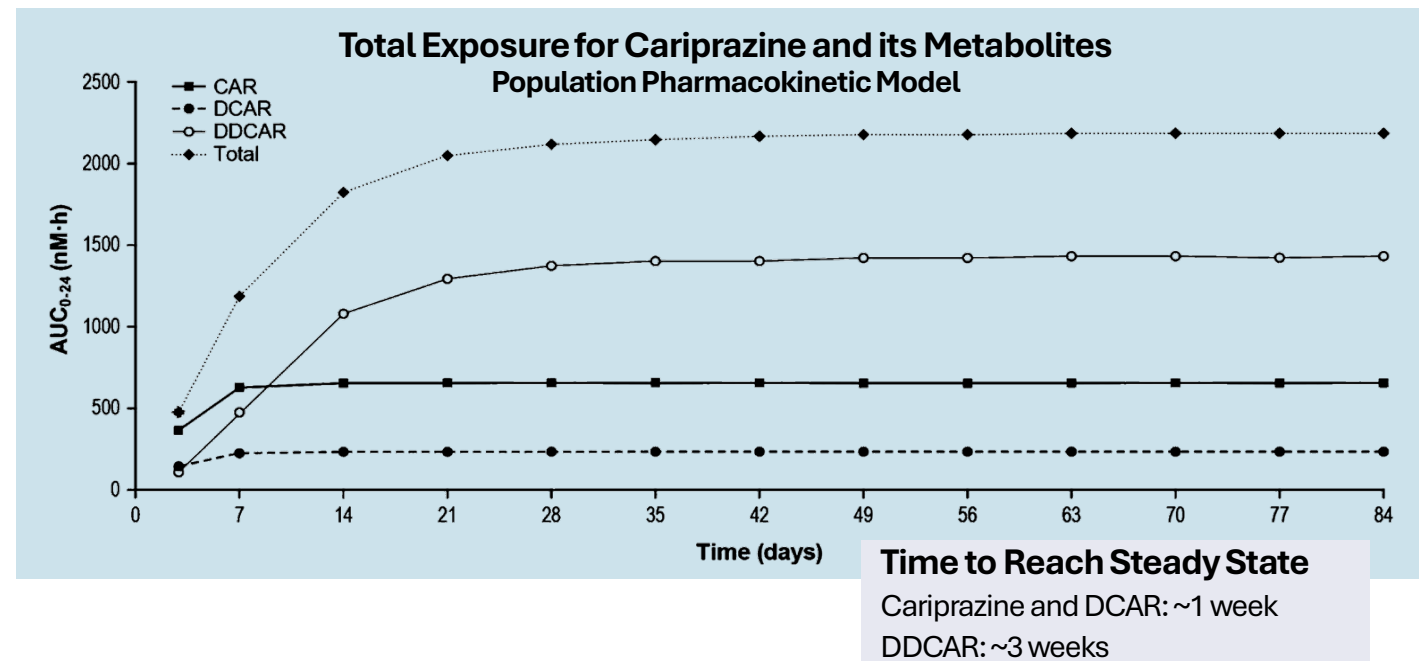
Dopamine has a higher affinity for D₃ than any other dopamine receptor

Cariprazine is the only antipsychotic in the US with a higher affinity for D₃ than dopamine itself



Cariprazine has a half-life of ~1 week, and two active metabolites with similar pharmacodynamics

The second metabolite makes up about 2/3 of the total exposure at steady-state



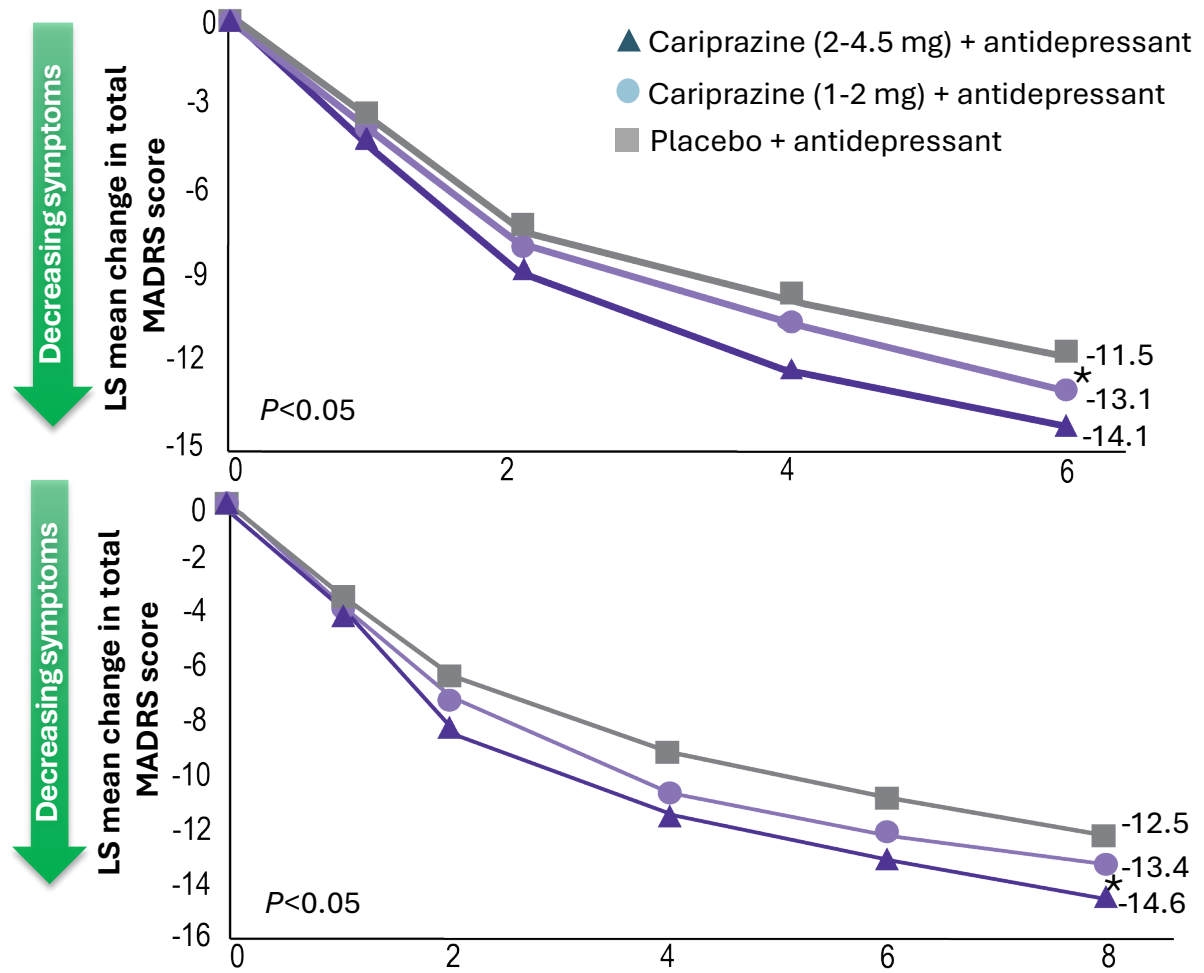
The D₃ receptor has a more limited distribution pattern than D₂, with the highest level of expression in the limbic areas

AUC = area under the curve; CAR = cariprazine; DCAR = desmethyl-cariprazine; DDCAR = didesmethyl-cariprazine.

Beaulieu JM, Gainetdinov RR. *Pharmacol Rev.* 2011;63(1):182-217. Stahl SM. *CNS Spectr.* 2017;22(4):305-311. Periclou A, et al. *Eur J Drug Metab Pharmacokinet.* 2021;46(1):53-69. Stahl SM, et al. *Ther Adv Psychopharmacol.* 2020;10:2045125320905752.

Pivotal Trials of Adjunctive Cariprazine for Adult MDD

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



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

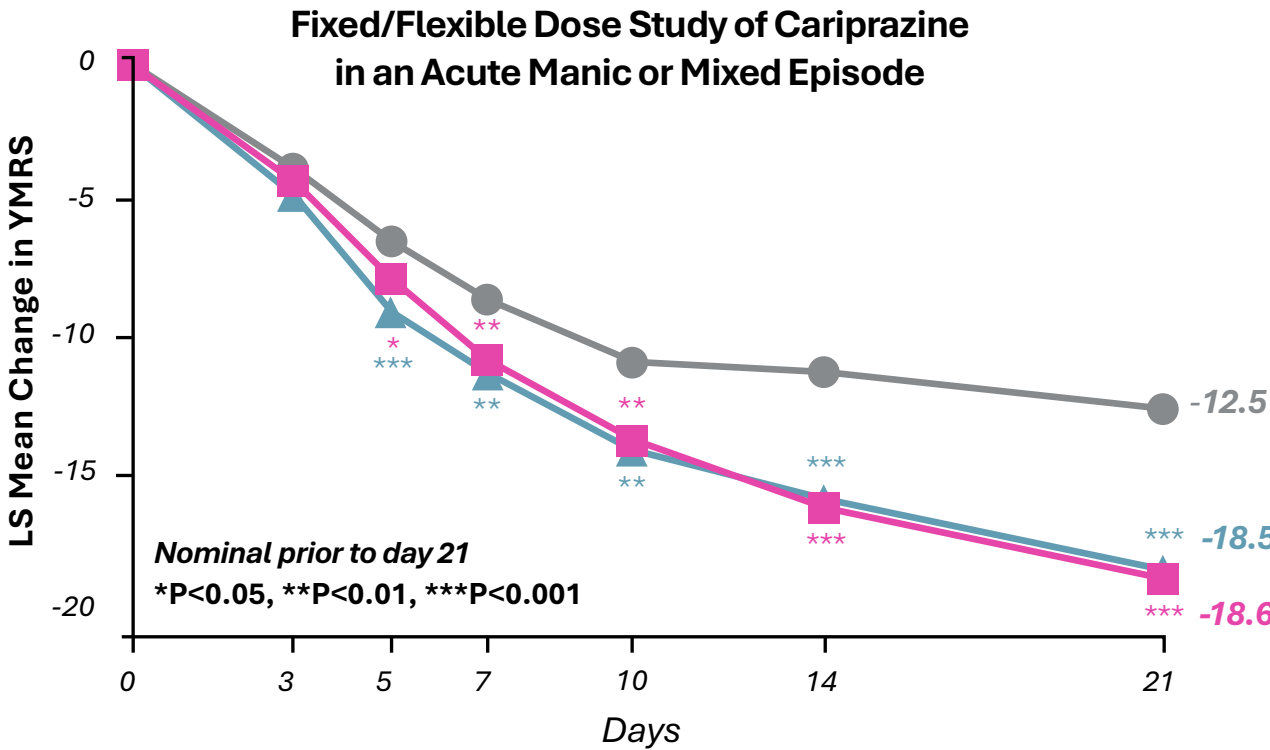
half-life ~1 week for active metabolite; metabolized primarily by 3A4

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%

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

Efficacy of Cariprazine Monotherapy in Acute Manic or Mixed Episodes of Adult Bipolar I Disorder



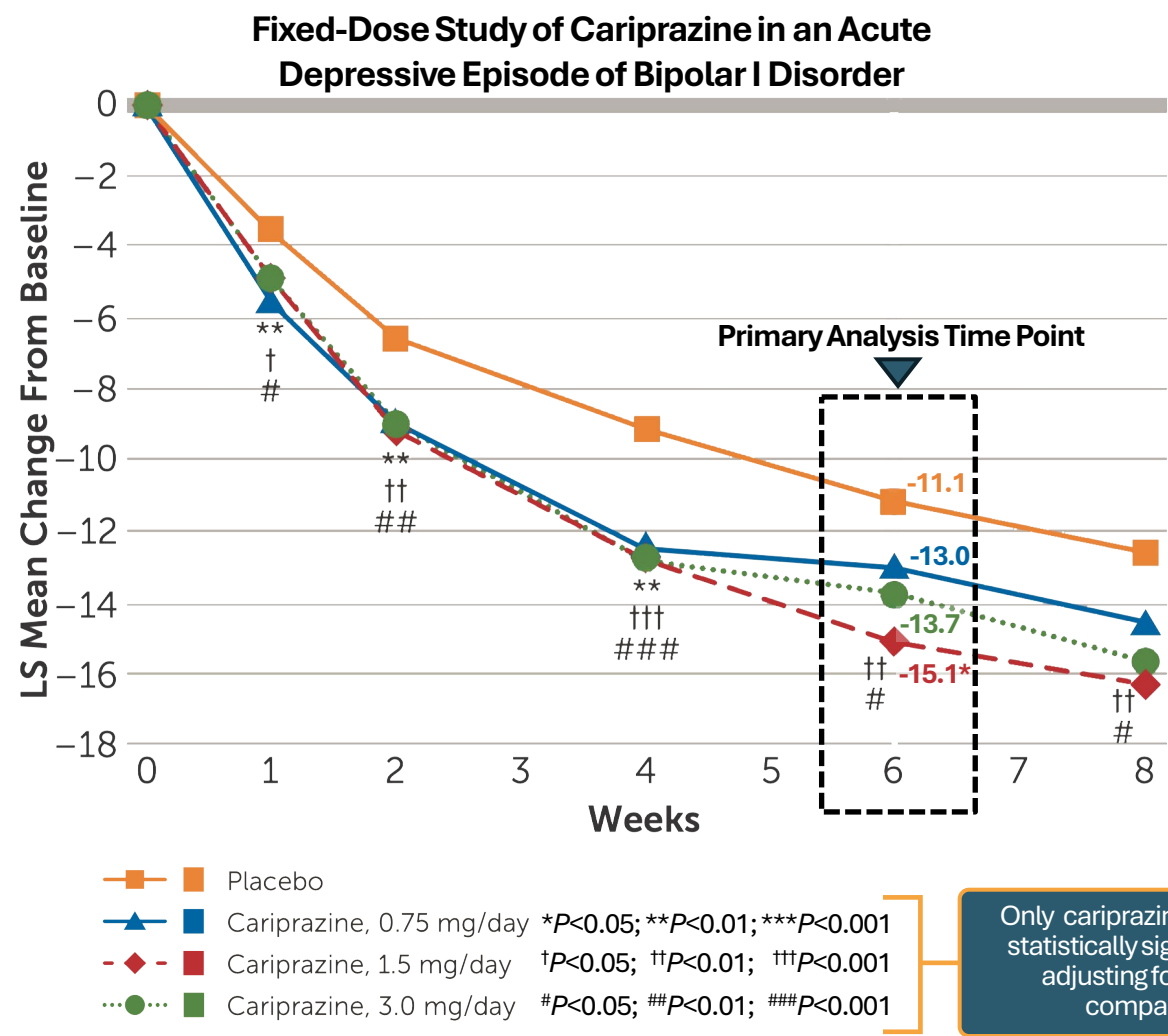
LS Mean Difference in YMRS vs Placebo at Primary Endpoint

	Study 1	Study 2	Study 3
cariprazine 3-12 mg/d	n/a	-6.1***	-4.3***
cariprazine 3-6 mg/d	-6.1***	n/a	n/a
cariprazine 6-9 mg/d	-5.9***	n/a	n/a

Titration varied between trials, but cariprazine was generally increased by 1.5-3 mg increments every 1-2 days, with dosages of 12 mg/d reached as soon as day 5.

Mean daily dose: 9.1 mg
Mean daily dose: 4.8 mg

Phase 3 Studies of Cariprazine in Adult Bipolar I Depression



LS Mean Difference in MADRS vs Placebo at Primary Endpoint

	Study 1	Study 2	Study 3
cariprazine 0.75 mg	-1.9	n/a	n/a
cariprazine 1.5 mg	-4.0*	-2.5*	-2.5*
cariprazine 3 mg	-2.5	-3.0*	-1.8

Titration was slower in the Bipolar I Depression studies:
3 mg arms did not reach that dose until after 2 weeks of treatment.

MADRS = Montgomery-Åsberg Depression Rating Scale.

Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-281. Earley W, et al. *Am J Psychiatry*. 2019;176(6):439-448. Earley WR, et al. *Bipolar Disord*. 2020;22(4):372-384.

Most Common Adverse Events in Cariprazine BP I Trials ≥5% and at Least Twice the Rate of Placebo

Pooled Short-Term Studies in Manic/Mixed Episodes

	Placebo n=442	cariprazine 3-6 mg n=263	cariprazine 9-12 mg n=360
“EPS” (w/o akathisia/restlessness)	12%	26%	29%
Akathisia	5%	20%	21%
Vomiting	4%	10%	8%
Dyspepsia	4%	7%	9%
Somnolence	4%	7%	8%
Restlessness	2%	7%	7%
Mean Weight Change	+0.4 lb	+1.1 lb	+1.3 lb
Weight Gain ≥7%	2%	1%	2%
D/C due to AE	7%	Pooled = 12%	

Pooled Short-Term Studies in Bipolar I Depression

	Placebo n=468	cariprazine 1.5 mg n=470	cariprazine 3 mg n=469
Akathisia	2%	6%	10%
Nausea	3%	7%	7%
Restlessness	3%	2%	7%
“EPS” (w/o akathisia/restlessness)	2%	4%	6%
Mean Weight Change	-0.2 lb	+1.5 lb	+0.9 lb
Weight Gain ≥7%	1%	3%	3%
D/C due to AE	5%	Pooled = 6%	

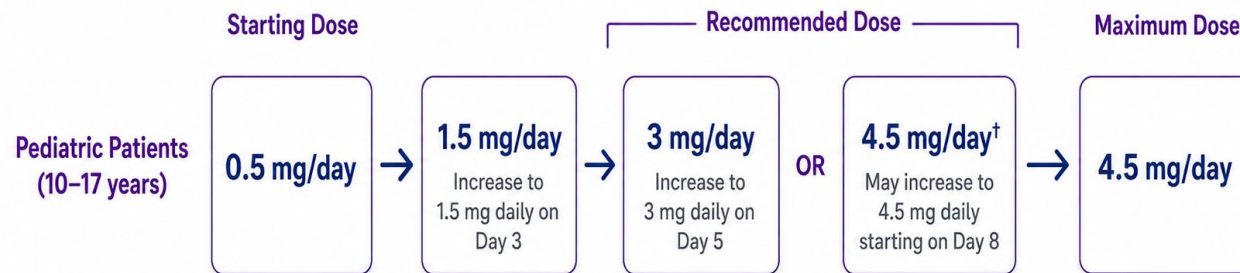


Across All Bipolar I Trials: No meaningful increase in mean prolactin levels;
Proportion of patients with metabolic shifts of fasting glucose, total cholesterol,
or fasting triglycerides for approved dosages was similar to placebo

EPS = extrapyramidal symptoms.
Cariprazine Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2025.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/204370s012lbl.pdf. Calabrese JR, et al. *J Clin Psychiatry*. 2015;76(3):284-92. Durgam S, et al. *Bipolar Disord*. 2015;17(1):63-75. Sachs GS, et al. *J Affect Disord*. 2015;174:296-302. Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-281. Earley W, et al. *Am J Psychiatry*. 2019;176(6):439-448. Earley WR, et al. *Bipolar Disord*. 2020;22(4):372-384.

Cariprazine - Bipolar I Manic/Mixed Episodes in Pediatrics (Ages 10-17)

Pediatric Dosing



Pediatric indication supported by previous adult studies, PK data from adults and pediatrics and long-term open label safety study .

Generally safe, well-tolerated, and safety data was consistent with adult studies.

Mean change in age- and gender-adjusted body weight z-score was < 0.5 for all indications, indicating that on average, clinically significant weight gain was not observed; for individuals experiencing clinically significant weight gain (12.9% of overall population)

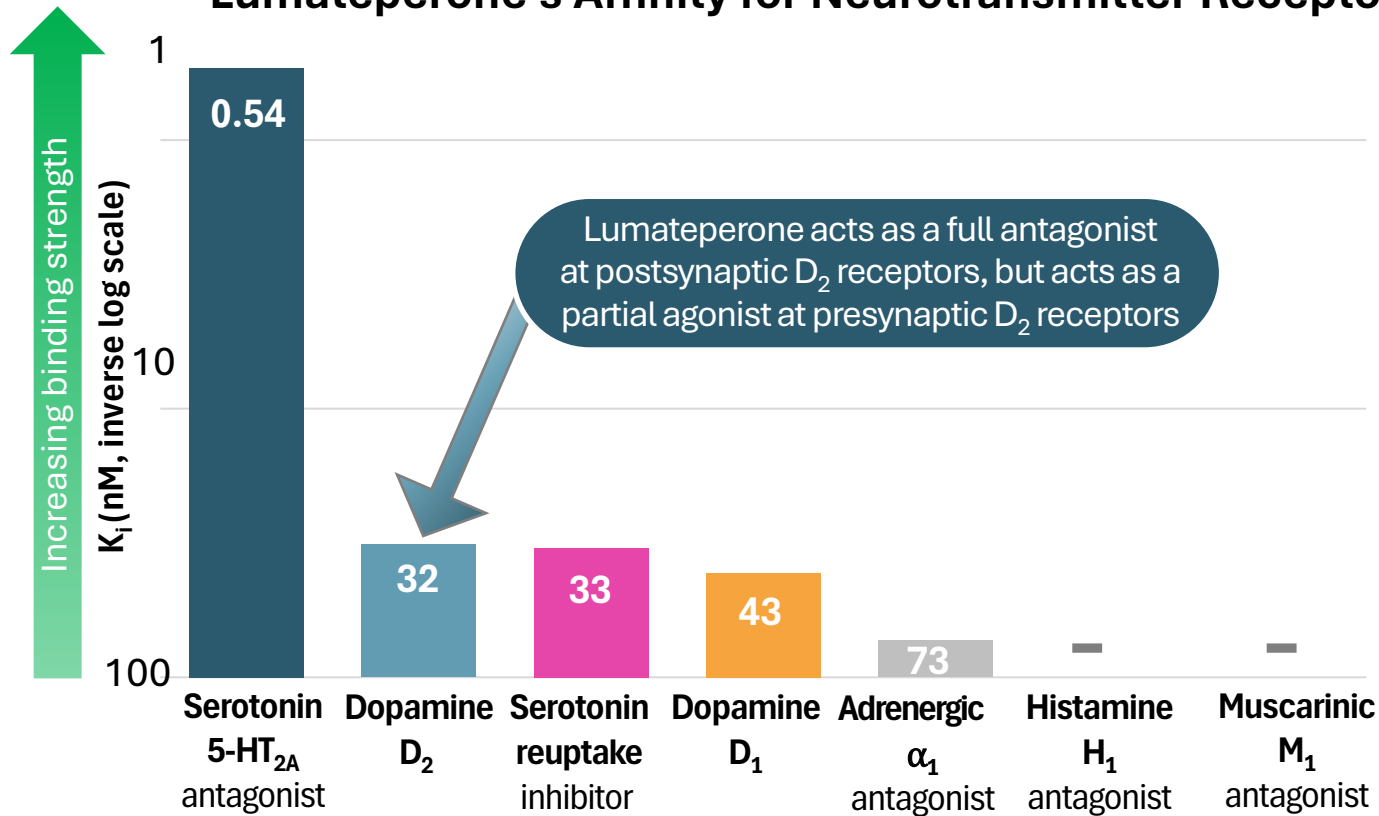
Most common TEAEs during the OLTP (≥5%)	BP-I (N=143)
Weight increased	11.2%
Somnolence	11.2%
Nausea	7.7%
Headache	7.0%
Fatigue	8.4%
Vomiting	4.2%
Agitation	6.3%
Akathisia	7.0%

Lumateperone

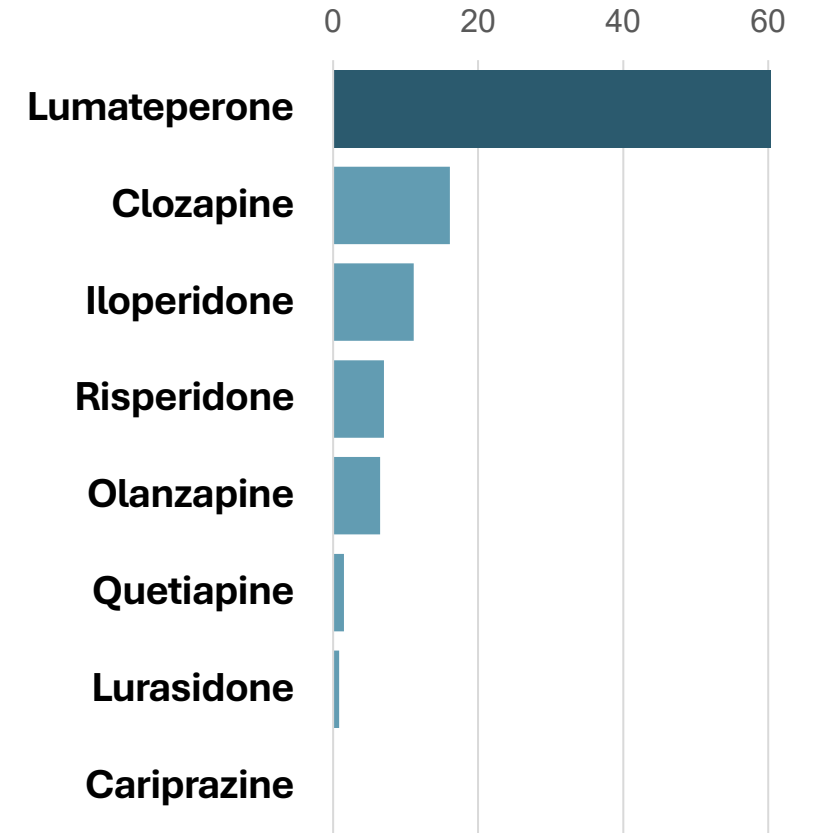
Lumateperone Pharmacology

Lumateperone's 60x greater selectivity for 5-HT_{2A} to D₂ receptor affinity is higher than that of any other antipsychotic

Lumateperone's Affinity for Neurotransmitter Receptors



5-HT_{2A} to D₂ ratios



Lumateperone Prescribing information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2025.

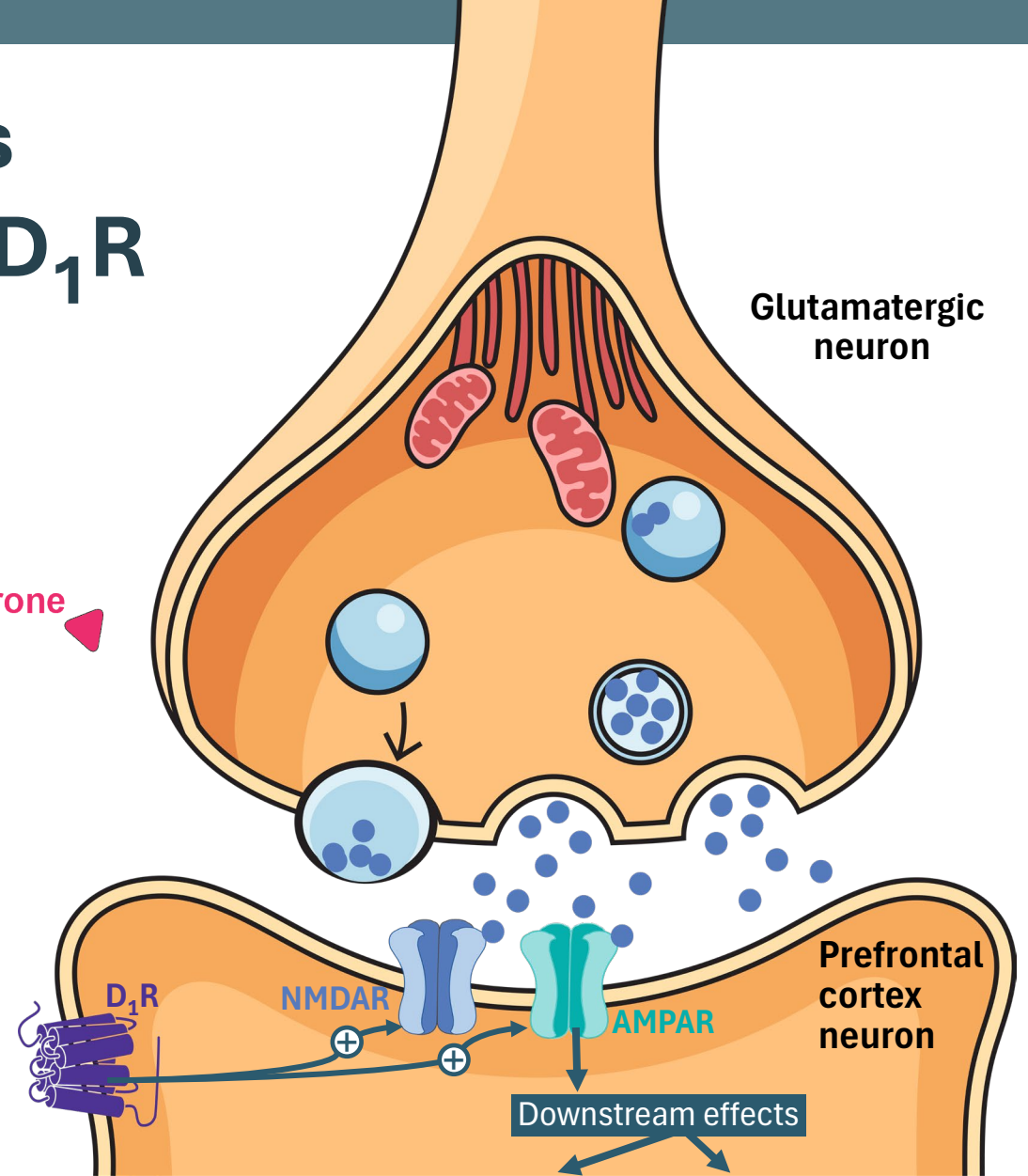
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209500s011lbl.pdf. Li P, et al. *J Med Chem*. 2014;57(6):2670-2682. Kantrowitz JT. *CNS Drugs*. 2020;34(9):947-959.

Lumateperone Modulates Glutamate Indirectly Via the D₁R

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

1. Lumateperone binds the D₁R receptor
2. Activation of the D₁R receptor strengthens AMPA and NMDA glutamate signaling
3. The AMPA receptor activates multiple downstream processes that are important for learning, memory, and mood

Lumateperone



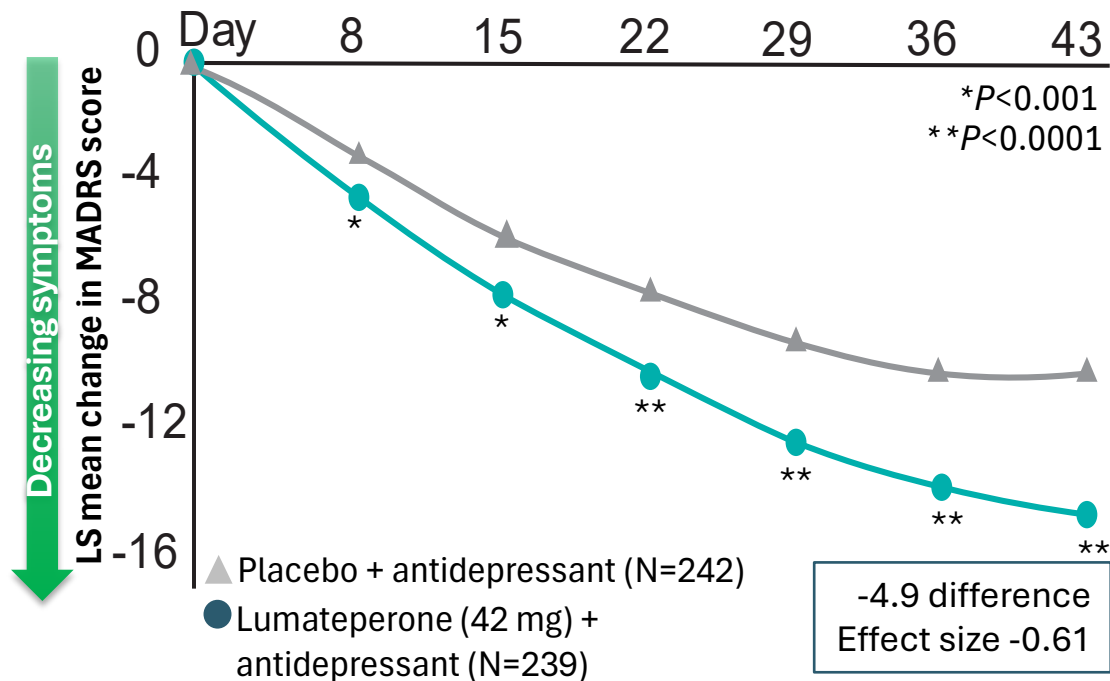
AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor; D1R = D1 dopamine receptor; NMDAR = N-methyl-D-aspartate glutamate receptor.

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

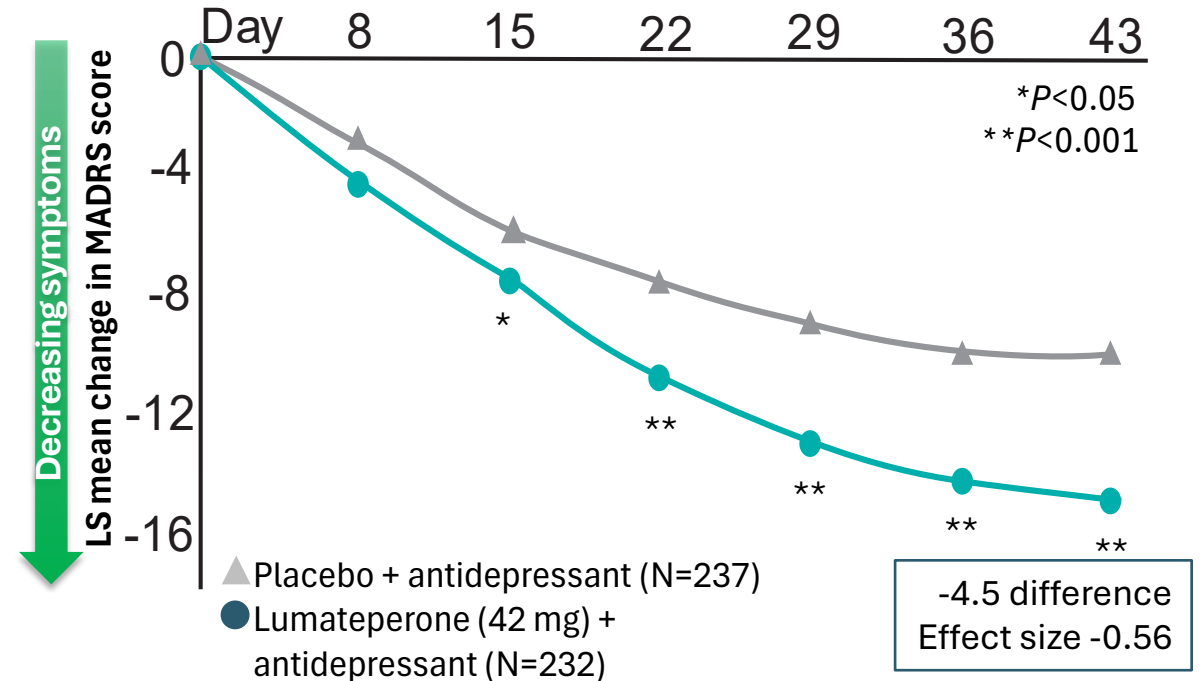
Lumateperone Efficacy for Adult Adjunctive MDD

Treatment in Phase 3 Studies

Study 1 of Lumateperone Plus Antidepressant for MDD



Study 2 of Lumateperone Plus Antidepressant for MDD



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

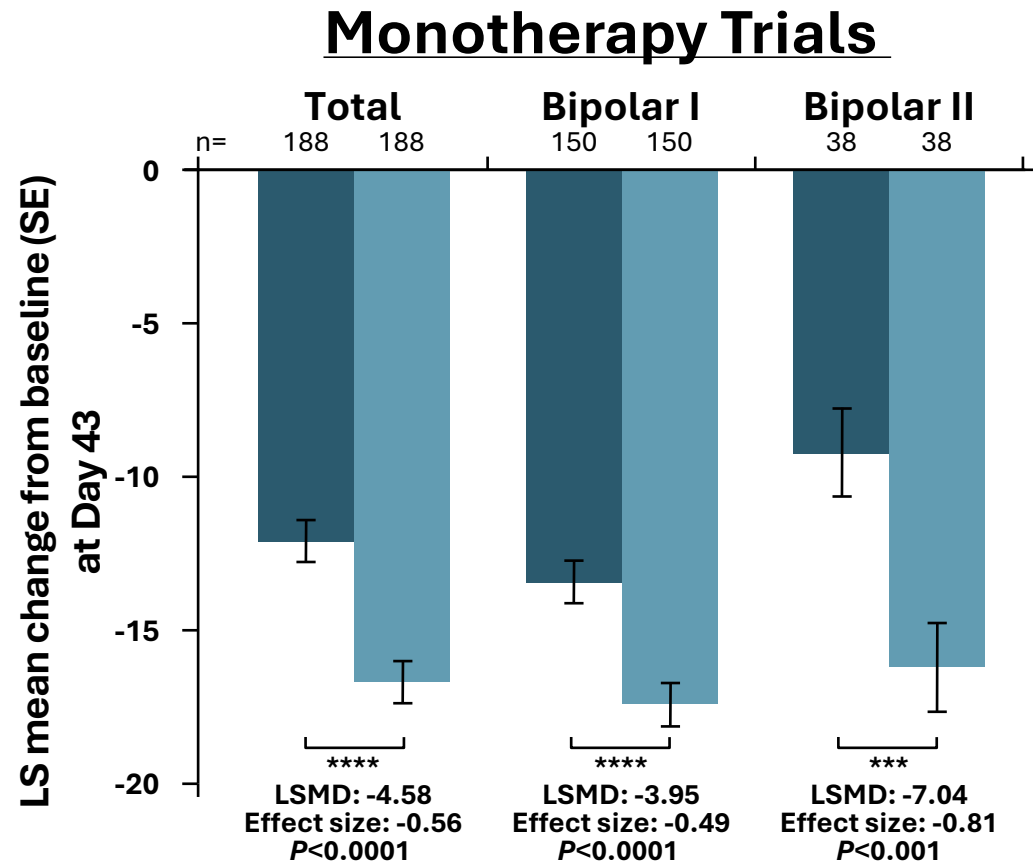
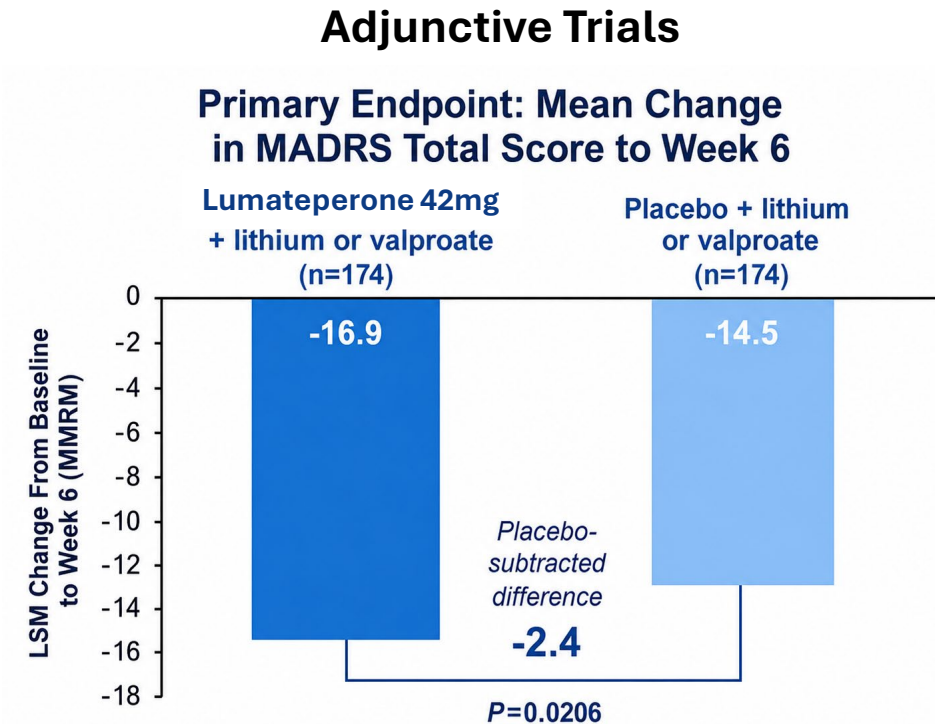
Phase 3 Studies of Lumateperone for Adult Adjunctive MDD Treatment

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

Adverse Events in Study 502		
	Lumateperone 42 mg (N=242)	Placebo (N=243)
All AEs	138 (57%)	54 (23%)
Occurring in >5%		
Dry Mouth	35 (14%)	11 (5%)
Nausea	29 (12%)	9 (4%)
Diarrhea	13 (5%)	2 (0.8%)
Fatigue	12 (5%)	1 (0.4%)
Dizziness	54 (22%)	9 (4%)
Somnolence	39 (16%)	7 (3%)
Headache	49 (20%)	35 (15%)
D/C due to AE	29 (12%)	1 (0.4%)

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

Lumateperone Bipolar I and II Depression in Adults – Monotherapy/Adjunct



Lumateperone Bipolar I and II Depression in Adults – Monotherapy and as adjunct to Li/Val Safety

	Monotherapy		Adjunct	
	Lumateperone (n=372)	PBO (n=374)	Lumateperone (n=177)	PBO (n=175)
Somnolence/sedation	13%	3%	13%	3%
Dizziness	8%	4%	11%	2%
Nausea	8%	3%	9%	4%
Dry mouth	5%	1%	5%	1%
Mean wt change (lb)	0.1	0.4	0.0	0.5
EPS (incl akathisia)	1.3%	1.1%	4.0%	2.3%

Comments:

- No clinically significant changes in glucose or lipid parameters or serum prolactin
- Mean weight gain at 6 months: 0.02 lb

PBO = placebo.

CAPLYTA (lumateperone) [prescribing information]. Bedminster, NJ: Intra-Cellular Therapies, Inc; 2026.

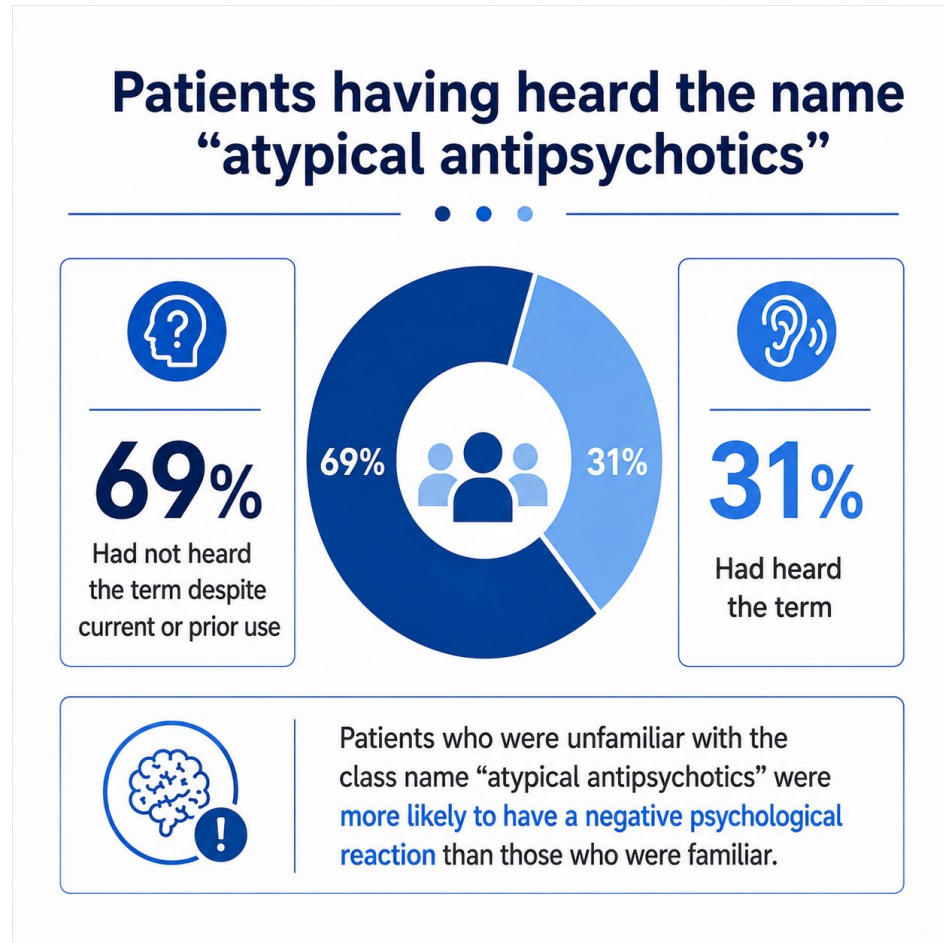
Key Learning Points



- Atypical antipsychotics differ in receptor pharmacology, efficacy, and tolerability, supporting individualized treatment selection across MDD and bipolar disorder
- Aripiprazole, quetiapine, cariprazine, and lumateperone have demonstrated efficacy across specific depressive, manic, and mixed presentations, but their approved indications vary
 - Across clinical studies in bipolar I for cariprazine, there were no clinically meaningful increases in mean prolactin levels compared to placebo

Faculty Discussion: Overcoming Clinical Challenges in Early Clinical Practice

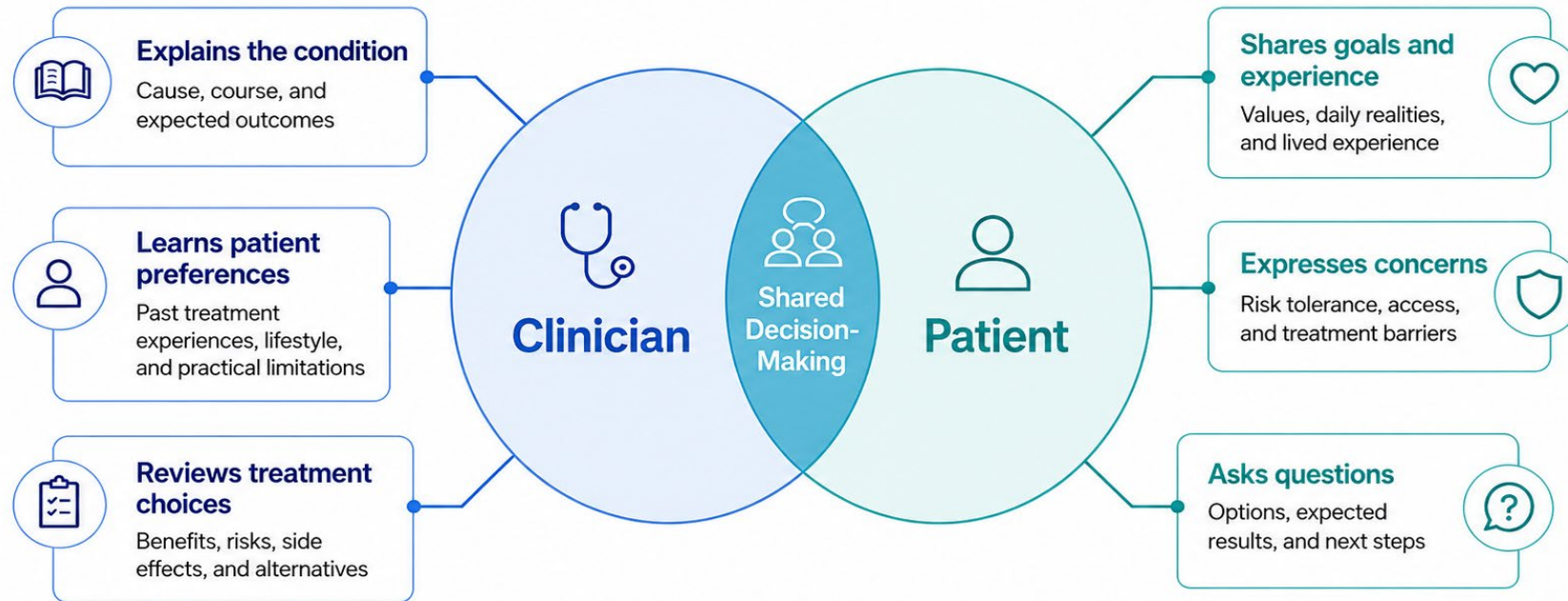
Words Matter When Discussing Care in Context of Treatment



- Patients were **more likely to report concerns with atypical antipsychotics** compared with mood stabilizer including:
 - More likely to associate medication with **negative feelings**, such as “feeling crazy” , fear and confusion.
 - **Lower medication adherence**
 - More likely to **research the medication before filling the prescription**

Importance of Appropriate Expectations, Dosing Strategies, and Patient Selection

Shared Decision-Making



Drivers of Nonadherence in Mood Disorder Populations and Strategies to Enhance Persistence

Education, Follow-up, and Drug Selection

- Identify the specific driver of nonadherence rather than assuming lack of motivation.
 - Ask about AEs, efficacy, cost, forgetfulness etc.
- Use education and early follow-up to address concerns before treatment is discontinued.
 - Set expectations at onset, plan of what to do if problem occurs and when to reach out.
- Select treatments with efficacy, tolerability, convenience, and patient priorities in mind.

Age-Related Challenges in Treatment of Bipolar I Disorder

Medication choice should reflect life stage, reproductive risk, FDA-labeled options, comorbidities, and dosing/monitoring needs.

Clinical framing question: Is this treatment effective, safe, covered, and practical for this patient at this age?

Children & adolescents

- Fewer FDA-labeled options
- Off-label use may create prior authorization / reimbursement barriers
- Monitor growth, weight/metabolic risk, EPS, prolactin, and family adherence burden

Women of childbearing potential

- Avoid/limit valproate unless no acceptable alternative
- Discuss contraception, folate, pregnancy planning, and lactation
- Consider level changes with pregnancy or estrogen-containing contraceptives

End of reproductive potential

- Valproate is no longer a “no counseling needed” option
- Discuss emerging paternal exposure signal and uncertainty
- EU/UK guidance: contraception and no sperm donation during treatment and 3 months after stopping

Comorbidity & later-life dosing

- Renal/thyroid disease, hepatic disease, obesity/diabetes, CVD, TD/EPS risk, and substance use can drive selection
- Start lower and titrate slower when frailty, polypharmacy, or renal/hepatic vulnerability is present

Age changes risk, access, and dosing. Document the rationale when using off-label treatment or when valproate is considered in reproductive-age patients.

DailyMed/FDA labels (lithium, lurasidone, cariprazine, olanzapine/fluoxetine); FDA valproate labeling; WHO valproate statement; EMA/MHRA valproate safety communications.

Akathisia:

Early Recognition, Prevention, and Management

Subjective feeling of inner restlessness accompanied by mental distress and inability to be still.

1

Why It Matters

- Distress associated with akathisia can reduce treatment adherence
- May increase risk of agitation, aggression, and suicide

2

Assessment

- Use the Barnes Akathisia Rating Scale to assess and monitor symptoms

3

Management

- Reduce the antipsychotic dose when clinically appropriate
- Switch to an antipsychotic with lower risk of akathisia
- Initiate adjunctive medication when needed:
 - Beta-blocker: propranolol
 - Benzodiazepine: clonazepam
 - 5-HT_{2A} antagonist: mirtazapine

Barnes TR: A Rating Scale for Drug-Induced Akathisia. *British Journal of Psychiatry* 154:672-676,1989. LohrJB et al. *CNS Spectr* 2015;20(Suppl 1):1-16; Pringsheim T et al. *Can J Psychiatry* 2018;63(11):719-29; Salem et al. 2017. Revisiting Antipsychotic-induced Akathisia: Current Issues and Prospective Challenges. *Current neuropharmacology*, 15(5), 789–798.

Somnolence/Sedation: Dose Timing, Mitigation Strategies, and Functional Assessment



- Sedation can be common in early/initial phases of treatment. Tolerance to sedation can occur over time.
- ***If patients voice “wanting to do things” but feels too tired, this is likely sedation side effect.*** Must be careful to distinguish from negative symptoms or depression.
- Target/off target drug receptor binding responsible for sedation- Antagonism at serotonergic, adrenergic, muscarinic, dopaminergic and histaminergic receptor activity. Persistent day time drowsiness can lead to adverse effects on the patient's:
 - Cognition
 - Social/recreational activities
 - Vocational function

Case Discussion

Maria

- 28 yo mother of two
- History of ADHD and depression

Maria

- 28 yo mother of two
- History of ADHD and depression

What do you do next?

Maria

- 28 yo mother of two
- History of ADHD and depression
- First episode of depression when 15
- PHQ9 = 22
- ADHD meds help some but “antidepressants don’t do much”

What do you want to know?

Maria

- 28 yo mother of two
- History of ADHD and depression
- First episode of depression when 15
- PHQ9 = 22
- ADHD meds help some but “antidepressants don’t do much”
- MDQ = 9
- Further questioning reveals several episodes of mania in the spring and multiple episodes of depression in the fall and winter

Is there a medicine that could treat both?



Q&A