



Stepping Out of Mania's Shadow: Understanding the Nuances of ***Recognizing and Treating Bipolar I and II Disorder***

MasterClass

Faculty

Craig Chepke, MD, DFAPA

Chief Medical Officer, Psych Congress

*Adjunct Associate Professor of
Psychiatry,*

Sandra & Leon Levine Psychiatry

Residency Program at Atrium Health

Charlotte, NC

*Medical Director, Excel Psychiatric
Associates*

Huntersville, NC

Kristian Dambrino, DNP, APRN, PMHNP-BC

Founder & Psychiatric Nurse

Practitioner, Dambrino Wellness

Adjunct Professor, Belmont University

College of Nursing

Nashville, Tennessee

Faculty Disclosures

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Learning Objectives

01

Recognize and differentiate BD2 from MDD and BD1

02

Evaluate the clinical implications of specifiers like anhedonia, anxious distress, and mixed features

03

Assess the limitations of traditional treatments and the evolving clinical paradigm in BD2

04

Apply shared decision-making and other patient-centered strategies for optimal tailored treatment selection

BD1 = bipolar I disorder; BD2 = bipolar II disorder; MDD = major depressive disorder.

Bipolar Disorder Overview

Evolution of Bipolar Disorder in DSM

(DSM-I to DSM-5)

Edition	Year	Terminology Used	Key Features & Specifiers
DSM-I	1952	Manic Depressive Reaction	“Affective Disorders” – Two forms: manic and depressed phases – Psychotic and non-psychotic subtypes
DSM-II	1968	Manic Depressive Illness	“Affective Disorders” No major changes, continued focus on manic and depressive episodes
DSM-III	1980	Bipolar Disorder	Differentiated Bipolar I and Bipolar II – Recognized Cyclothymic Disorder – Introduced “Mixed Episode”
DSM-III-R	1987	Bipolar Subtypes Defined	Further clarification of Bipolar I, II, and Cyclothymia – Added specifiers for severity (mild, moderate, severe)
DSM-IV	1994	Refinement of Specifiers	Introduced Rapid Cycling (4+ episodes/year) – Distinguished Bipolar I, Bipolar II, and NOS (Not Otherwise Specified)
DSM-IV-TR	2000	Updated Criteria	Further refined mixed states – Minor updates on mood episode descriptions
DSM-5	2013	Extended Specifiers 	Eliminated “Mixed Episode” → replaced with “With Mixed Features” – Added specifiers: Anxious Distress, Mood-Congruent/Incongruent Psychotic Features, Catatonia, Peripartum Onset, and Seasonal Pattern

NOS = not otherwise specified.

American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. APA Publishing; 1952, 1968, 1980, 1987, 1994, 2000, 2013.

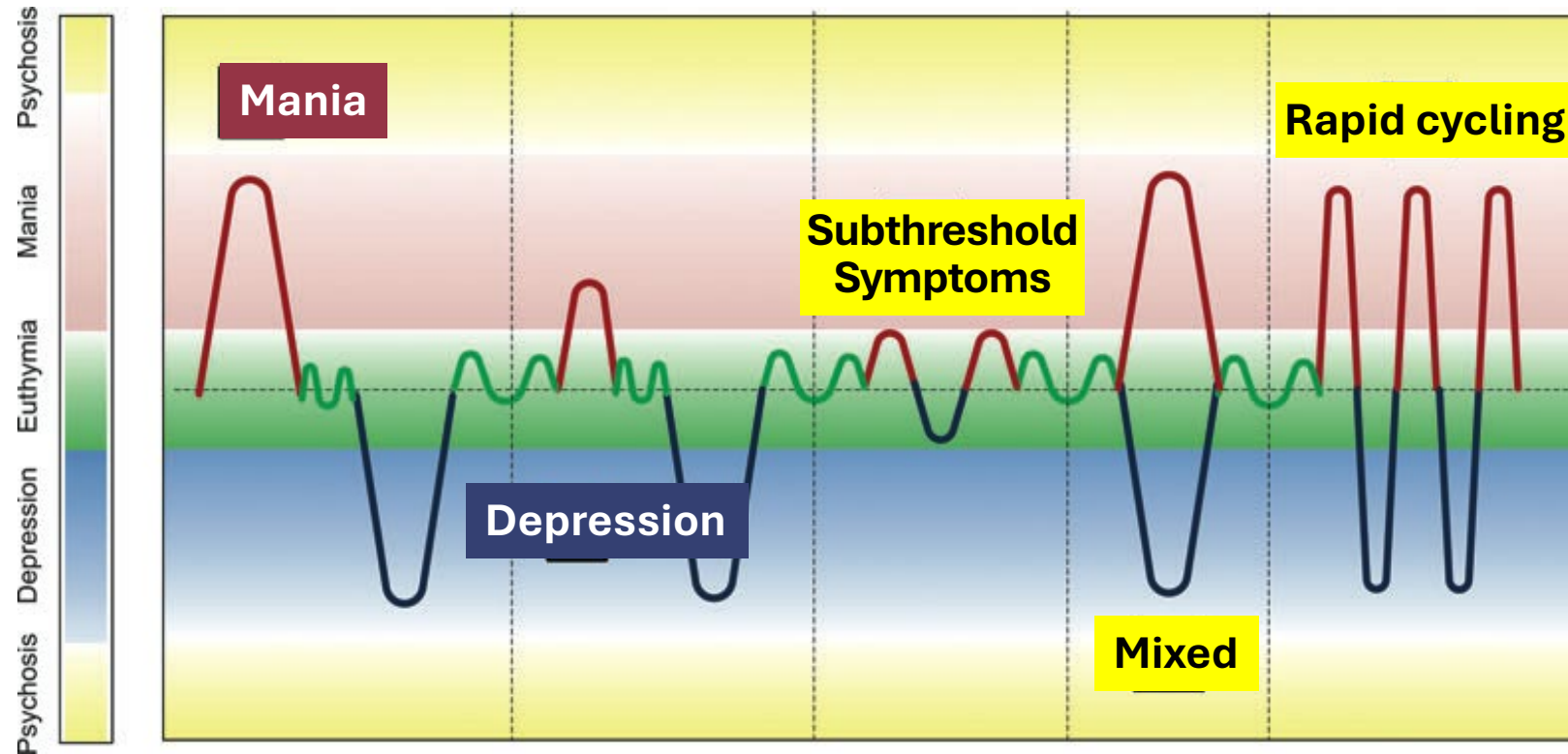
Diagnostic Clues or Bipolar Disorder

Dimension	Observations
Age at onset	20%-30% of adolescent major depression patients eventually manifest a manic or hypomanic episode
Family history	DZ twins: ~43% concordance 1st degree relative(s): 7%-20% 2 nd or 3 rd degree relatives: more ambiguous contribution Consider endophenotypes: creativity, high IQ, high associative fluency
Episode durations (brevity/high recurrence)	Sustained chronicity rare; mean episode duration 13 weeks
Core symptoms	Hypersomnia, hyperphagia, anergia; mixed features; psychosis
Common comorbidities	Anxiety, substance use disorders, attention deficit disorder
Response to treatment	Antidepressants tend not to be helpful, may destabilize mood in some patients

DZ = dizygotic.

Kovacs M. *J Am Acad Child Adolesc Psychiatry*. 1996;35(6):705-715. Kieseppä T, et al. *Am J Psychiatry*. 2004;161(10):1814-1821. Joyce PR, et al. *Compr Psychiatry*. 2004;45(3):168-174. Solomon DA, et al. *Arch Gen Psychiatry*. 2010;67(4):339-347. Mitchell PB, et al. *J Clin Psychiatry*. 2001;62(3):212-216.

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.

Bipolar I and II:

Examining the Differences between Manic and Hypomanic Episodes

Bipolar I

- Abnormally & persistently elevated, expansive, or irritable mood & abnormally or persistently increased goal-directed activity
 - **Lasting at least 7 days**, most of the day, nearly every day (unless hospitalized)



Bipolar II

- Abnormally & persistently elevated, expansive, or irritable mood & abnormally or persistently increased goal-directed activity
 - **At least 4 days**, most of the day, nearly every day

DSM-5-TR, the symptom **criteria for a major depressive episode (MDE)** are the same whether the episode occurs in **Major Depressive Disorder (MDD)** or in **Bipolar I or II Disorder (bipolar depression)**.

MDE = major depressive episode.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. APA Publishing; 2013.

Depressive Episodes in Bipolar Disorder

Depressive episodes are:

- ❖ often the **first presentation** of BD
- ❖ **the most common reason** why patients visit an HCP

*A 2015 study reported the prevalence of mood types among bipolar I patients experiencing a current mood episode (N=225), **a majority of patients experienced depressive episodes**, with or without concurrent mania*

75%

were experiencing a **bipolar I depressive episode** with or without concurrent manic symptoms

25%

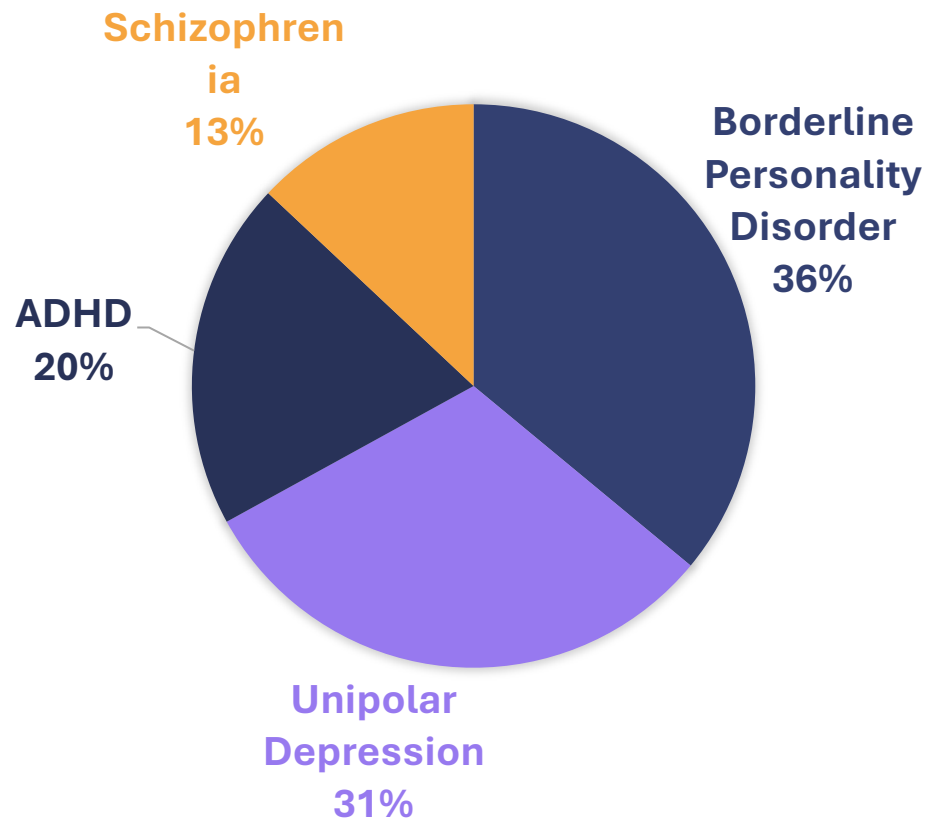
were experiencing a **bipolar I manic/hypomanic episode** with or without concurrent depressive symptoms

HCP = healthcare professional.

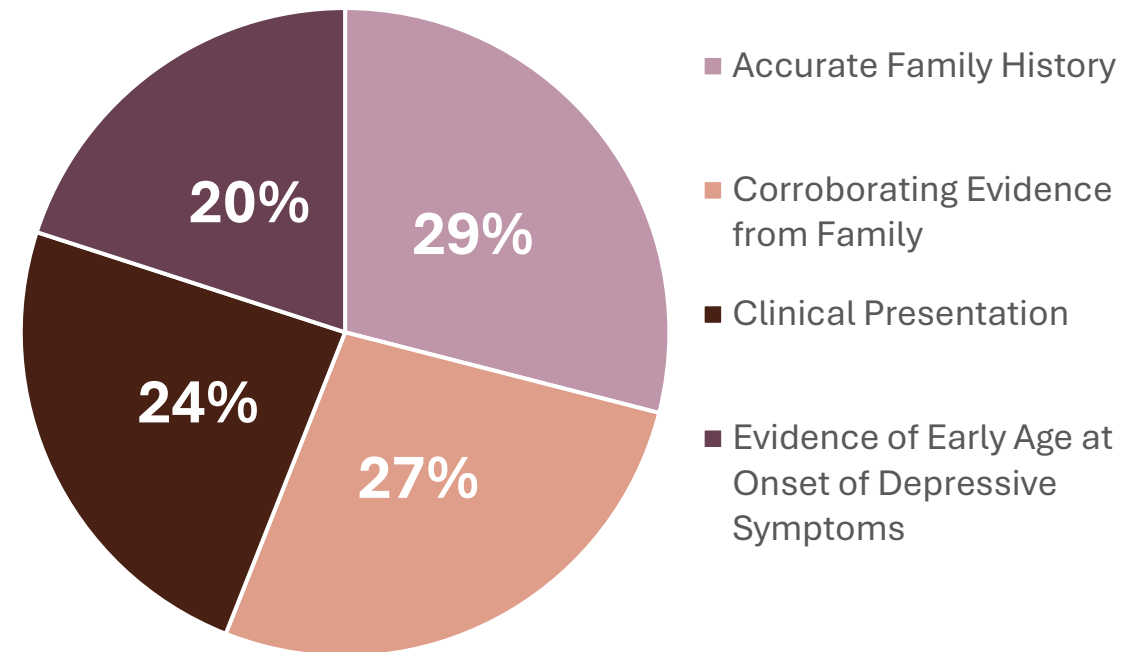
McIntyre RS, et al. *J Affect Disord*. 2015;172:259-264. Culpepper L. *Prim Care Companion CNS Disord*. 2014;16(3):PCC.13r01609. Chengappa KNR, et al. *Am J Psychiatry*. 2003;160(9):1636-1642.

Differentiating Bipolar Disorder from MDD

Disorders Most Difficult to Differentiate from Bipolar Disorder (N=154)

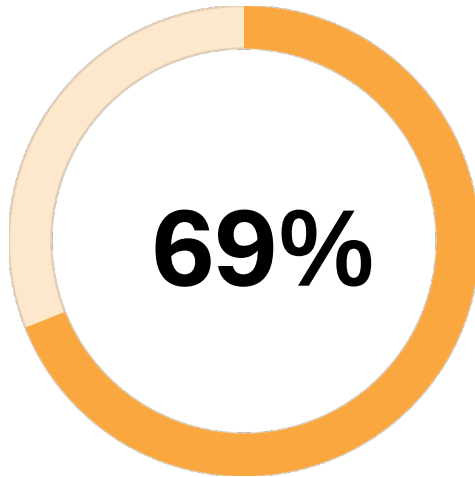


Best Predictors for Achieving Differential Diagnosis between MDD vs BD (N=168)

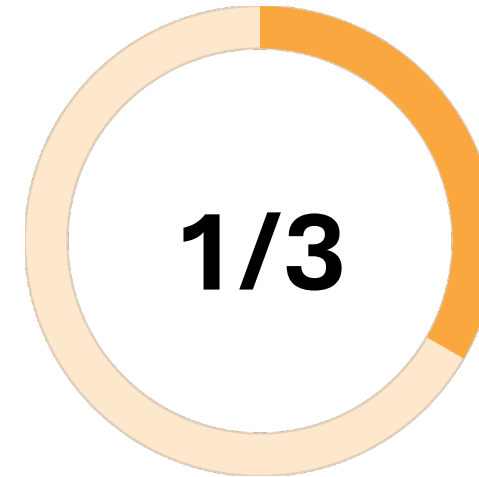


Missed or Misdiagnosis Is Common in Bipolar Disorder

600 surveys were analyzed of patients living with Bipolar Disorder



reported they were misdiagnosed



waited 10+ years before an accurate diagnosis was made

Most frequent misdiagnosis: **MDD**

Other common misdiagnoses included:
schizophrenia, anxiety disorder, personality disorder,
and substance use disorder

Consequences of Missed or Delayed Diagnosis

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, and more hospitalizations

Use of traditional antidepressants may be less effective in improving outcomes than mood stabilizers and atypical antipsychotics

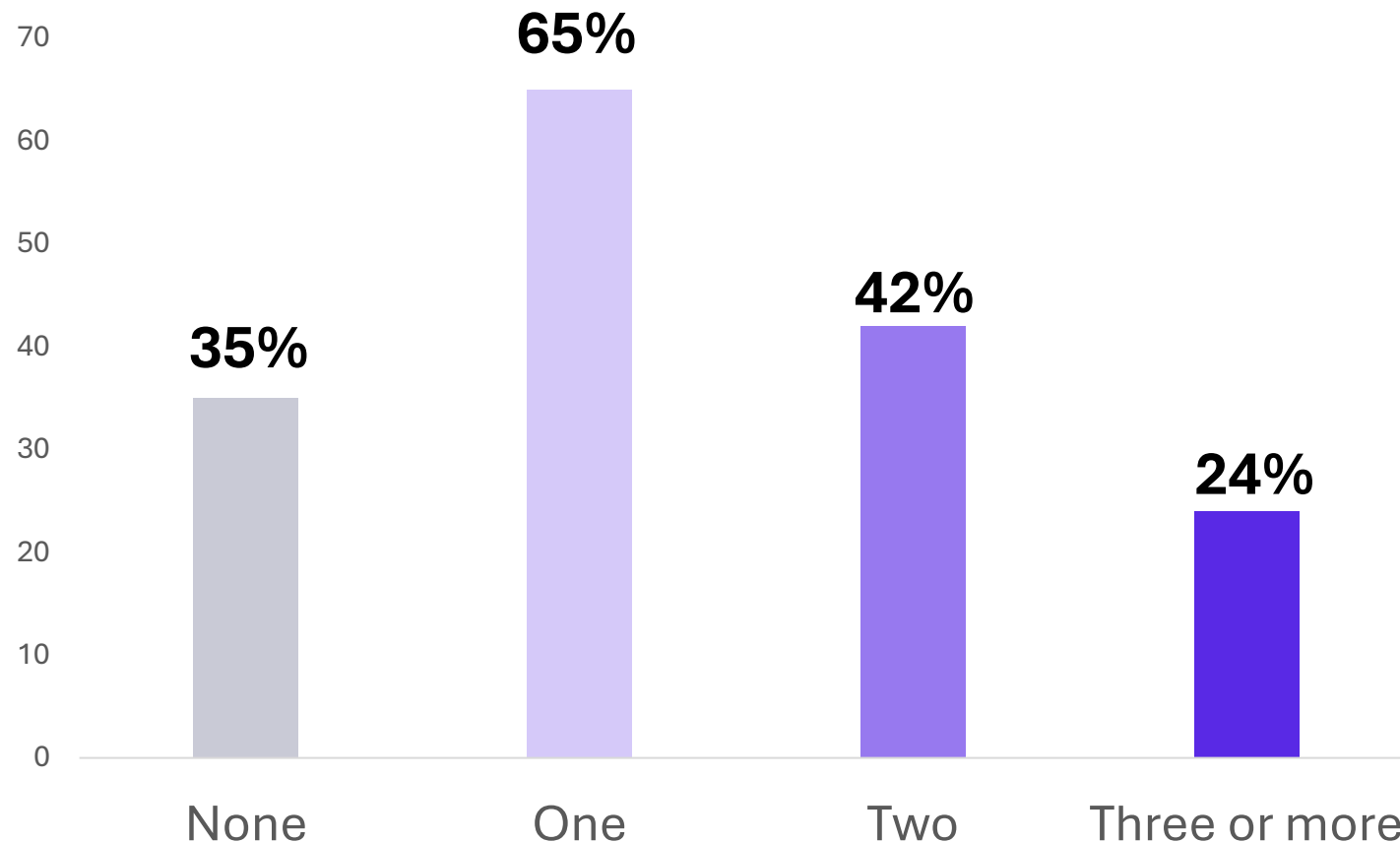
Some medications (eg, lithium) may be less effective if begun after the passage of multiple episodes

Goldberg JF, Ernst CL. J Clin Psychiatry. 2002;63:985-991. Gitlin MJ. Int J Bipolar Disord. 2018;6(1):25. Kessing LV, et al. Br J Psychiatry. 2014;205(3):214-220.



Most People with Bipolar Disorder Have Multiple Psychiatric Comorbidities

288 patients from the Stanley Foundation Bipolar Treatment Outcome Network



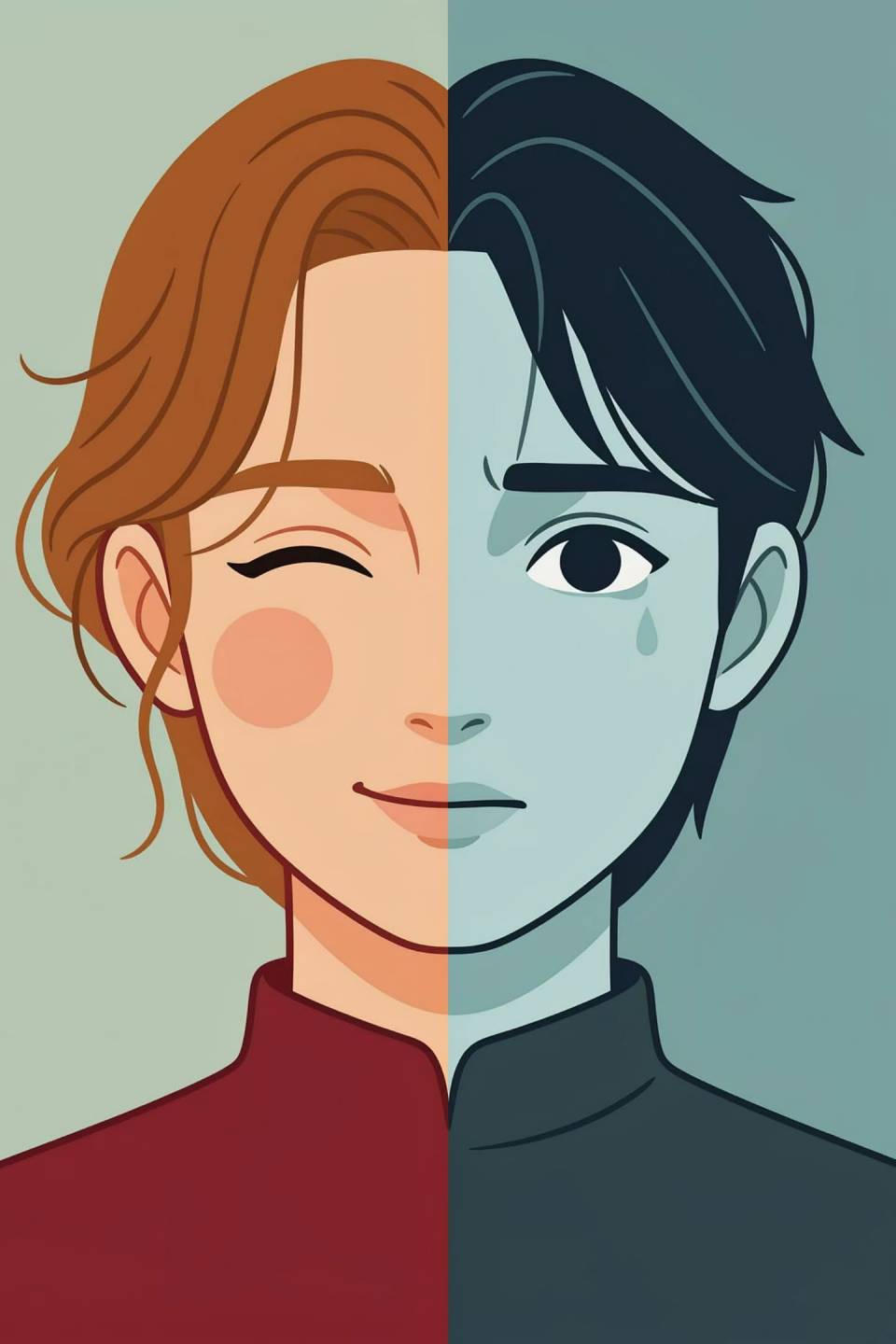
Anxiety (42%) and substance use disorders (42%) were the most common psychiatric comorbidities

Mood Disorder Spectrum



*Categorical classifications may be helpful in clinical practice, but evidence points to a **dimensional** or “**spectrum**” view of mood disorder, considering other factors, e.g., treatment response and family history of bipolar disorder*

MDD with mixed features or subsyndromal manic symptoms carries a 3- to 8-fold higher risk of conversion to bipolar disorder (20%–48% vs ~6%–9% in unselected MDD)

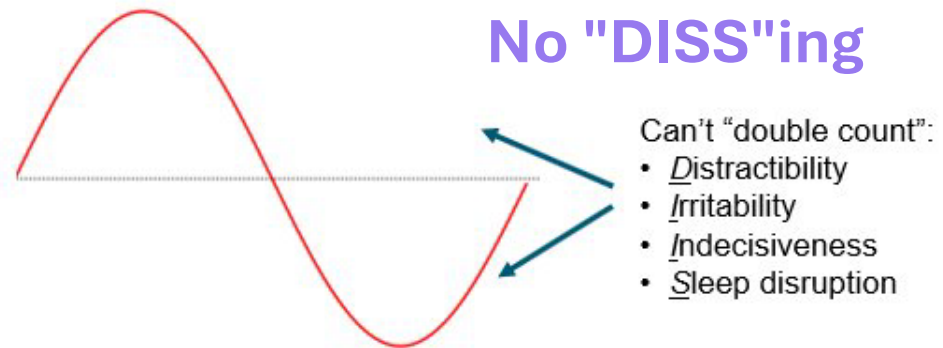


Bipolar Episodes with Mixed Features

>3 symptoms of (hypo)mania or depression during a full syndrome of the opposite polarity

Can occur in unipolar or bipolar I or II disorder

Don't confuse with rapid cycling or affective lability



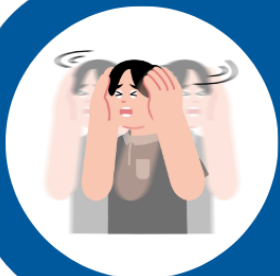
The “Four As” Increase Suspicion of Mixed Features



ANXIETY



ANGER /
IRRITABILITY



AGITATION

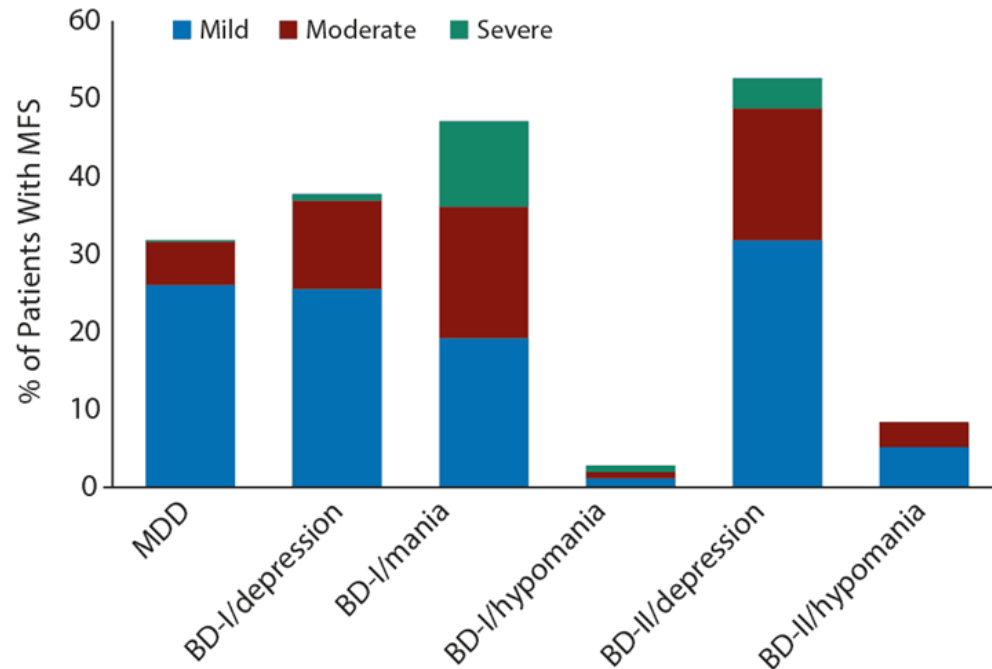


ATENTIONAL
DISTURBANCE-
DISTRACTIBILITY

These symptoms are highly suggestive of mixed features in individuals with mood disorders.

Mixed Features Across Bipolar Disorder

Prevalence of DSM-5 Mixed Features Specifier in Adults with Major Depressive Disorder of Bipolar Disorder



- 25%-45% of patients with BPD I, II, and MDD have mixed features
- Those with mixed features also have higher rates of SUDs and comorbid cardiovascular disease
- *First do no harm*
- Unmet need for treatment for mixed features

BPD = bipolar disorder; SUD = substance use disorder; MFS = mixed features specifier.

McIntyre RS, et al. *J Clin Psychiatry*. 2023;84(3):22m14739. McIntyre RS, et al. *J Affect Disord*. 2015;172:259-264. Jain R, et al. *J Clin Psychiatry*. 2017;78(8):1091-1102.

Anxious Distress in Bipolar Depression: The Hidden Driver

48%–78%

of bipolar depressive episodes meet criteria for the anxious distress specifier

DSM-5-TR Criteria (≥2 of 5)

1. Feeling keyed up or tense
2. Feeling unusually restless
3. Difficulty concentrating because of worry
4. Fear that something awful may happen
5. Feeling of losing control of oneself

Severity: Mild (2) → Moderate (3) → Moderate-Severe (4-5)
→ Severe (4-5 + motor agitation)

Why It Matters Clinically

- Increased suicide risk
- Longer illness duration
- Greater likelihood of treatment nonresponse
- More frequent adverse events with antidepressants
- Shorter time to relapse, shorter euthymic periods

⚠️ Treatment Gap: 12 years after DSM-5 introduced this specifier, **no FDA-approved treatment exists specifically for BD with anxious distress**, and **current anxiolytic options may be contraindicated in BD**

Anhedonia in Bipolar Disorder: More Than Sadness

~91%

of BD patients experience threshold anhedonia during their most severe depressive episode¹

Two Types of Anhedonia

- **Anticipatory:** Inability to look forward to pleasurable activities ("nothing to look forward to")
- **Consummatory:** Inability to enjoy activities in the moment ("it just doesn't feel good anymore")

Both types impair motivation, social engagement, and functional recovery

Why is BD Anhedonia Unique?

- Persists even during euthymia; may be a trait feature, not just a state symptom
- ~20% of euthymic BD patients show clinically significant anhedonia (vs. 7.5% healthy controls)
- Correlated with cognitive impairment independent of depression severity

Neurobiology

- **MDD:** reward system hypofunction (blunted ventral striatum)
- **BD:** reward system dysregulation, not simply blunted, but oscillating
- Suggests potentially divergent pathophysiology → may need different treatment approaches



Clinical Pearl: Anhedonia is often undertreated because standard depression scales may improve while pleasure and motivation remain impaired. Consider using the SHAPS (Snaith-Hamilton Pleasure Scale) or TEPS (Temporal Experience of Pleasure Scale) to specifically track anhedonia as a treatment target.

Conversion from MDD to BD: What the Evidence Shows

Baseline risk

Annual conversion rate from MDD to BD ≈ **1.25%/year**, with cumulative rates of ~6%–9% over 13–20 years in large registry studies

12%

of individuals initially diagnosed with MDD will eventually be reclassified as BD2 when a hypomanic episode is recognized (DSM-5-TR)

One longitudinal study found **48% of children with transient manic symptoms** converted to BD within 18 months

19.6%

of individuals with subthreshold manic symptoms converted to BD (cumulative probability ~**25%** on survival analysis)

Screening Tool: Mood Disorder Questionnaire

5 Psych Clinics (N=198)

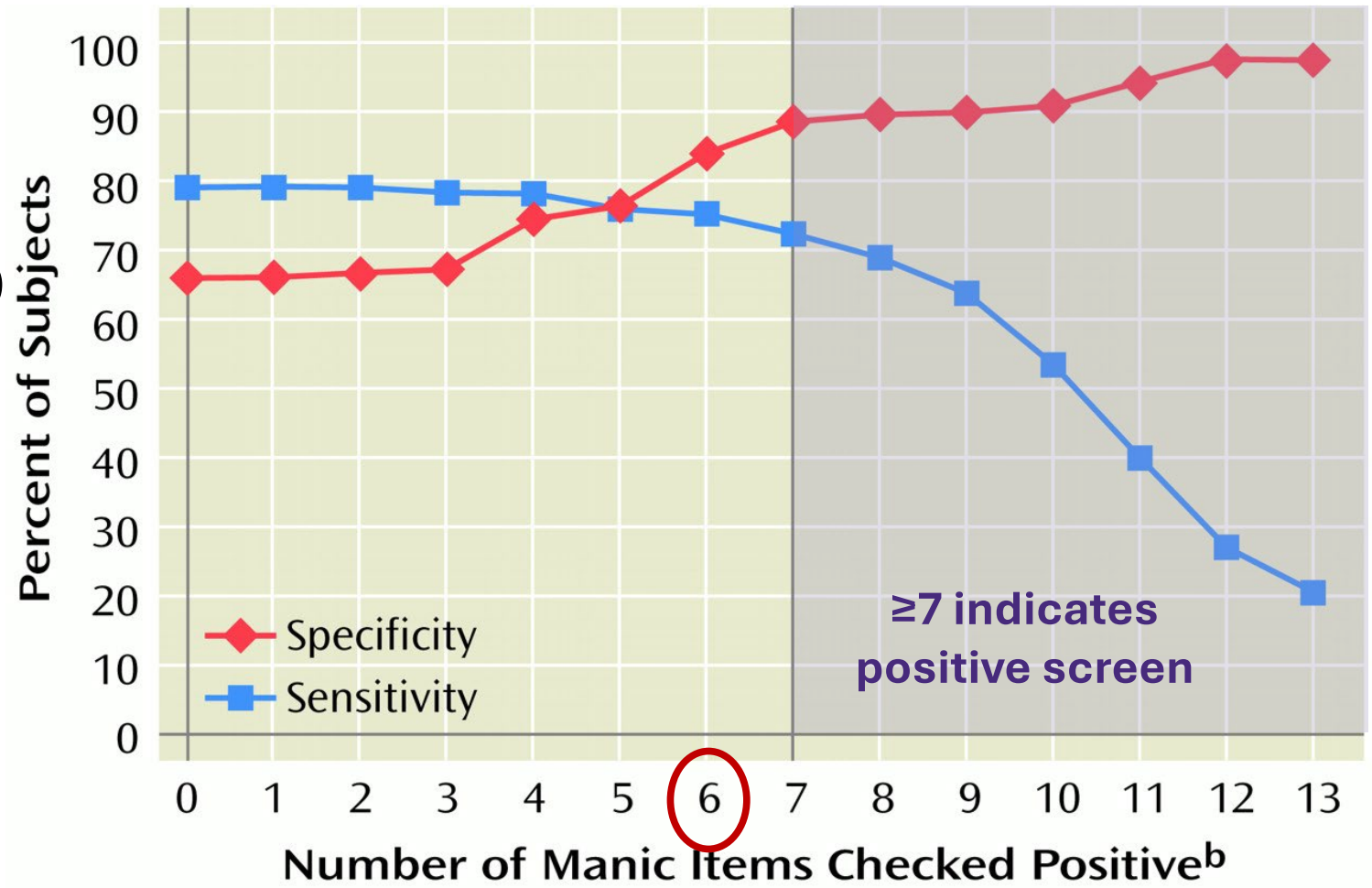
- 73% Sensitivity
- 90% Specificity

UT Family Med (N=649 on MDD tx)

- 21.3% were MDQ+
- 58% Sensitivity
- 93% Specificity



More recent meta-analytic data suggests screening performance may vary by population, setting, and bipolar subtype



UT = University of Tennessee; tx = treatment; MDQ+ = Mood Disorders Questionnaire–positive.

Hirschfeld RM, et al. *Am J Psychiatry*. 2000;157(11):1873-1875; Wang YY et al. *Psychiatry Res*. 2019;273:461-466; Carvalho AF et al. *J Affect Disord*. 2015;172:337-346.

The Rapid Mood Screener for Bipolar I Disorder

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

The RMS has not been validated as a screen for BP II disorder.
As a screening tool, it has also not been studied for its ability to discriminate bipolar disorder from other conditions

Symptom-Based Subgroups in Bipolar Depression

Anxious Distress

↑ Suicide risk & illness severity

Greater functional impairment

Higher psychiatric comorbidity

Mixed Features

Depressive + hypomanic symptoms

Risk of mood destabilization

Prominent Anhedonia

Reward circuitry dysfunction

Reduced motivation & functioning

May reflect distinct neurobiology

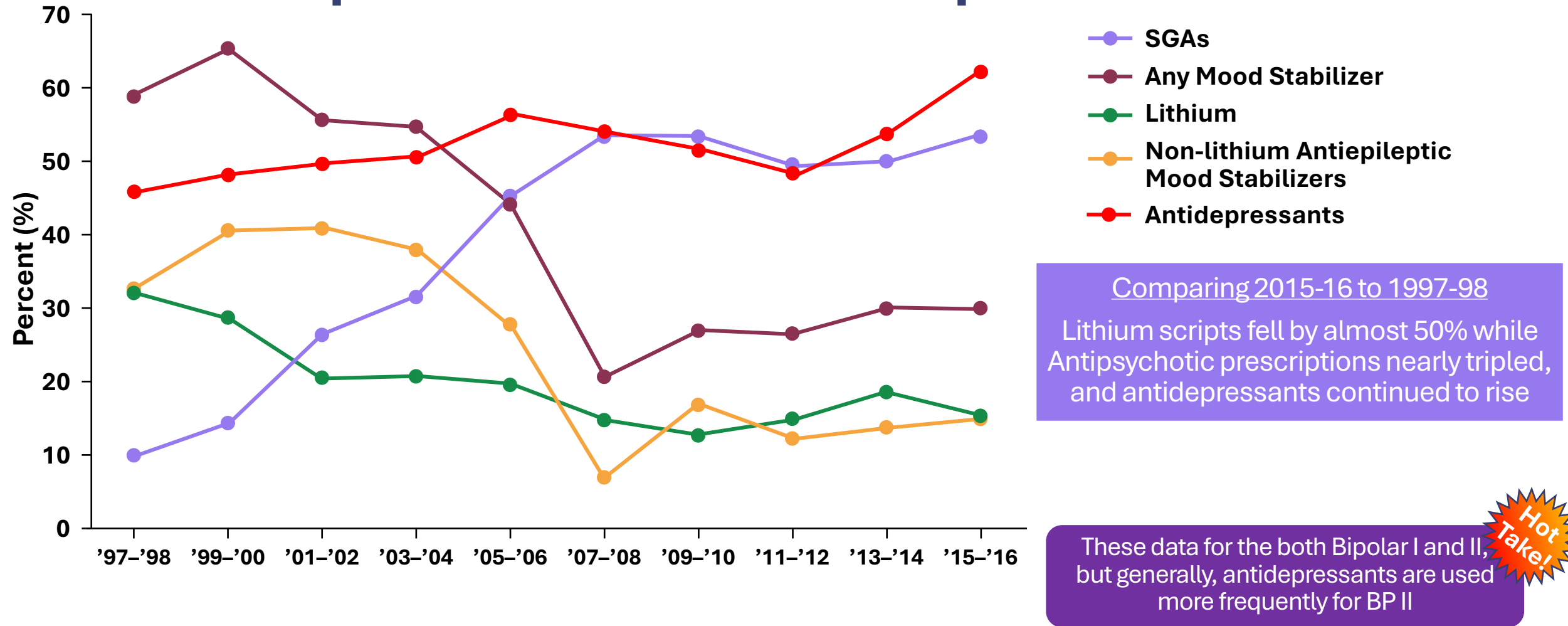
Key Learning Points



- ✓ Manic episodes associated with BDI typically last ≥ 7 days nearly every day for most of the day and cause marked impairment
- ✓ Mixed features can be present across mood disorders and can result in more polypharmacy, poorer outcomes, and prognosis
 - ✓ DSM-5 eliminated the “mixed episode” category and introduced the “with mixed features” specifier for mood episodes with symptoms of the opposite polarity
- ✓ Screening tools can help clinicians and their patients determine personalized treatment targets to address their bipolar illness
- ✓ Be sure to screen all patients, every time! Dig deeper for clues of potential Bipolar Disorder!

Traditional Approaches to Bipolar Disorder 2 Treatment

20-Year Trends in the Outpatient Treatment of Bipolar Disorder



SGA = second-generation antipsychotic.
Rhee TG, et al. *Am J Psychiatry*. 2020;177(8):706-715.

Treatment with Antidepressants in BD May Increase the Risk of Hypomanic/Manic Switching

N=1629

adults with BD treated
with an antidepressant

BD1 (n = 913) or BD2 (n = 716)

~28%

experienced
hypomania/mania
switching during
antidepressant
treatment

BD1: **24.5%**

BD2: **31.4%**

**Factors independently
associated with switching**

Psychiatric family history

More episodes per year

Suicide attempts

Older age

DMI illness course

Strengths and Limitations of Atypical Antipsychotics in Bipolar Disorder

Agent	Strengths	Limitations
Aripiprazole	Acute mania and maintenance efficacy; LAI	2 (-) trials in bipolar depression
Asenapine	Acute mania and 26-wk maintenance efficacy	No data in bipolar depression
Brexipiprazole	None	2 (-) trials in acute mania
Cariprazine	Bimodal acute mania and depression efficacy	(-) maintenance data
Lumateperone	Efficacy in BD-I or BD-II depression	No data in mania or maintenance (as of August 2026)
Lurasidone	Efficacy in depression alone or with Li/VPA	(-) maintenance data; no mania data
Olanzapine	Efficacy in acute mania and maintenance	Sedation, metabolic/weight liability
Quetiapine	Acute mania, BD-I or BD-II depression, and 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; VPA = valproic acid.

The Polarity Index of Medications May Be Useful in Considering Treatments for Mixed Features

These polarity indices were calculated in maintenance trials of bipolar disorder

Polarity Index value **above** 1.0 indicates a relative greater **antimanic** prophylactic efficacy.

Polarity Index **below** 1.0 indicates a relative greater **antidepressive** prophylactic efficacy.

	NNT Mania	NNT Depression	Polarity Index
Aripiprazole-weighted mean	8.81	38.55	4.38
Aripiprazole monotherapy	6.2	50	8.06
Aripiprazole combined with Li/VPA	10	33.3	3.33
Lamotrigine	50.4	20.2	0.40
Lithium	4.4	6.1	1.39
Olanzapine-weighted mean	4.7	14	2.98
Olanzapine monotherapy	4.4	17.2	3.90
Olanzapine combined with Li/VPA	11.2	6.2	0.55
Oxcarbazepine*	8.2	5.1	0.62*
Quetiapine-weighted mean	3.5	4	1.14
Quetiapine combined with Li/VPA	7.1	5.9	0.83
Quetiapine monotherapy	2.4	3.3	1.38
Risperidone LAI	4.4	53.2	12.09
Risperidone LAI monotherapy	4	36.4	9.1
RLAI + treatment as usual	7.9	15.8	2
Valproate*	21.3	10.5	0.49*
Ziprasidone	14.1	55.1	3.91

*Polarity index of valproate and oxcarbazepine may not be reliable due to the failure of their maintenance trials.

NNT=Number Needed to Treat; Li=Lithium; VPA=Valproic acid; LAI=Long-Acting Injectable

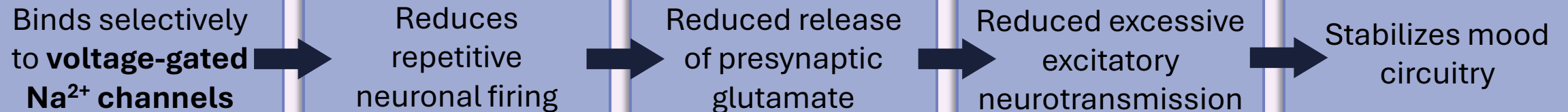
Popovic D, et al. *Eur Neuropsychopharmacol.* 2012;22(5):339-346.

Treatments for Bipolar Disorder 2

Lamotrigine

Lamotrigine Pharmacology

Mechanism of Action



- **Half-life:** 15 hours, age-dependent, and depends upon whether other agents are used
- The target dose of lamotrigine is 200 mg/day
 - 100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine
 - 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, rifampin and lopinavir/ritonavir, which increase the apparent clearance of lamotrigine

XR = extended release.

Besag FMC, et al. *Ther Adv Psychopharmacol*. 2021;11:20451253211045870. Stahl SM. *Essential Pharmacology*. Cambridge University Press; 2021. Lamictal XR (lamotrigine) extended-release tablets Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed March 14, 2023. RxList. Updated May 12, 2025. Accessed March 2026.

Lamotrigine Has BP-1 Depression Prevention Efficacy, Where Traditional Antidepressants Don't



Review of 13 RCTs using lamotrigine support:

Evidence for **prevention of depressive relapse, long-term maintenance, and favorable tolerability**

Limited BD2 data in adults and pediatrics; slow dose escalation and risk of rash can be a challenge

Evidence does not support established efficacy for acute mania, rapid cycling, acute bipolar depression, or treatment of unipolar depression

FDA-approved for maintenance treatment of BP1 only—not BD2

RCT = randomized controlled trial.

Besag FMC, et al. *Ther Adv Psychopharmacol*. 2021;11:20451253211045870; Keramatian K, et al. *Focus (Am Psychiatr Publ)*. 2023;21(4):344-353.

Lamotrigine Adverse Events

Adverse Event	LTG N = 668 (n, %)	PLB N = 552 (n, %)	LTG–PLB (%)
Nausea	86 (12.9)	51 (9.2)	3.6
Rash	48 (7.2)	25 (4.5)	2.7
Headache	141 (21.1)	104 (18.8)	2.3
Insomnia	41 (6.1)	24 (4.3)	1.8
Accidental injury	17 (2.5)	6 (1.1)	1.5
Abdominal pain	11 (1.6)	4 (0.7)	0.9
Oropharyngeal pain	10 (1.5)	4 (0.7)	0.8
Pruritus	11 (1.6)	6 (1.1)	0.6
Suicidal ideation	4 (0.6)	0	0.6
Pulmonary problems	3 (0.4)	0	0.4
Hypertension	3 (0.4)	0	0.4

LTG = lamotrigine; PLB = placebo.

Besag FMC, et al. *Ther Adv Psychopharmacol*. 2021;11:20451253211045870. Fukasawa T, et al. *Allergol Int*. 2021;70(3):335-342. Gronich N, et al. *Am J Clin Dermatol*. 2022;23(2):257-266.

Key Learning Points



- ✓ Lamotrigine is approved for maintenance treatment of Bipolar I Disorder and evidence is robust for mood maintenance
- ✓ Lamotrigine is not recommended for the acute treatment of mood episodes in Bipolar Disorder
- ✓ The most prominent component of Lamotrigine's MOA can be described as inhibition of voltage-gated sodium channels, reducing neuronal excitability, blocking presynaptic glutamate, modulating calcium currents, and enhancing the release of GABA
- ✓ Slow titration due to rash, but otherwise safety and tolerability, especially in women of childbearing age, are considerations

Quetiapine

Pharmacology of Quetiapine

Receptor Affinity, in vitro (k_i , nM)	D ₁	D ₂	5-HT _{1A}	5-HT _{2A}	α_1	α_2	H ₁	M ₁	NET
Quetiapine	428	626	1040	38	14.6	617	4.4	1086	927
Norquetiapine	99.8	489	45	2.9	46.4	1290	1.1	38.3	12

Quetiapine XR's half-life is 7 hr
while quetiapine's is 6 hr
However, its T_{max} is 6 hr vs
quetiapine's 1.5 hr

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

NET = norepinephrine transporter.

Quetiapine Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed February 28, 2025.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022047s048lbl.pdf. Bauer M, et al. Journal of Affective Disorders. 2010;127(1-3):19-30. Jensen NH, et al. Neuropsychopharmacology. 2008;33(10):2303-2312.

Quetiapine in Acute Bipolar Depression: Efficacy in Adult and Pediatric Samples

Meta-analysis of quetiapine vs placebo in 11 RCTs* (n=3,488)

Key Finding:

Greater improvement in
depressive symptoms vs placebo
(Mean Difference = -4.66)

Response

RR 1.31

NNT = 6

Remission

RR 1.36

NNT = 6

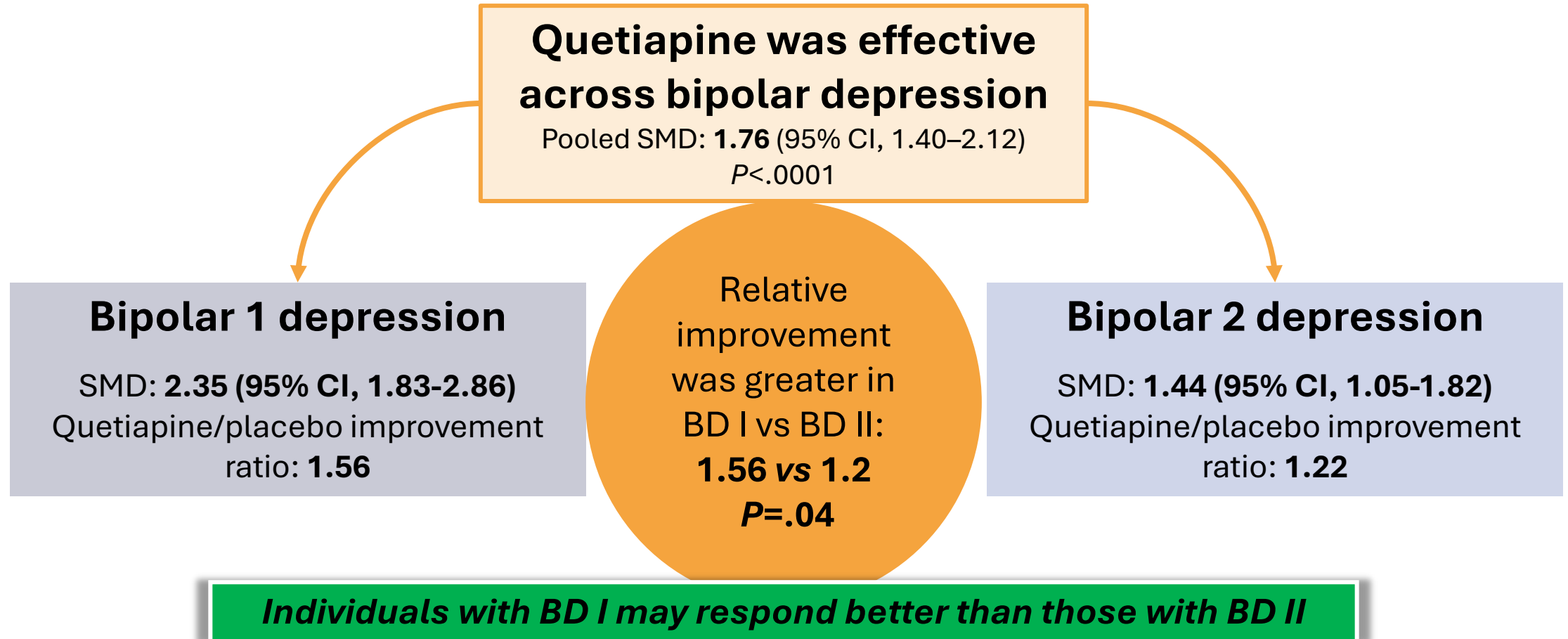
- Quetiapine monotherapy was **effective for acute bipolar depression** and the **prevention of mania/hypomania switching**
- Most common adverse events were extrapyramidal reactions, sedation, somnolence, dizziness, fatigue, constipation, dry mouth, increased appetite, and weight gain

*includes both adult (9) and pediatric (2) studies

Muneer A. Clin Psychopharmacol Neurosci. 2015;13(1):25-35; Suttajit S, et al.

Drug Des Devel Ther. 2014;8:827-838.

Does the Antidepressant Efficacy of Quetiapine Differ in Bipolar Subtypes?



Key Learning Points

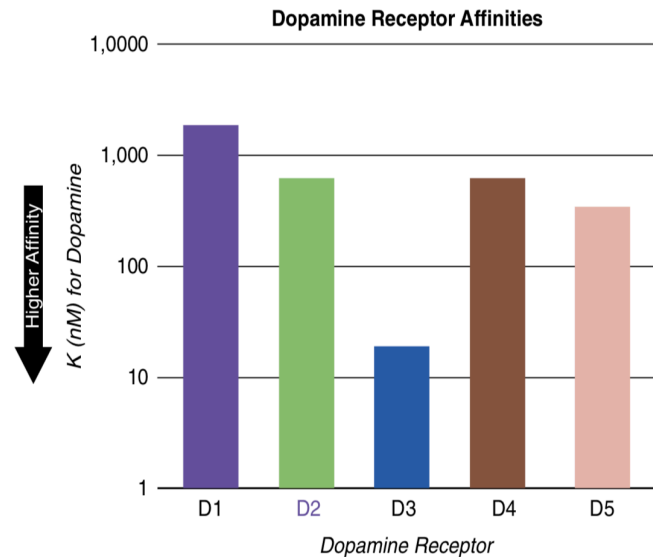
- ✓ Quetiapine is approved for the treatment of depressive episodes in bipolar 2 disorder, adjunctively for MDD, and adjunctively with lithium or divalproex sodium for maintenance in bipolar I disorder
- ✓ The most prominent component of Quetiapine's MOA can be described as antagonism of D2 and serotonin 2A (5HT_{2A})
- ✓ Antagonism of H₁ receptors, adrenergic α₁ receptors, and M₁ muscarinic receptors contribute to side effect profile. It has not been associated with clinically significant weight gain, cardiometabolic lab changes, or movement disorders

Cariprazine

Cariprazine Pharmacokinetics and D₃ Pharmacology

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

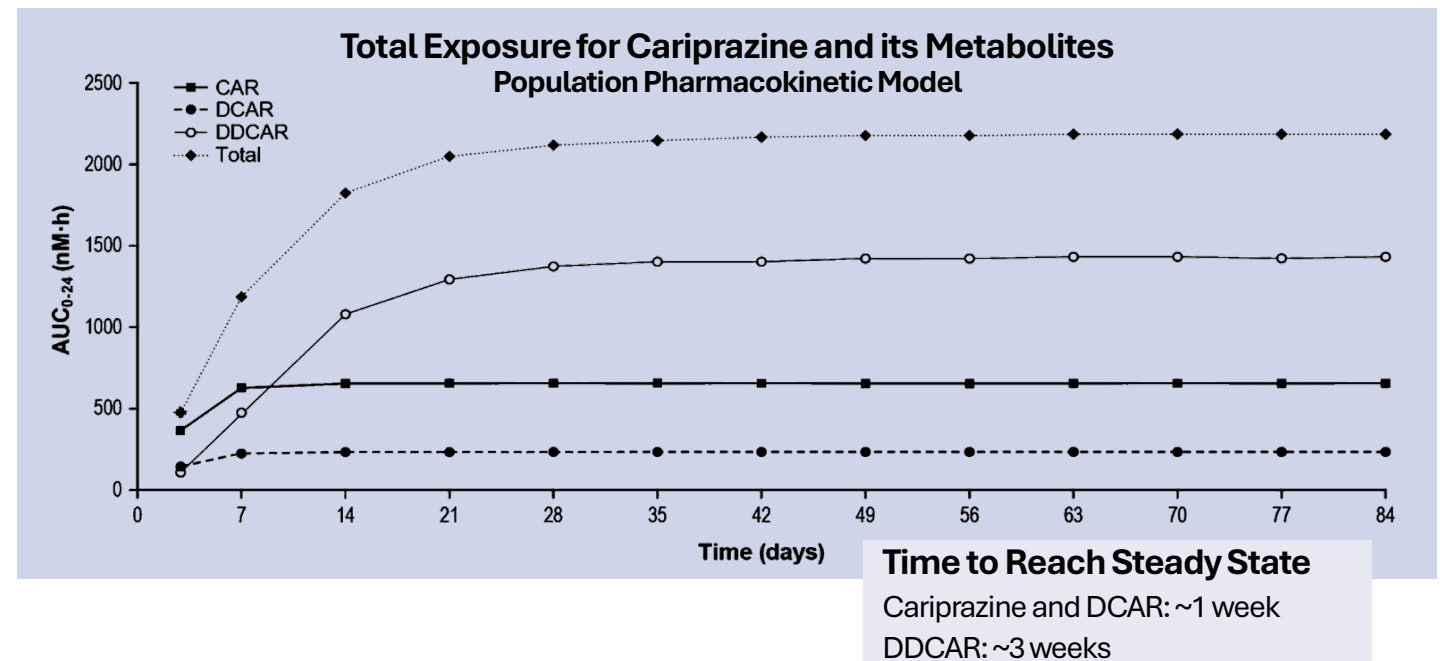
Cariprazine is the only antipsychotic in the US with a higher affinity for D₃ than dopamine itself



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

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

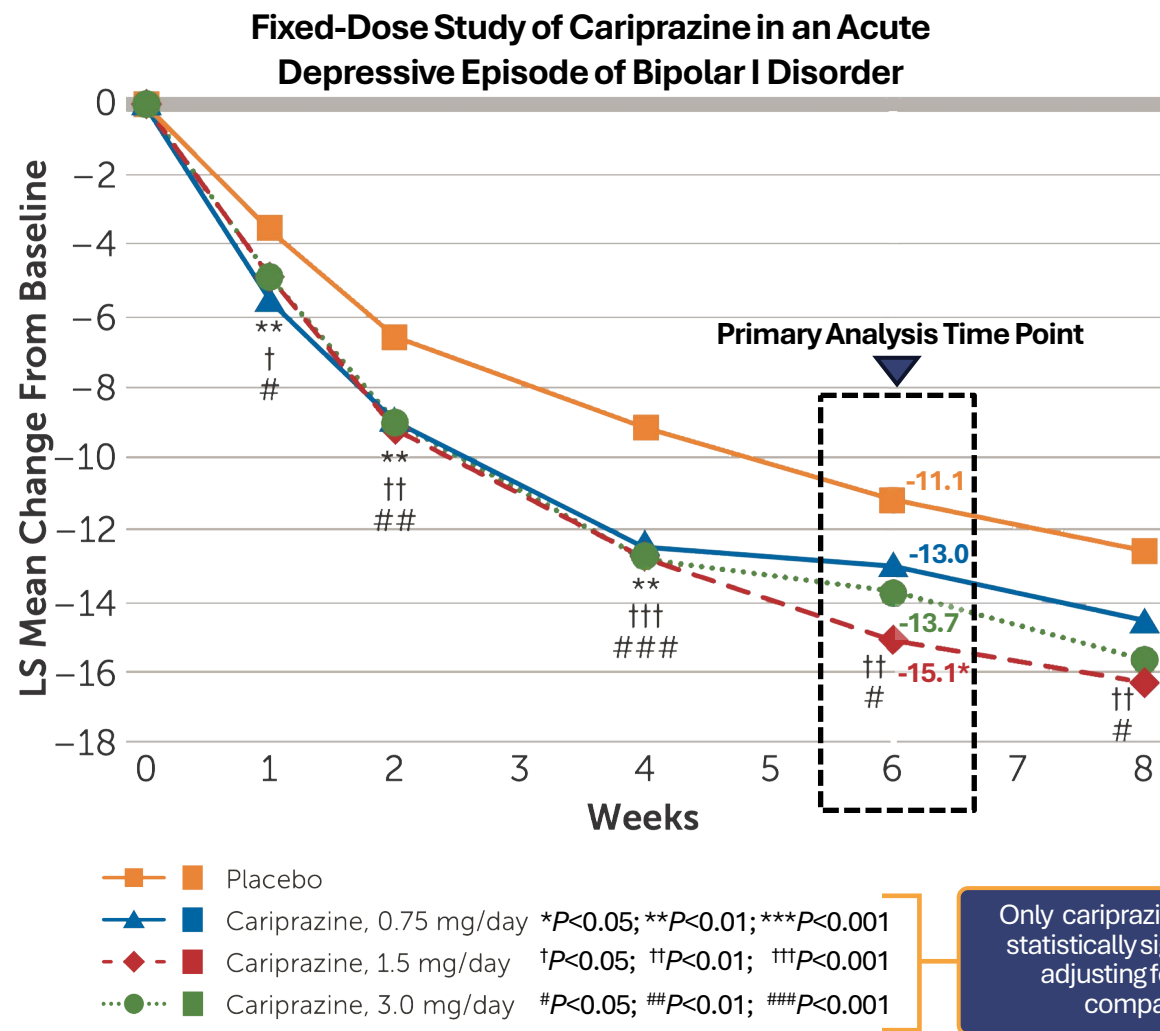
The second metabolite makes up about $\frac{2}{3}$ of the total exposure at steady-state



CAR=cariprazine; DCAR=desmethylcariprazine; DDCAR=didesmethylcariprazine

Beaulieu J-M and RR Gainetdinov. "Pharmacological reviews 63.1 (2011): 182-217. Stahl SM. CNS spectrums 22.4 (2017): 305-311. Periclou A, et al. Eur. J. Drug Metab. Pharmacokinet. 46 (2021): 53-69. Stahl SM, et al. Ther. Adv. Psychopharmacol. 10 (2020): 2045125320905752.

Phase 3 Studies of Cariprazine in Bipolar I Depression



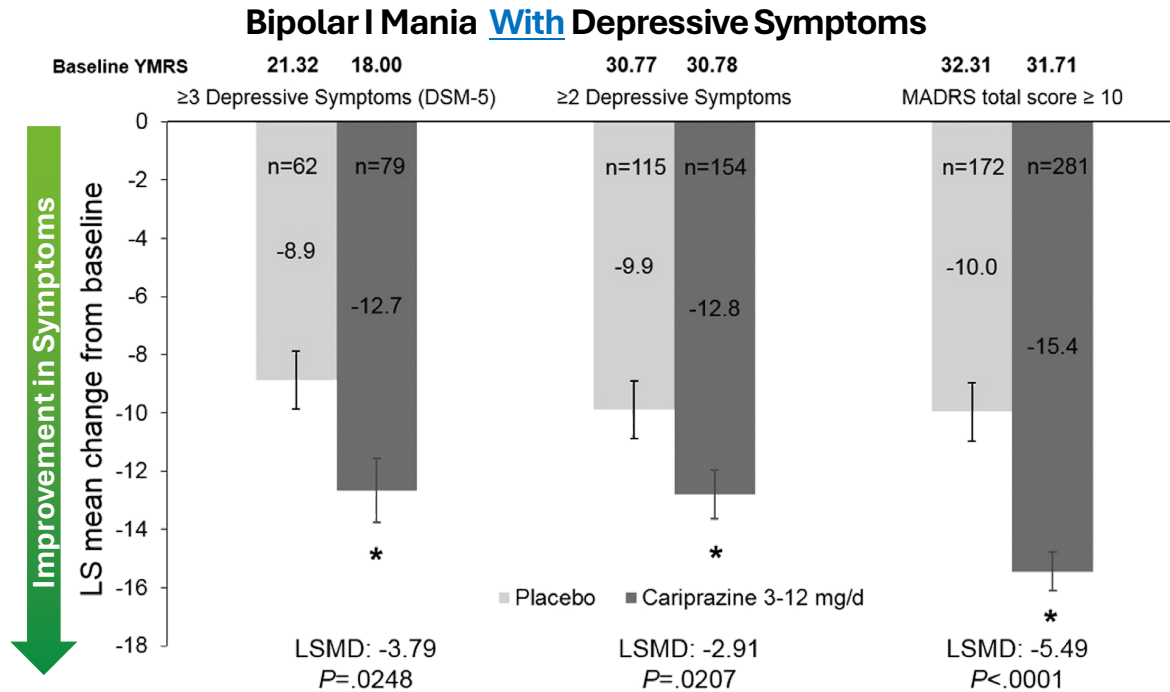
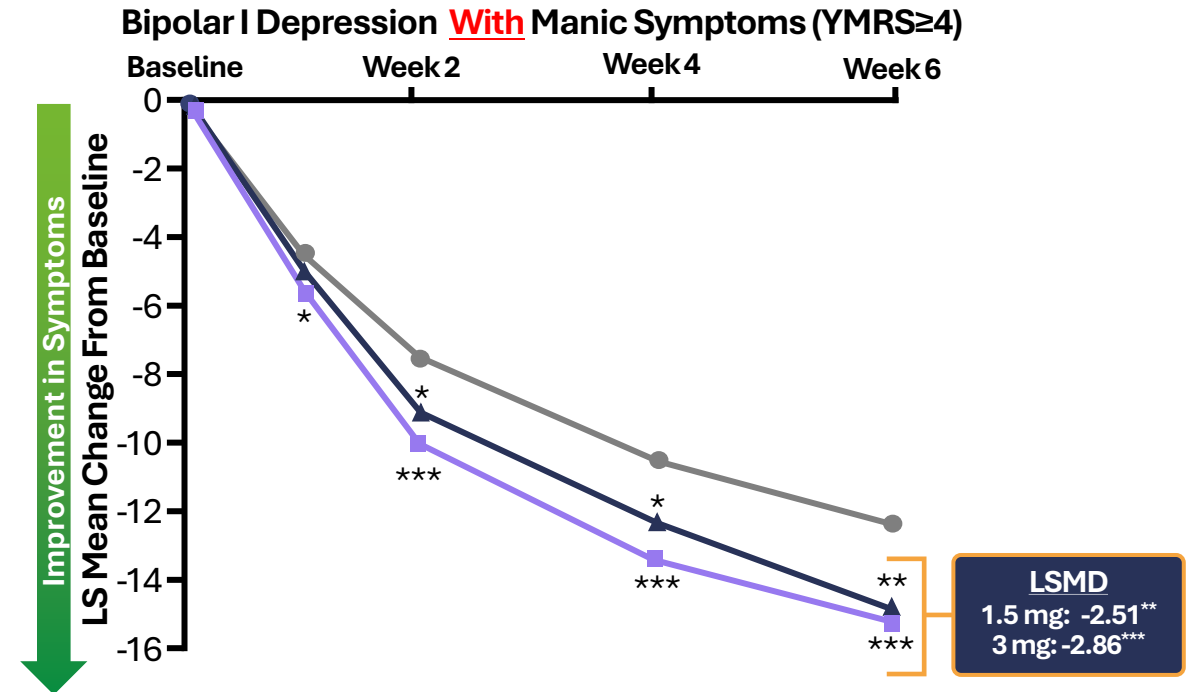
LS Mean Difference in MADRS vs. Placebo at Primary Endpoint

	Study 1	Study 2	Study 3
cariprazine 0.75 mg	-1.9	<i>n/a</i>	<i>n/a</i>
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.

Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-81. Earley, WR, et al. *Am J Psychiatry* 176.6 (2019): 439-448. Earley, WR, et al. *Bipolar disorders* 22.4 (2020): 372-384.

Pooled Post-Hoc Analysis of Cariprazine in Episodes of Bipolar Disorder with Mixed Symptoms



These analyses suggest cariprazine may have efficacy in mood episodes of either pole with mixed features



LS=least squares; MD=Mean Difference; YMRS=Young Mania Rating Scale

McIntyre, RS, et al. *Journal of Affective Disorders* 257 (2019): 600-606. McIntyre, RS, et al. *CNS Spectr.* 2020;25:502.

Most Common Adverse Events in Cariprazine BPI Trials $\geq 5\%$ 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 $\geq 7\%$	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 $\geq 7\%$	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

Dosing speed matters in observed AEs of
cariprazine—keep it low if you can

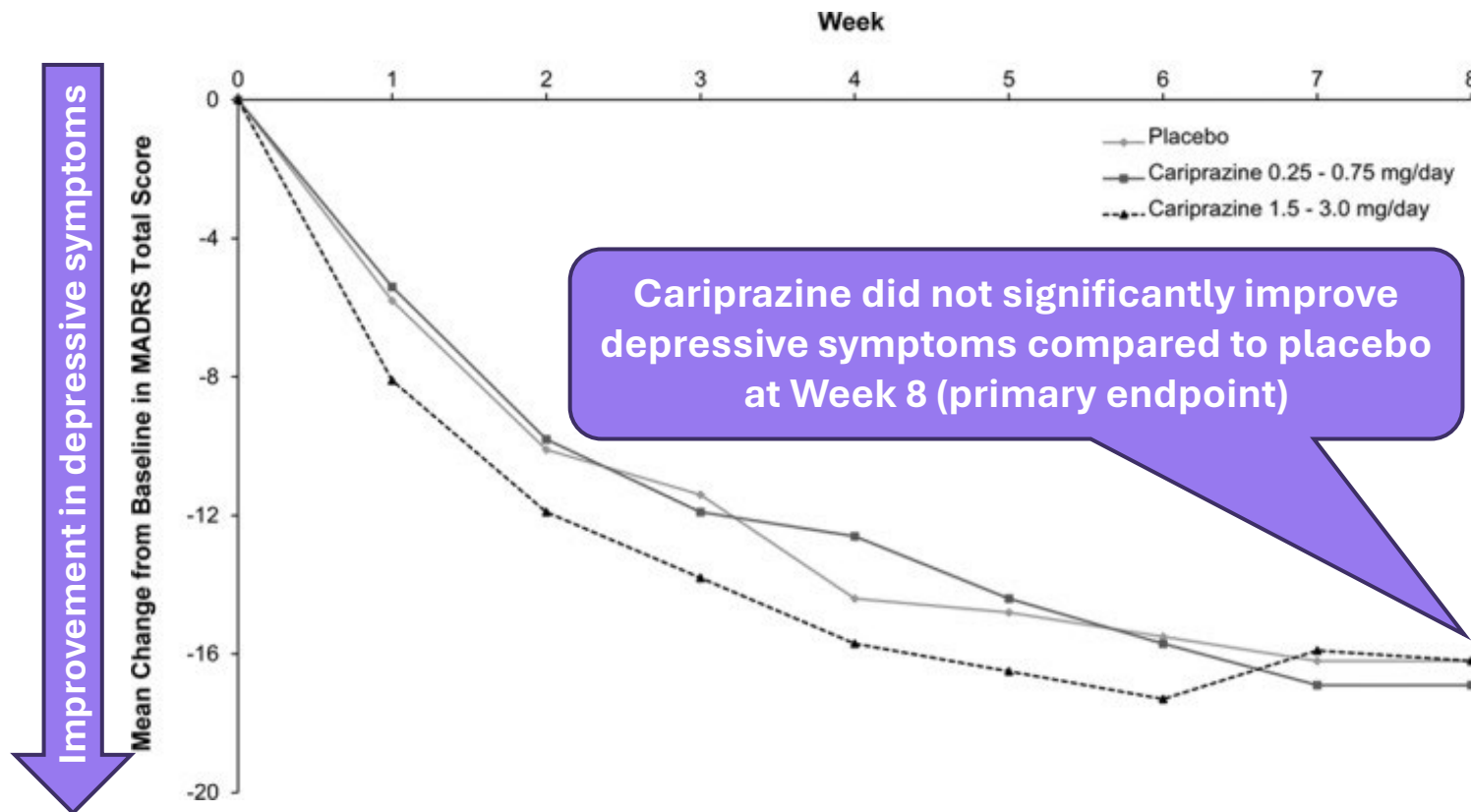


EPS = Extrapyramidal Symptoms; D/C = discontinuations; AE = Adverse Events.

Cariprazine Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/. 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):271-81. Earley, WR, et al. *Am J Psychiatry*. 2019;176(6): 439-448. Earley WR, et al. *Bipolar Disord*. 2020;22(4): 372-384.

Cariprazine in Bipolar II Depression: What Do We Know?

In an RCT of individuals with bipolar I or II depression (N = 233):



Negative findings attributed to:

- 1) Clinical heterogeneity from combining BD1 and BD2 in sample population
- 2) Large placebo response

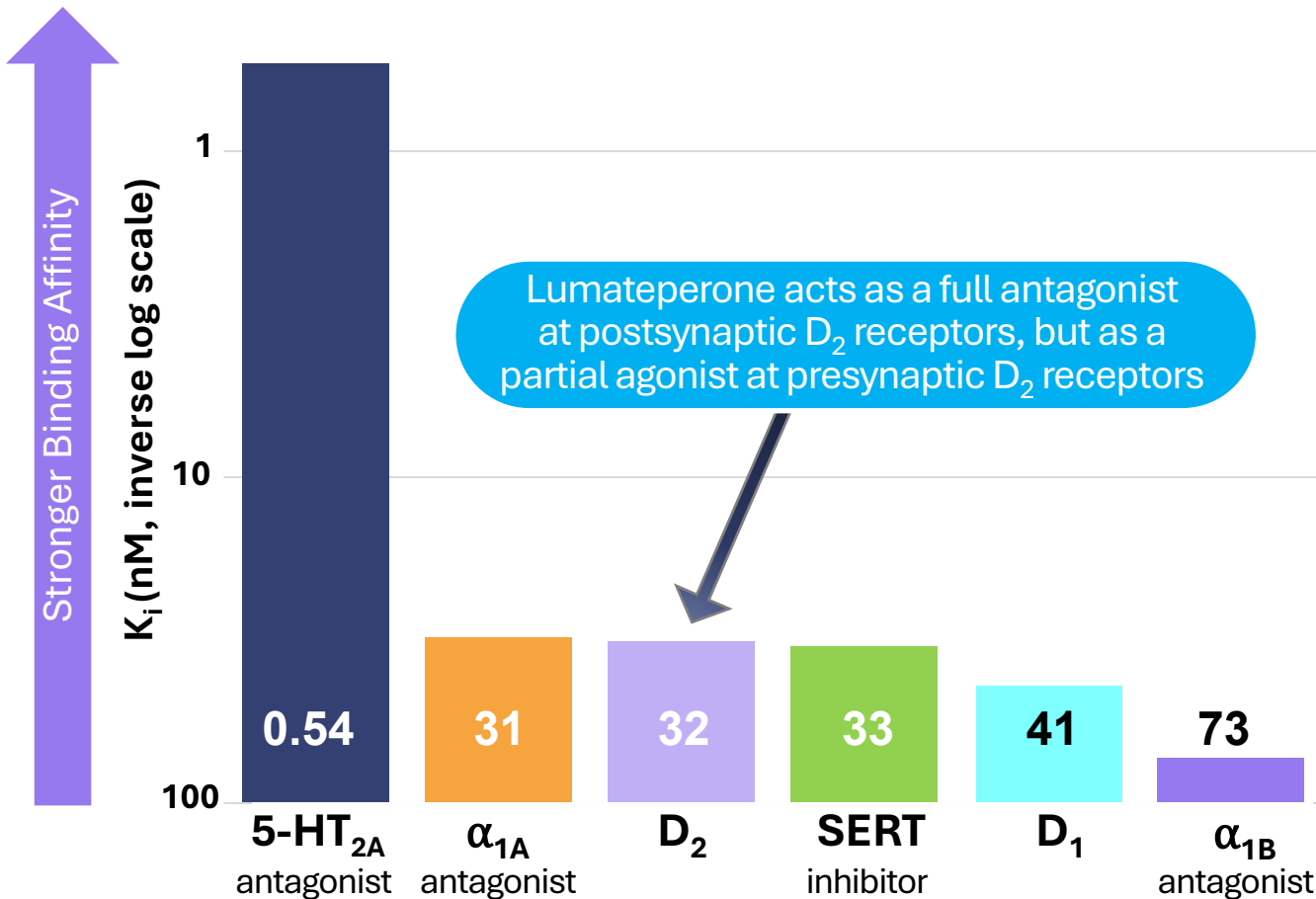
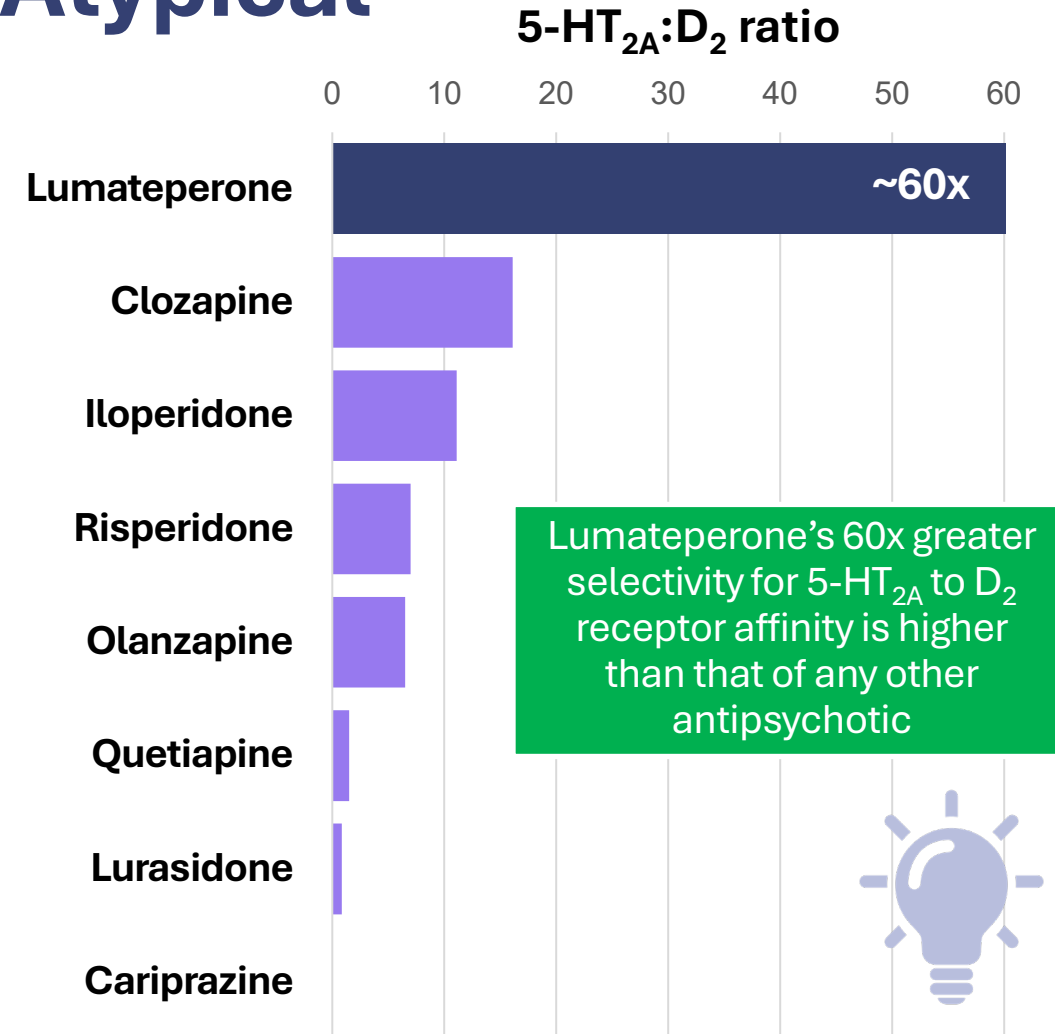
As of September 2026:
No dedicated RCT has evaluated cariprazine specifically in bipolar II depression

Key Learning Points

- ✓ Cariprazine has demonstrated consistent efficacy in acute manic/mixed and depressive episodes of Bipolar I disorder, and analyses suggest this may extend to mixed features in either pole
- ✓ Potent D₃ partial agonism may be especially relevant for symptoms related to reward, anhedonia
- ✓ Long half-life of cariprazine and its active metabolites may be especially useful in patients with historical poor adherence

Lumateperone

Lumateperone Receptor Binding: Not Your Typical Atypical

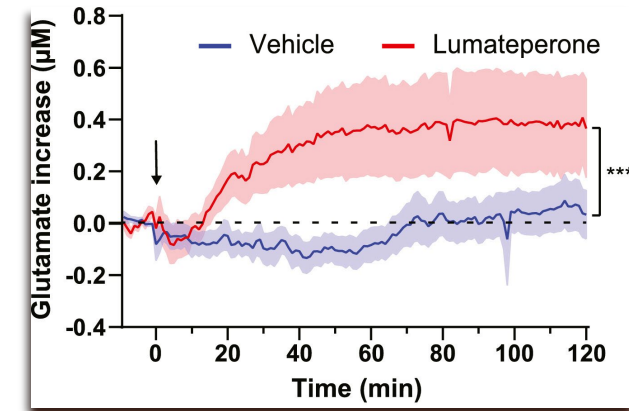
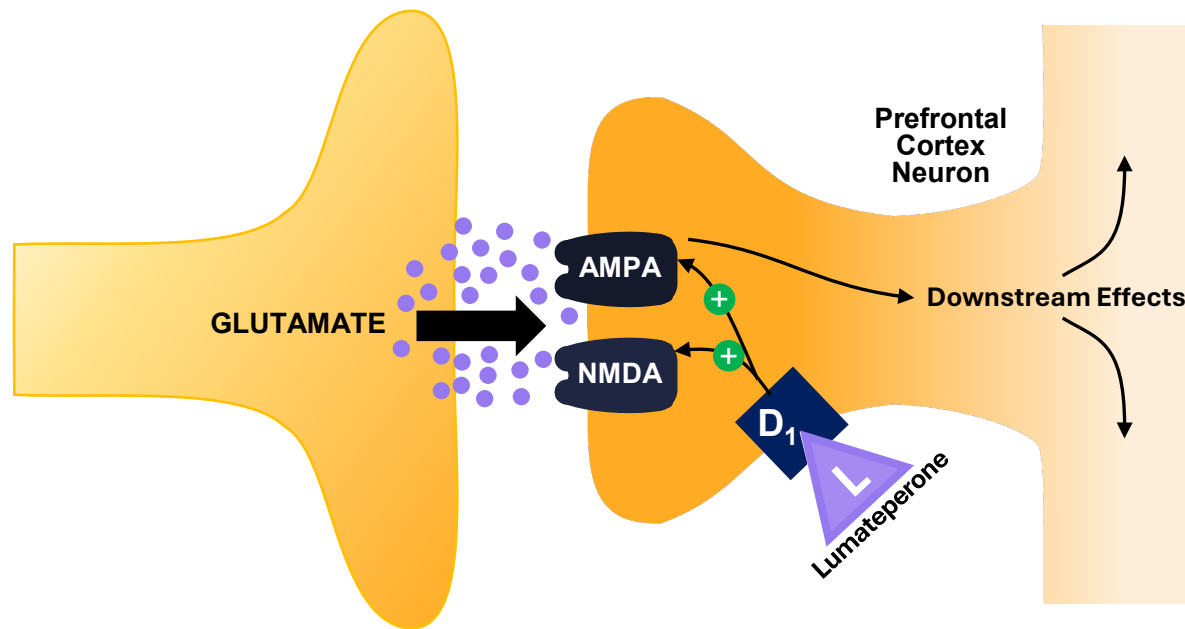
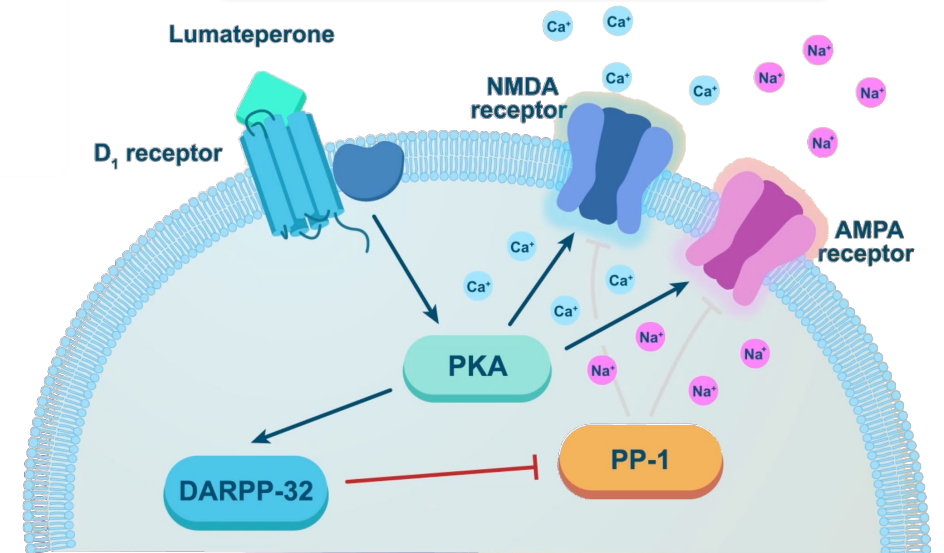


SERT = Serotonin Reuptake Transporter.

Lumateperone Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed May 20, 2025. www.accessdata.fda.gov/scripts/cder/daf/ Li P, et al. *Journal of Medicinal Chemistry*. 2014;57(6):2670-2682. Kantrowitz JT. *CNS Drugs*. 2020;34(9):947-959.

Lumateperone May Indirectly Activate Glutamate Receptors via D₁ Modulation

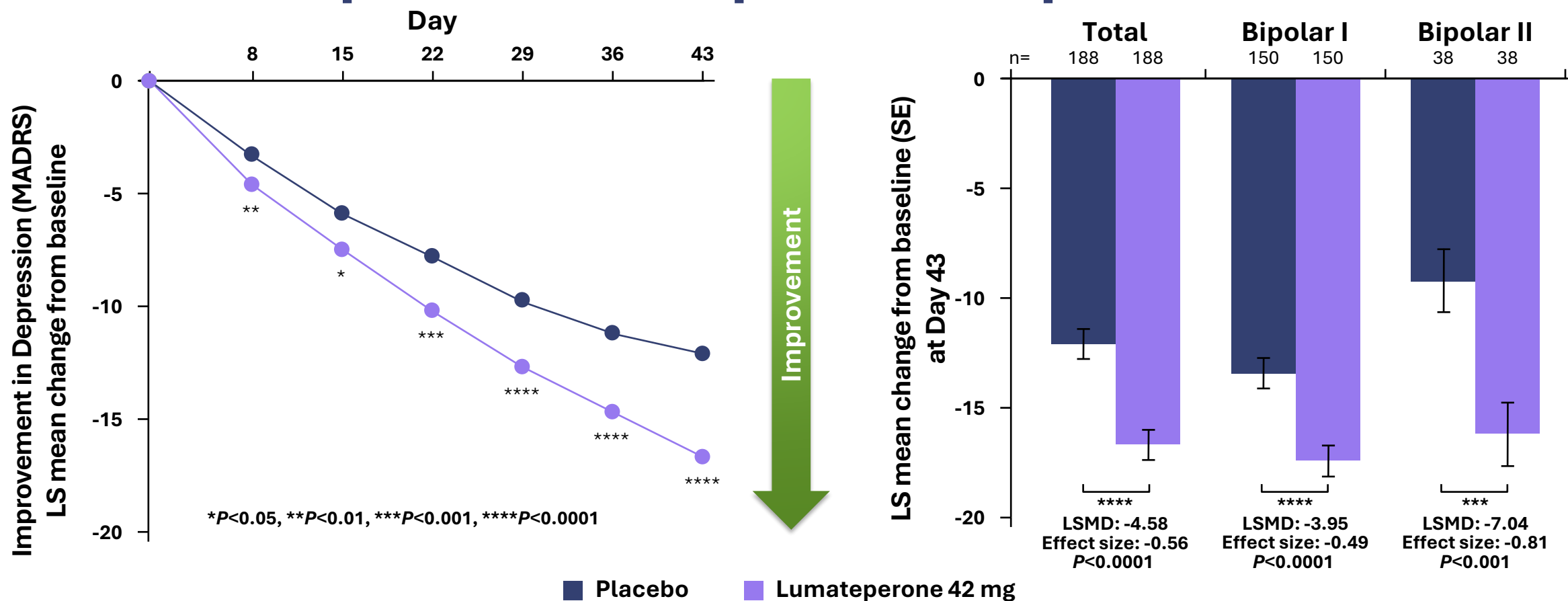
Preclinical data shows lumateperone indirectly activates both NMDA and AMPA glutamatergic receptors in the PFC via downstream effects from its action on D₁ receptors



AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartate; PKA = Protein Kinase A; PP-1 = Protein Phosphatase 1; DARPP-32 = dopamine and cyclic adenosine 3',5'-monophosphate-regulated phosphoprotein, 32 kDa.
 Greengard, P, et al. *Neuron*. 1999;23(3): 435-447. Harvey J, et al. *J Neurosci*. 1997;17(14):5271-5280. Snyder GL, et al. *Psychopharmacology*. 2015;232: 605-621.
 Vanover KE, et al. *Eur Neuropsychopharmacol* 2017;27:S660-S661; Titulaer J, Radhe O, Danielsson K, et al. *Eur Neuropsychopharmacol*. 2022;62:22-35.



Lumateperone in Bipolar I and Bipolar II Depression



Drug-Placebo differences of >2 points on MADRS are considered clinically relevant

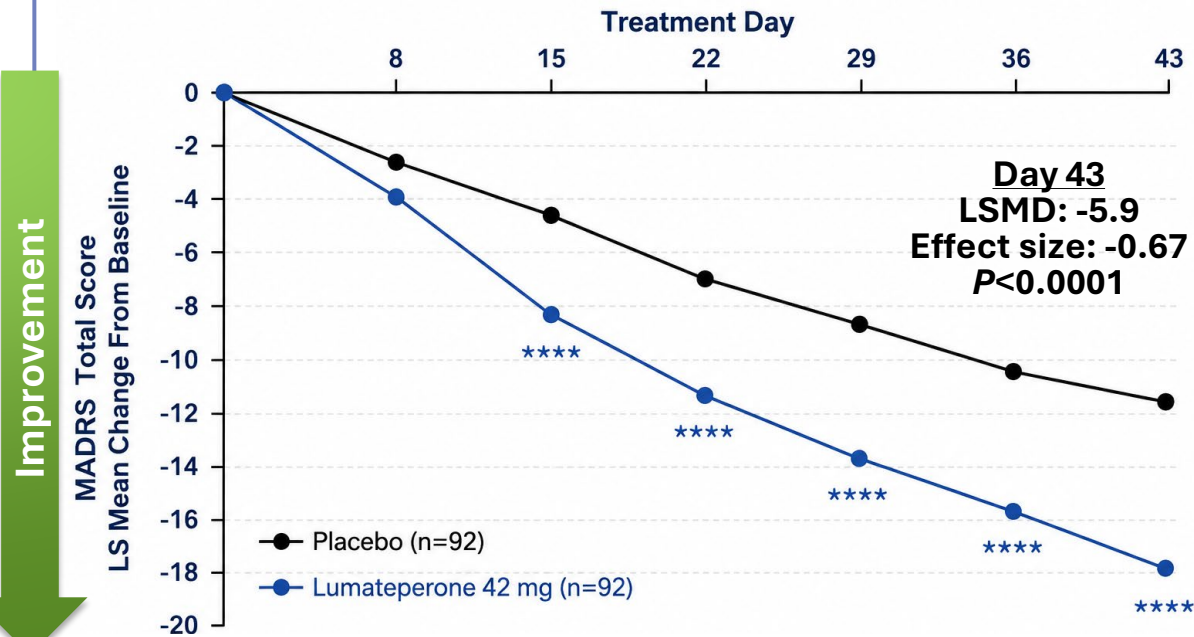
SE = standard error.

Calabrese JR, et al. *Am J Psychiatry*. 2021;178(12):1098-1106. Montgomery SA, et al. *Int Clin Psychopharmacol*. 2009;24(3):111-118.

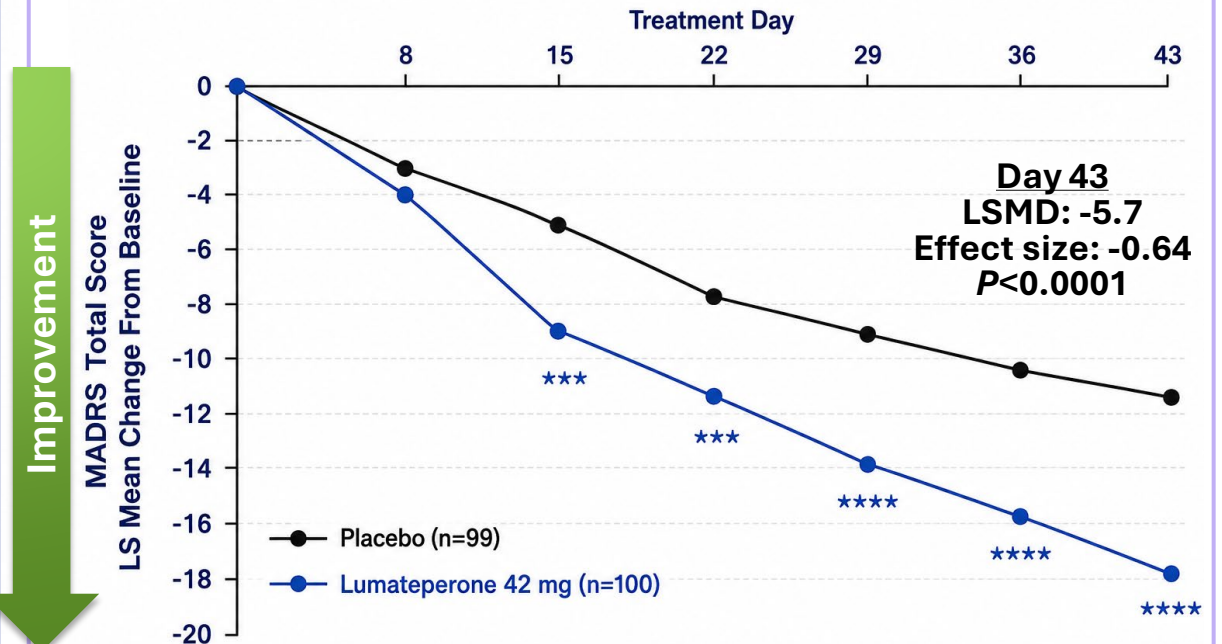


Lumateperone in MDD with Mixed Features and in Bipolar Depression with Mixed Features

MDD Population



Bipolar Depression Population

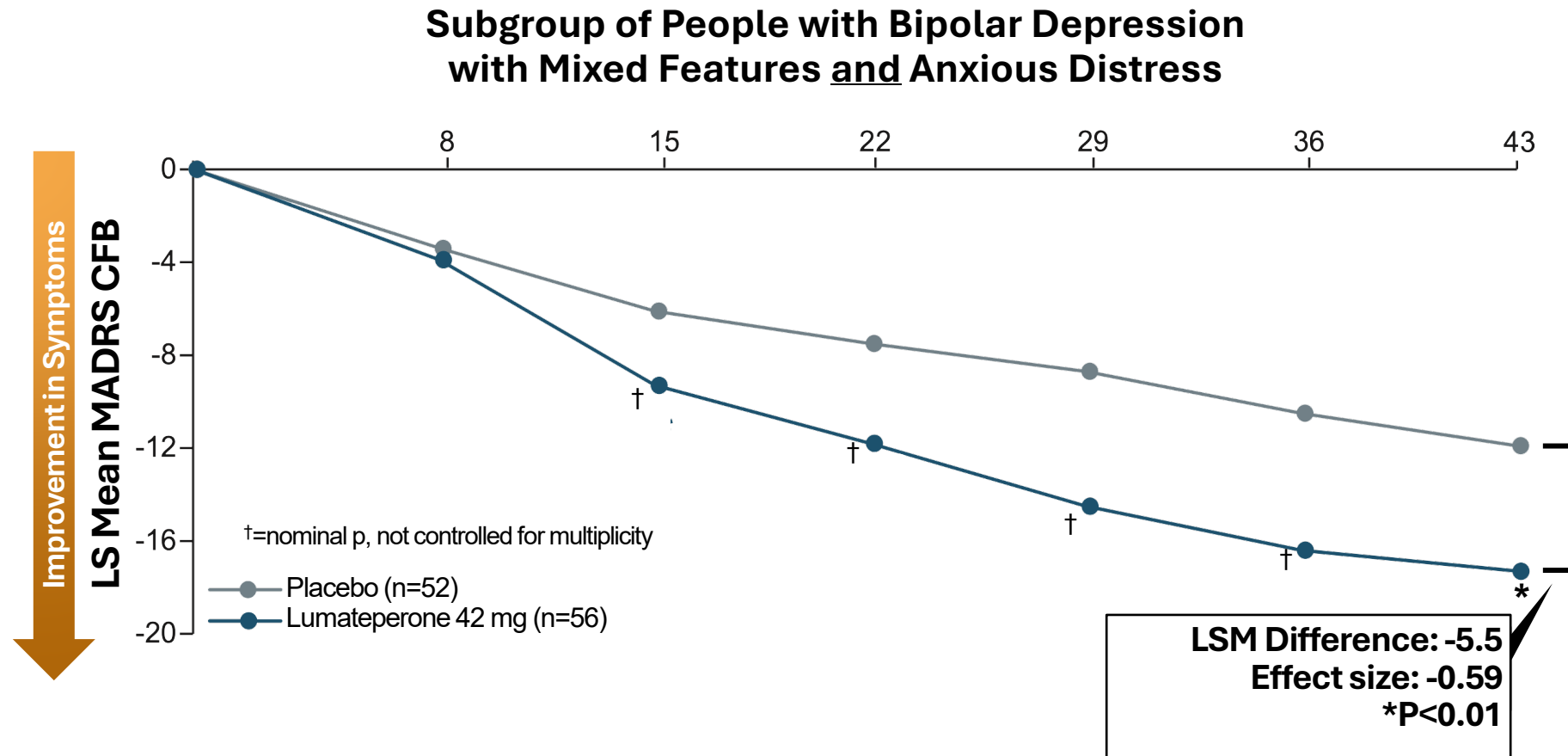


***Separates from placebo using MADRS by week 2 in both MDD and Bipolar Depression, and increasingly more improvements noted through week 6**

LSMD = least square mean difference

Durgam S, et al. *J Clin Psychopharmacol*. 2025;45(2):67-75.

Lumateperone in Bipolar Depression with Mixed Features And Anxious Distress



Lumateperone Adverse Event Profile

Across 6-Week Acute Bipolar Depression Trials

	Monotherapy		Adjunct to lithium/valproate	
	Lumateperone (n=372)	Placebo (n=374)	Lumateperone (n=177)	Placebo (n=175)
Somnolence/Sedation	13%	3%	13%	3%
Dizziness	8%	4%	11%	2%
Nausea	8%	3%	9%	4%
Dry mouth	5%	1%	5%	1%
EPS	1.3%	1.1%	4.0%	2.3%
Akathisia	0%	0.3%	0.6%	0%

No single adverse event led to discontinuation in >2% of participants

No change in prolactin compared to placebo

Levels of fasting glucose, insulin, cholesterol, and triglycerides were similar to placebo

Mean weight change and percentage of participants who gained ≥7% body weight were similar between lumateperone and placebo

Weight and Metabolic Parameters of Lumateperone Monotherapy in 6-month Open Label Extension

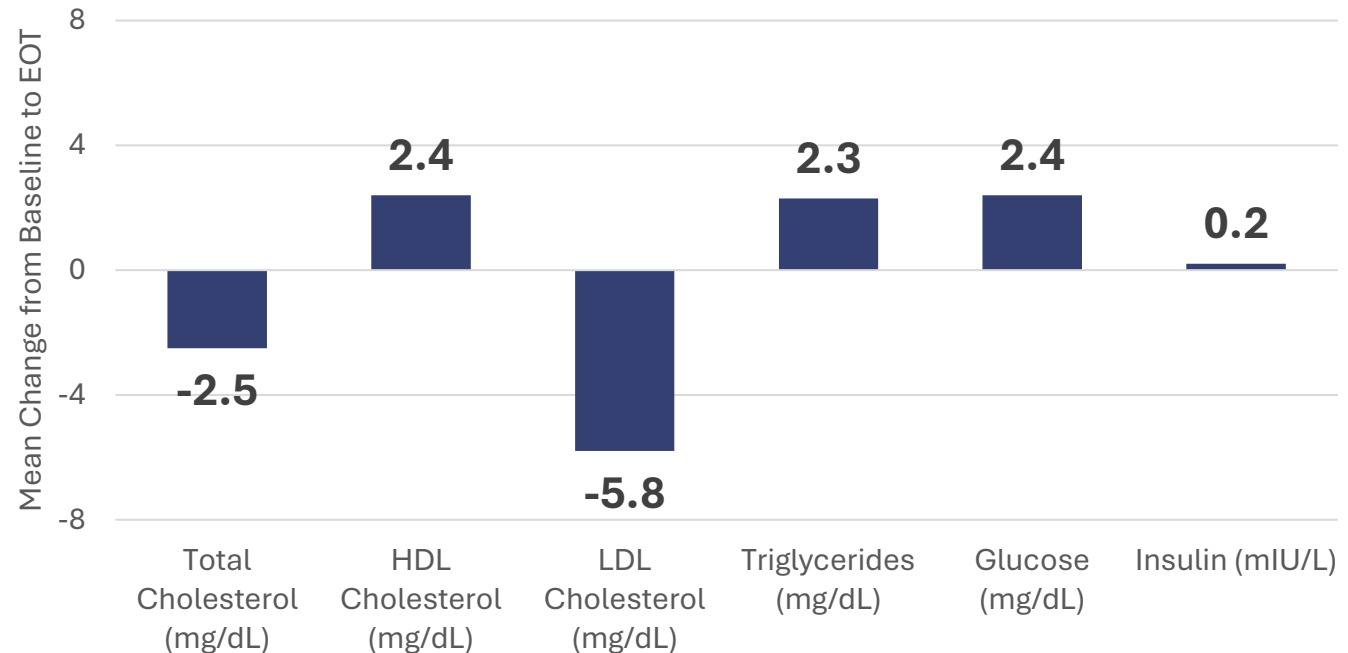
No notable changes in cardiometabolic parameters were observed over 6 months

Mean weight change: 0.0 kg

4.8% gained $\geq 7\%$ body weight

5.6% lost $\geq 7\%$ body weight

no significant changes in body morphology from baseline to end of treatment



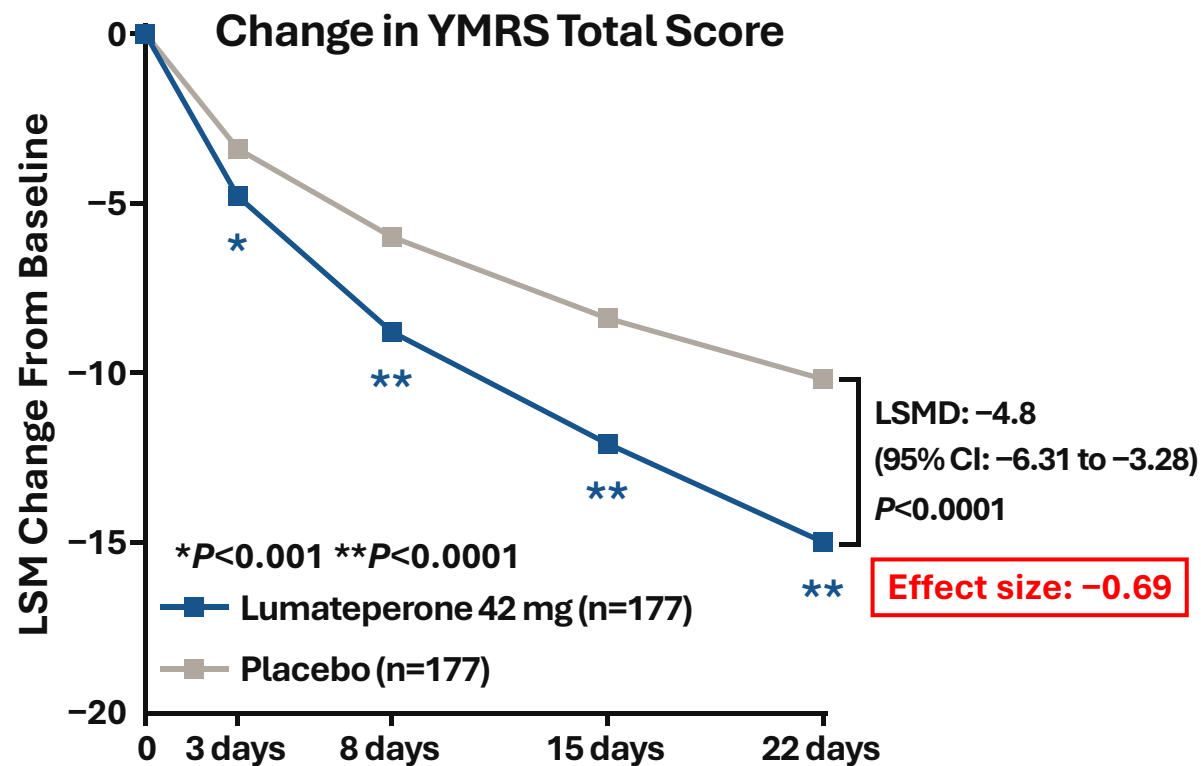
Lumateperone appears well-tolerated in the short and longer-term periods, but ongoing screening for weight, metabolics, and movement disorders is still necessary

Hot Take!

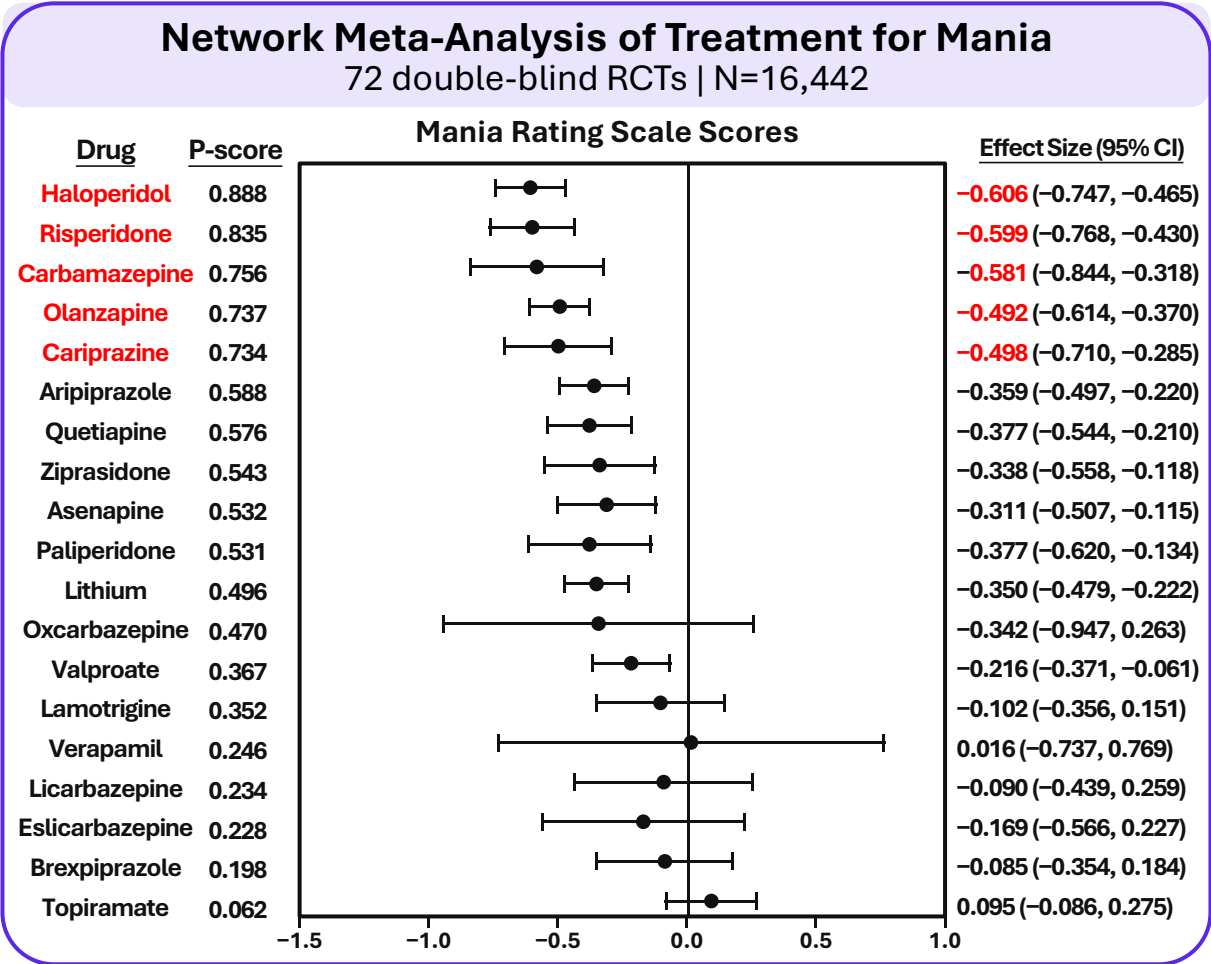
A Brief Step Back Into Mania



Lumateperone was Effective in a Phase 3 Study of Acute Mania with or without Mixed Features



Lumateperone 42 mg vs placebo also showed significantly greater **response rates** (45.8% vs 20.9%; $P < 0.0001$) and greater **remission rates** (30.5% vs 16.4%; $P = 0.0009$)



YMRS = Young Mania Rating Scale; 95% CI = 95% confidence interval; LSM = least squares mean
Kishi T, et al. *Mol Psychiatry*. 2022;27(2):1136-1144; Cutler et al., Lumateperone Treatment of Manic Episodes With or Without Mixed Features in Bipolar I Disorder: Results From a Double-Blind, Placebo-Controlled, Randomized, Phase 3 Trial. Poster presented at Psych Congress 2026; Sept 15-19, New Orleans, LA.



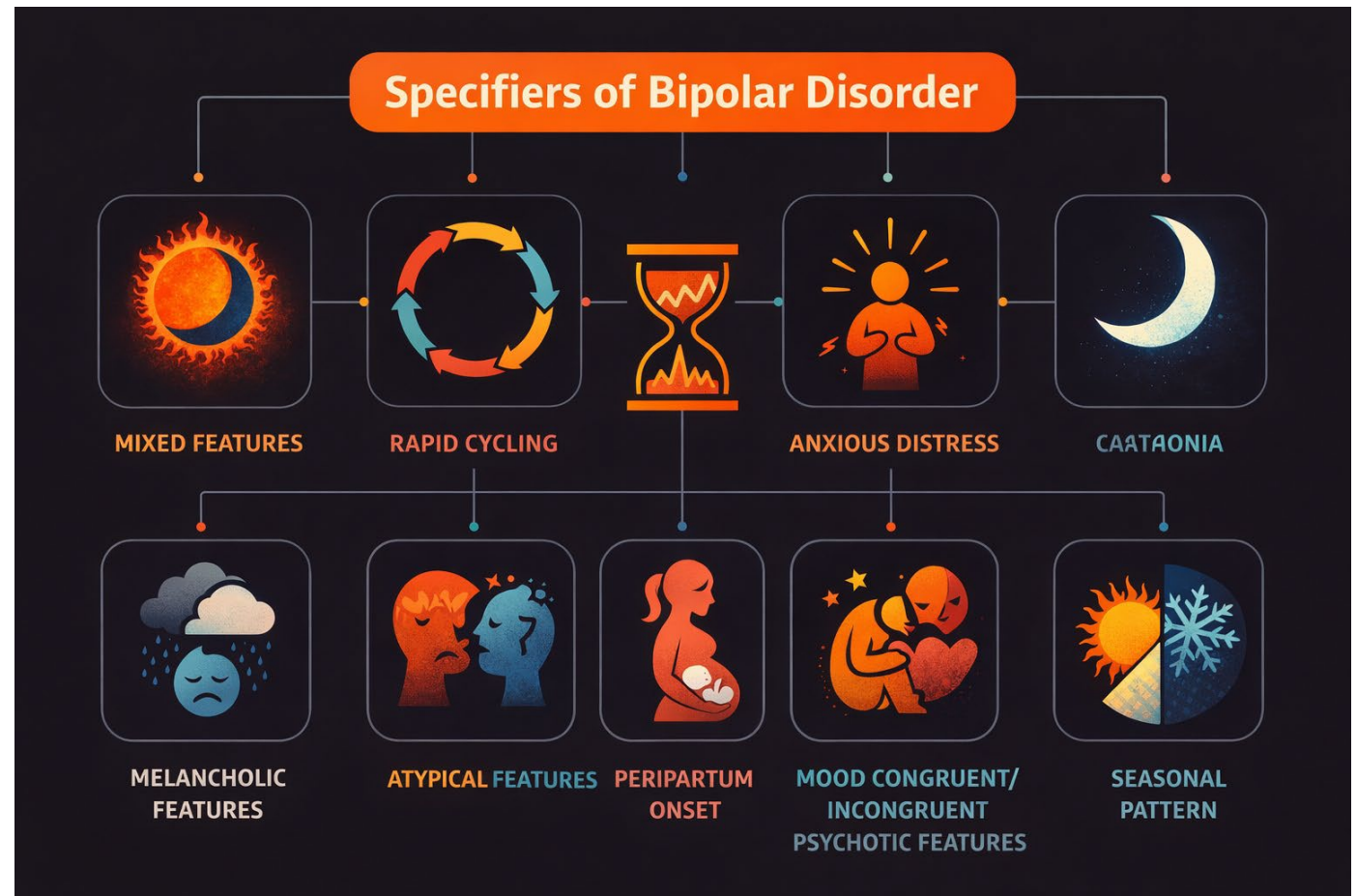
Key Learning Points

- Lumateperone is approved as both a monotherapy and adjunctive therapy (with lithium or valproate) in both bipolar 1 and bipolar 2 disorder
 - Lumateperone may indirectly activate NMDA and AMPA glutamate receptors via downstream effects from its action on D1 receptors
 - The most prominent component of lumateperone's MOA can be described as high-affinity serotonin 2A (5HT2A) receptor antagonism
- Lumateperone improved depressive symptoms in populations of individuals with mixed features in MDD or bipolar depression, with improvement seen at Week 2 for both groups through Week 6

Faculty Discussion and Patient Advocate Perspective

Utility of Specifiers

- Mixed Features
- With Rapid Cycling
- Anxious Distress
- Melancholic Features
- Mood-Congruent/Incongruent Psychotic Features
- Atypical Features
- Catatonia
- Peripartum Onset
- Seasonal Pattern



Clinical Relevance of Anhedonia



What it is

Reduced ability to feel pleasure from things that should be enjoyable, socially and physically



Why it matters

Tied directly to motivation; affects both anticipating and experiencing reward



Where it appears

A core symptom of MDD and a major component of bipolar II disorder

In a 2021 SHAPS study, people with bipolar II showed more severe anhedonia than those with MDD

Addressing anhedonia can reconnect patients with hope, pleasure, and engagement in the life they want

Bipolar Disorder and Anxious Distress

- Estimated lifetime prevalence of at least one anxiety disorder 40%-60%
- Patients with comorbid anxiety have
 - More depressive and manic/hypomanic episodes
 - Shorter periods of euthymia
 - Shorter time to relapse
 - More suicidal behavior
 - Increased substance misuse issues
 - Greater risk of residual symptoms
 - Reduced quality of life and functioning



No approved medications for anxiety in bipolar disorder

Off-label medications are often used



Many current options to treat anxiety may be detrimental to the control of bipolar disorder

Polypharmacy is common



More research is needed to explore how to address anxious distress

Developing Treatment Plans Based on Patient- and Disease-Specific Factors

Type of Bipolar Disorder

Appreciate the evidence base for treatments in BD-II vs BD-I

Course of illness, pattern of symptoms

Some patients with BP-I will have mania frequently, but others only very rarely

Polarity-specific properties of medications

Eg, antimanic efficacy less relevant in BD-II than it is in BD-I

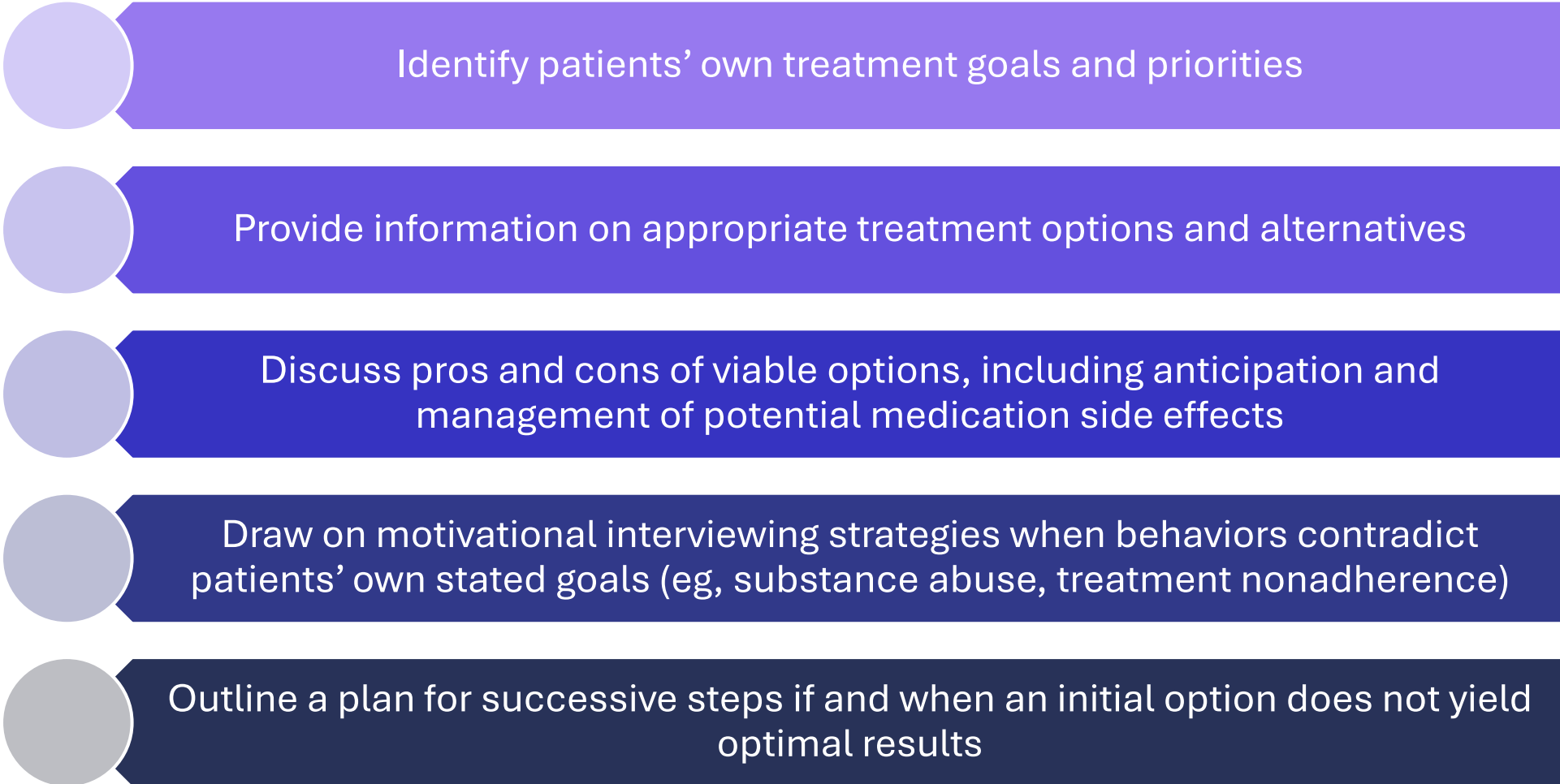
Past treatment responses, past adverse reactions

Eg, meds with high risk for akathisia are less favorable for patients with a past history of akathisia

Presence of comorbid disorders

Eg, meds with high weight/metabolic risk are less favorable for patients with obesity, diabetes, etc.

Shared Decision Making



Identify patients' own treatment goals and priorities

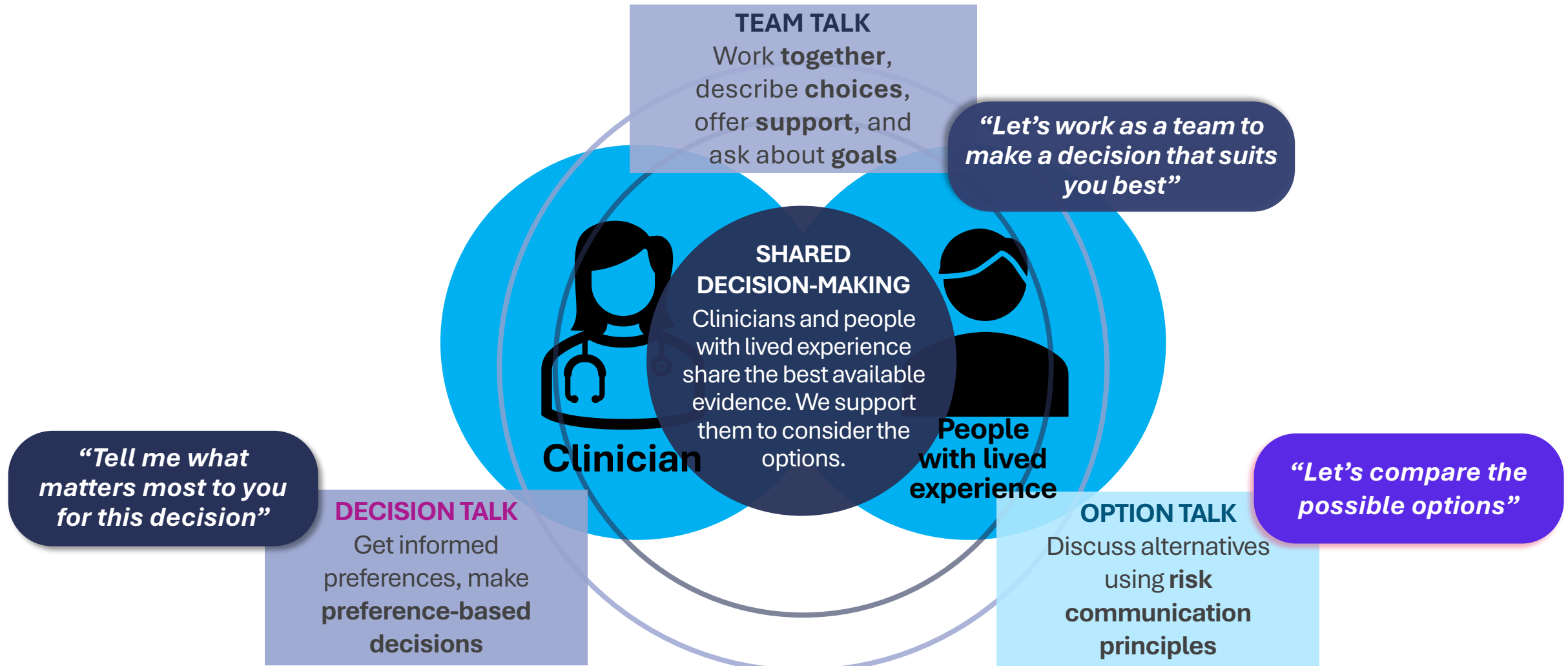
Provide information on appropriate treatment options and alternatives

Discuss pros and cons of viable options, including anticipation and management of potential medication side effects

Draw on motivational interviewing strategies when behaviors contradict patients' own stated goals (eg, substance abuse, treatment nonadherence)

Outline a plan for successive steps if and when an initial option does not yield optimal results

Positive Relationships Create Results





Q&A