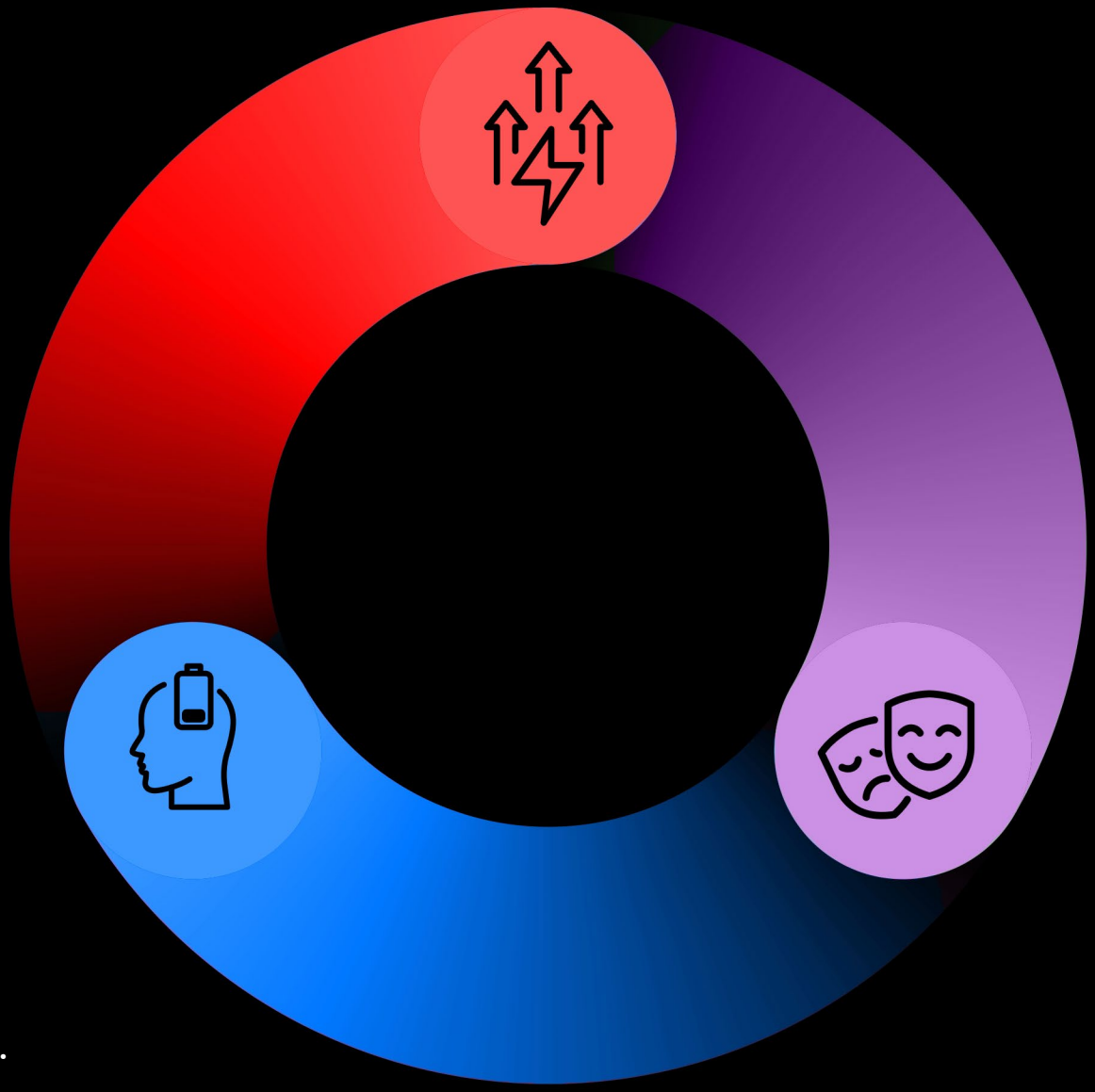
Coming Full Circle: Recent Advances in Treating Depression, Mania, and Mixed Features in Bipolar Disorder



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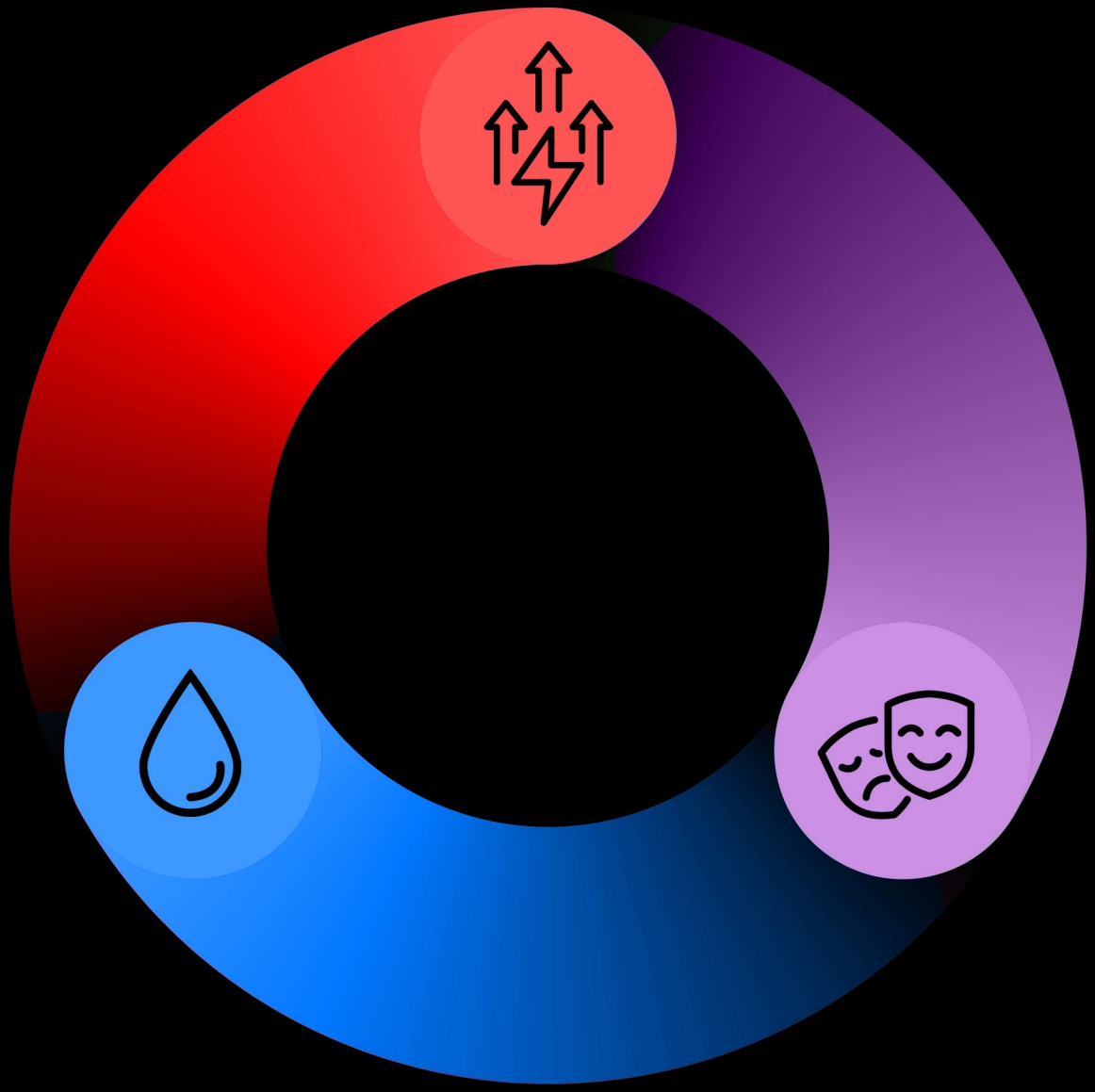
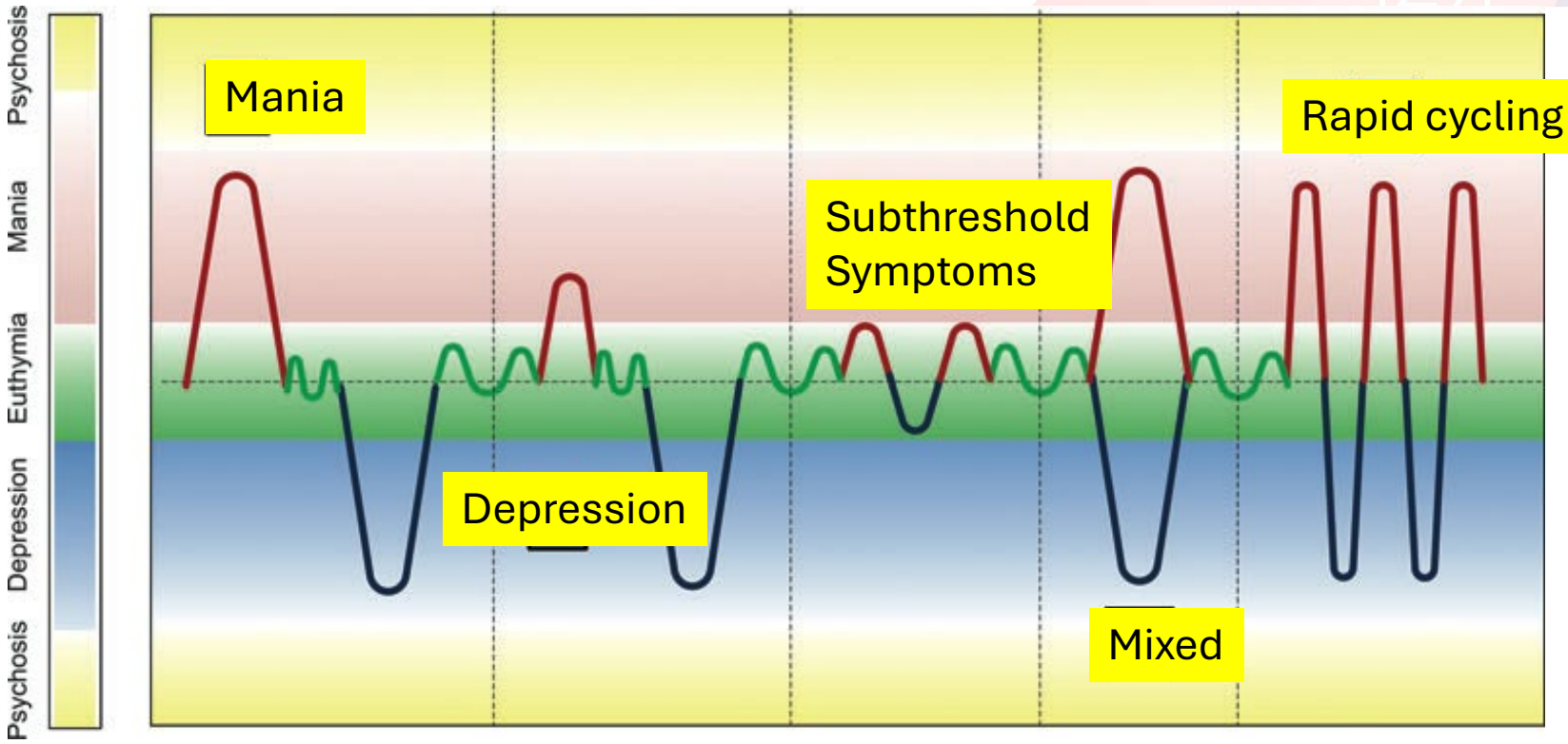
Learning Objectives

- Describe the clinical implications of changes in the conceptualization of bipolar disorder across DSM editions, including the specification of mixed features
- Assess and differentiate between BD-I, BD-II, MDD, and related disorders in accordance with current diagnostic criteria and guidelines
- Evaluate the limitations of conventional treatments and the optimal role of newer treatments for BD, based on their proposed MOAs, approved indications, and latest safety/efficacy data
- Implement strategies for personalized treatment selection/monitoring and shared decision-making to improve outcomes in BD

Introduction to Bipolar Disorder



Bipolar Disorder: 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.

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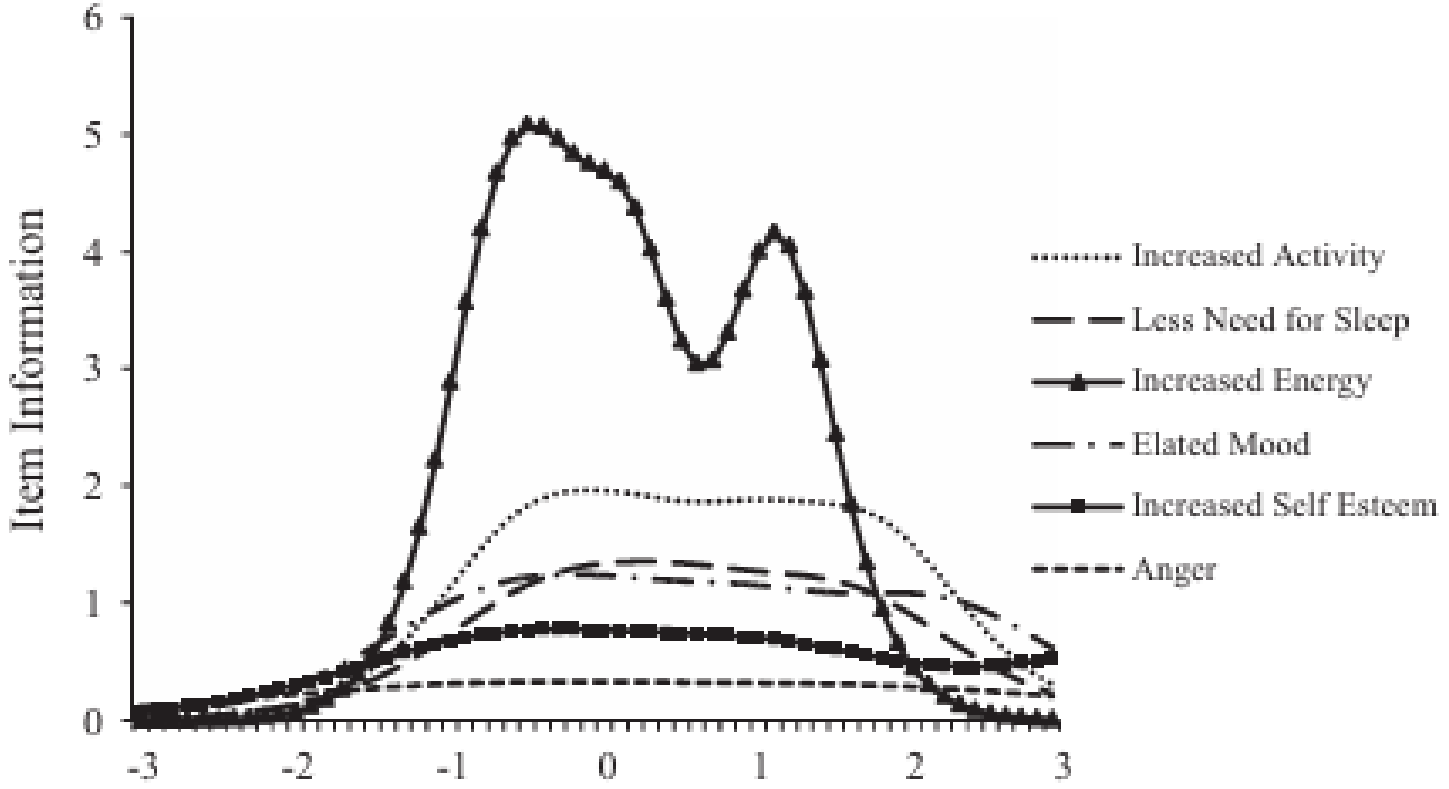
Increased Energy/Activity (Not Mood Changes) = The Core Feature of Mania



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

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Importance of Early Diagnosis and Treatment

Consequences of missed 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, 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

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.

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Assessment Challenges in Bipolar Disorder

Overlapping symptoms across other disorders

- Inattention
- Depression
- Poor impulse control
- Anxiety
- Sleep disruptions
- Psychosis
- Often hard to differentiate episode states from baseline traits (eg, personality disorder symptoms)
- Comorbidities (especially substance use disorders, anxiety disorders, ADHD, personality disorders)

ADHD = attention-deficit/hyperactivity disorder.

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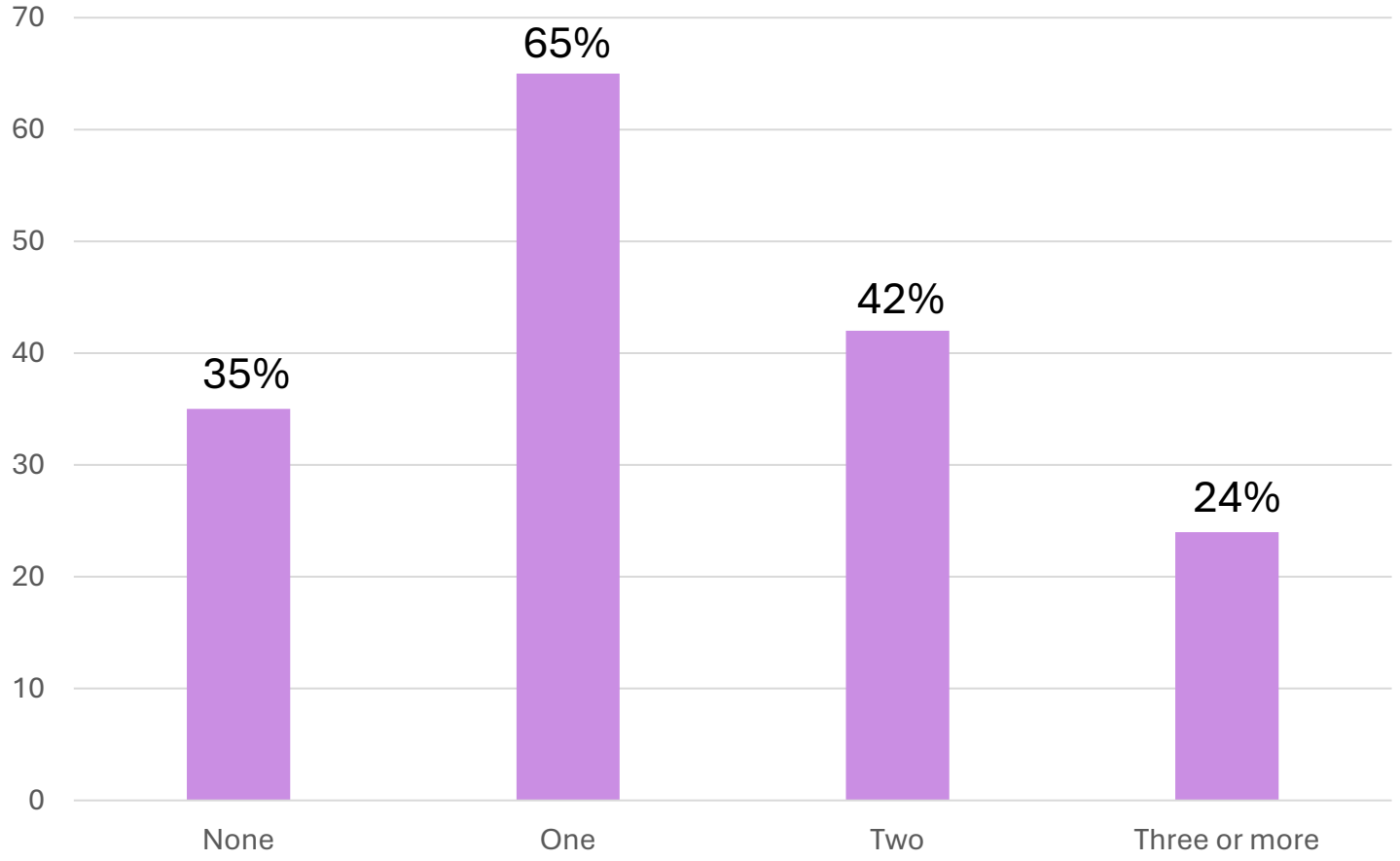
Most People with Bipolar Disorder Have Multiple Psychiatric Comorbidities

288 patients from the Stanley Foundation Bipolar Treatment Outcome Network



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

McElroy SL, et al. *Am J Psychiatry*. 2001;158(3):420-426.

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Missed or Misdiagnosis Is Common in Bipolar Disorder

600 surveys were analyzed of patients living with Bipolar Disorder

- 69% reported they were misdiagnosed
- Most frequent misdiagnosis – MDD
  - Other common misdiagnoses included: schizophrenia, anxiety disorder, personality disorder, and substance use disorder
- 1/3 waited more than 10 Years before an accurate diagnosis

MDD = major depressive disorder.

Hirschfeld RM, et al. *J Clin Psychiatry*. 2003;64(2):161-174.

Key Learning Points

- ✓ Bipolar Disorder presentation is variable, with defining feature of hypomania or mania
- ✓ Missed or misdiagnoses are common with unipolar depression being the most frequent
- ✓ Delayed or missed diagnosis leads to poorer psychosocial functioning, worsening disease course, eg, suicide attempts + reduced treatment response

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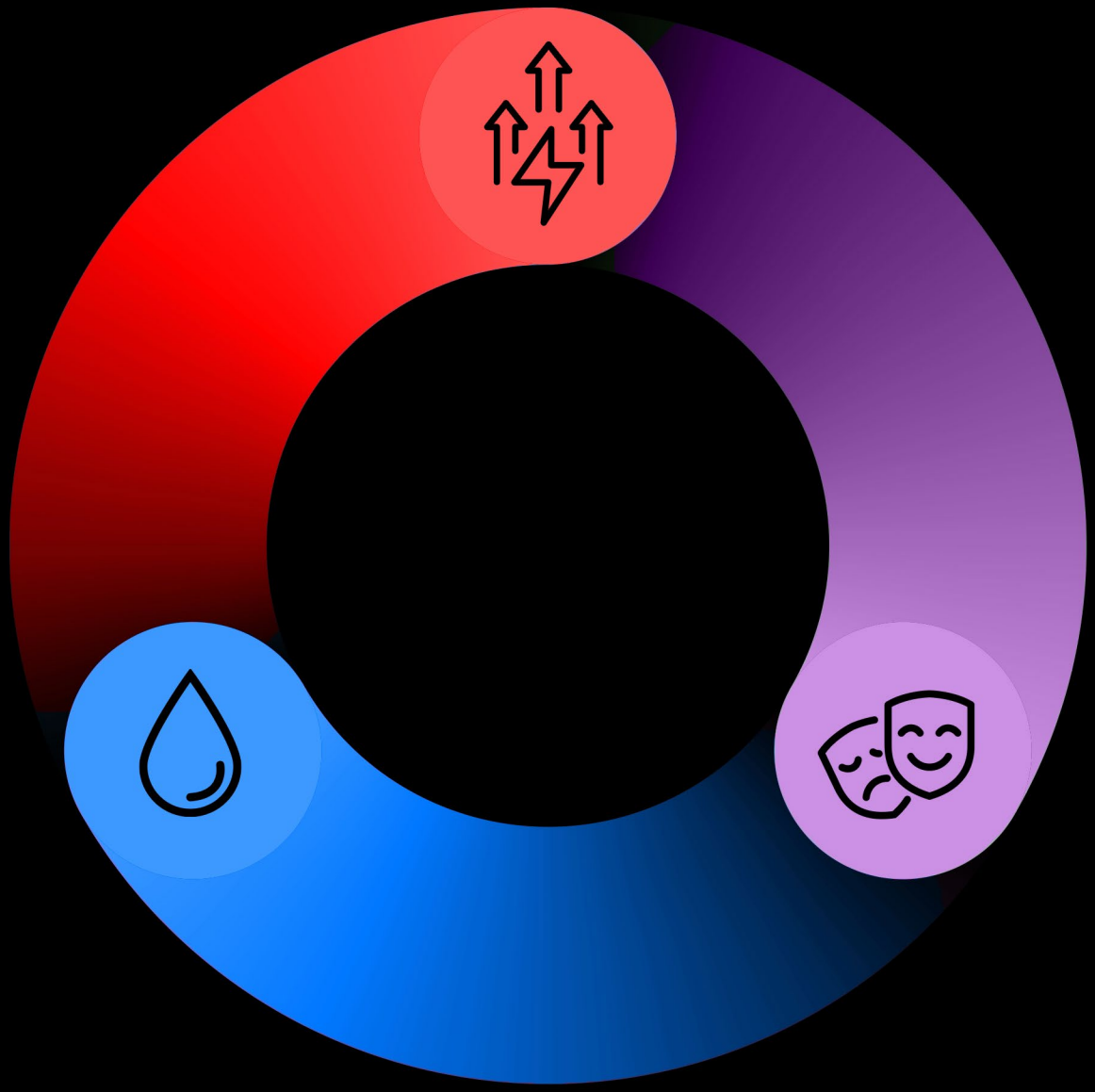
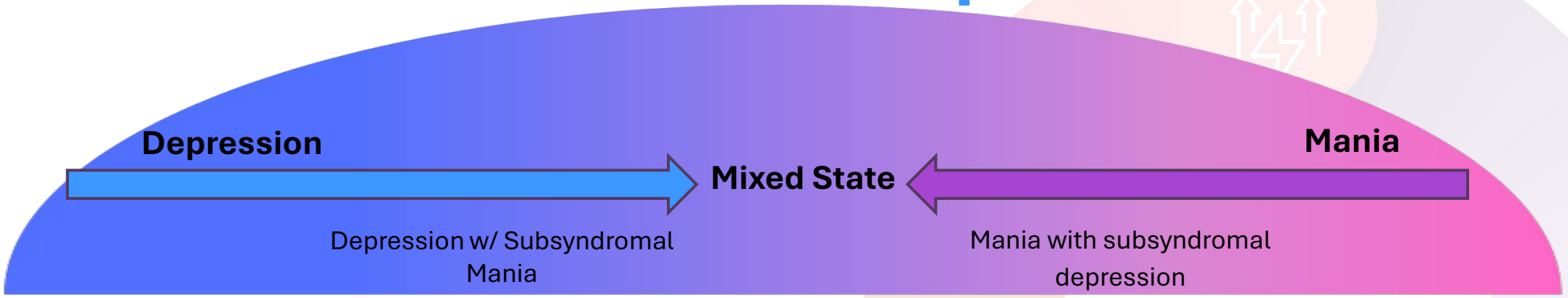
Assessing Bipolar Disorder Through a Mixed-Centric Perspective



Mood Disorder Spectrum



- Categorical classifications may be helpful in clinical practice, but evidence points to dimensional or "spectrum" view of mood disorder, considering other factors, eg, treatment response and family history of bipolar disorder

- Patients MDD w/ mixed features, or subsyndromal manic symptoms are more likely to convert to bipolar dx – 24% increase chance

dx = diagnosis.

Benazzi F. *Eur Psychiatry*. 2008;23(1):40-48. Hu J, et al. *Prim Care Companion CNS Disord*. 2014;16(2):PCC.13r01599. Sato T, et al. *J Affect Disord*. 2004;81(2):103-113. Vieta E, Valenti M. *J Affect Disord*. 2013;148(1):28-36.

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

American Psychiatric Association (APA). 1952, 1968, 1980, 1987, 1994, 2000, 2013. APA Publishing.

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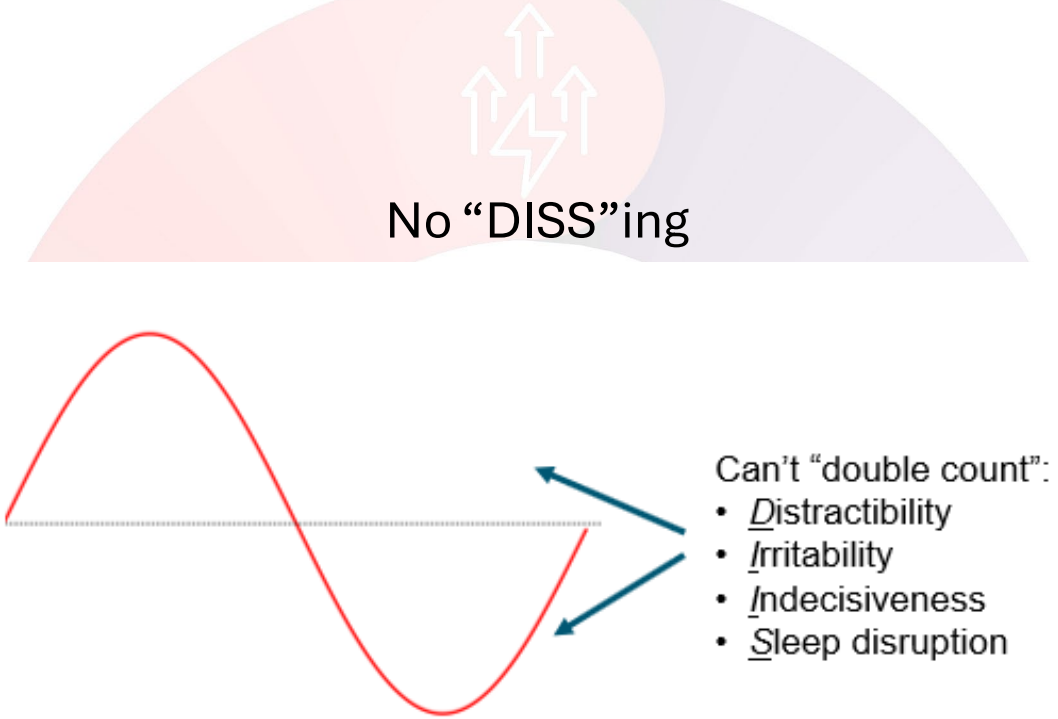
Bipolar Episodes with Mixed Features

- >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



American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed., Text Revision. APA Publishing; 2022.

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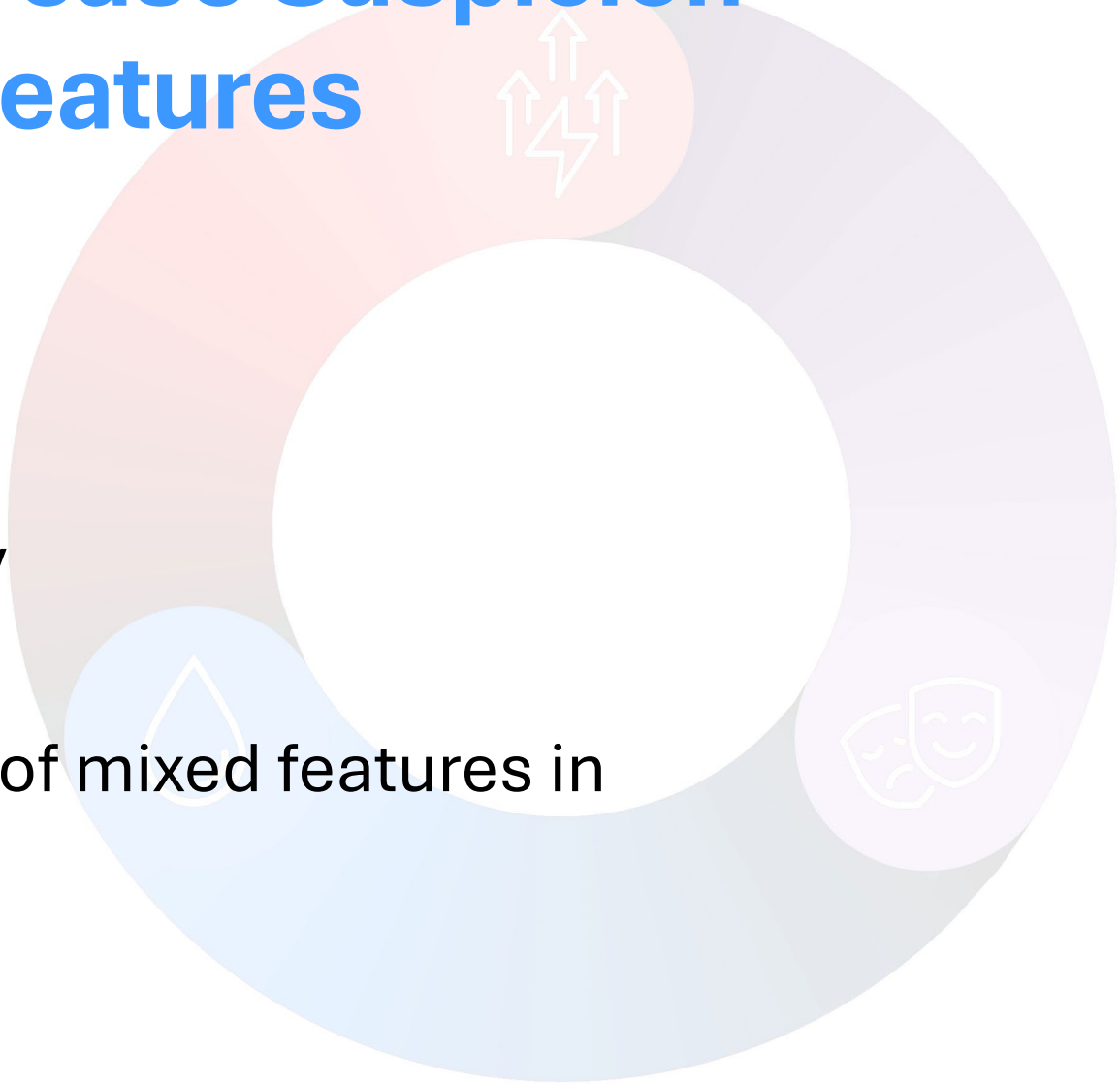
The “Four A’s” Increase Suspicion of Mixed Features

- Anxiety
- Agitation
- Anger/irritability
- Attentional disturbance-distractibility

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

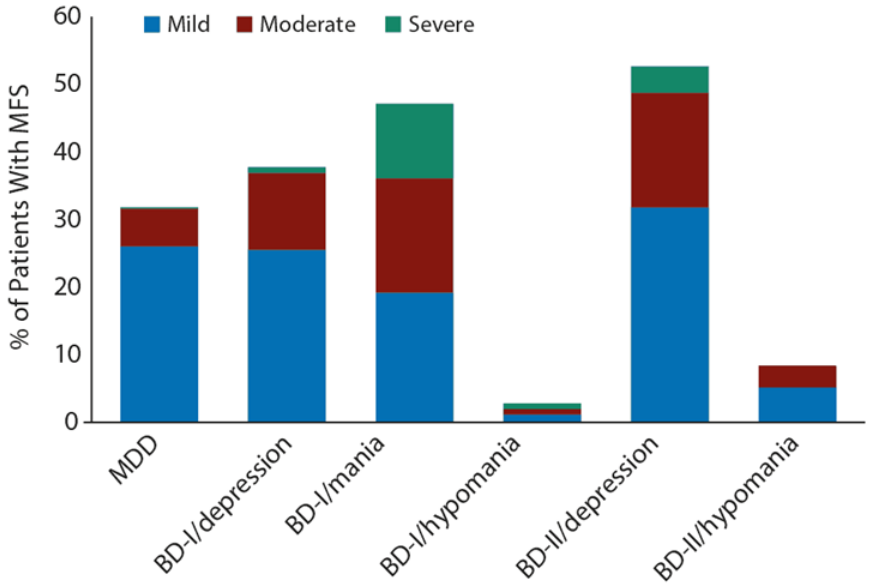


McIntyre RS, et al. *Lancet*. 2020;396(10265):1841-1856.

Mixed Episodes Across Bipolar Disorder

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

Figure 2. Prevalence of *DSM-5* Mixed Features Specifier in Adults With Major Depressive Disorder or Bipolar Disorder[a]



[a]Data from McIntyre et al.[13]
Abbreviations: BD = bipolar disorder; *DSM-5* = *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition; MDD = major depressive disorder, MFS = mixed features specifier.

- 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.

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Bipolar Disorder: Diagnostic Clues

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% 2nd or 3rd 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; quiz 217.

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Simple Screening – Ask Every Patient!

Any manic/hypomanic symptoms?

Family hx of Bipolar Disorder?

Obtain Collateral point of view, eg, family/significant other

hx = history.

Use of Screening Tools

- Not a proxy for diagnosis, but a starting point for more detailed assessment
- Mood Disorders Questionnaire (MDQ): Scores >7 are consistent with a diagnosis of bipolar disorder

Sensitivity	Specificity	PPV	NPV
61.3%	87.5%	58.0%	88.9%

Better sensitivity for BP I (66.3%) than BP II disorder (38.6%)

Mood Disorders Questionnaire

This is a test for bipolar disorder developed by a team of leading bipolar researchers.* The MDQ is widely known and used. You'll learn how to score this test when you're done, but remember, even a "positive" test result does not mean you have bipolar disorder. You'll see why when we come to scoring your results.

Here are the 3 sections. For section 1, write down the numbers 1-13 on a piece of paper and answer each question with a yes or no (or you can just print this page). Answer section 2 with a yes or no. Choose the answer in section 3 that best fits your situation and write it down.

1	**Has there ever been a period of time when you were not your usual self (while not on drugs or alcohol) and -**	Yes	No
	- you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	Yes	No
	- you were so irritable that you shouted at people or started fights or arguments?	Yes	No
	- you felt much more self-confident than usual?	Yes	No
	- you got much less sleep than usual and found you didn't really miss it? *	Yes	No
	- you were much more talkative or spoke faster than usual?	Yes	No
	- thoughts raced through your head or you couldn't slow your mind down?	Yes	No
	- you were so easily distracted by things around you that you had trouble concentrating or staying on track?	Yes	No
	- you had much more energy than usual?	Yes	No
	- you were much more active or did many more things than usual?	Yes	No
	- you were much more social or outgoing than usual? For example, you telephoned friends in the middle of the night.	Yes	No
	- you were much more interested in sex than usual?	Yes	No
	- you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	Yes	No
	- spending money got you or your family into trouble?	Yes	No
2	If you checked YES to more than one of the above, have several of these ever happened during the *same period of time*?	Yes	No
3	How much of a *problem* did any of these cause you -- like being unable to work; having family, money, or legal troubles; or getting into arguments or fights?		
	No Problem Minor Problem Moderate Problem Serious Problem		

MDQ = Mood Disorders Questionnaire; PPV = positive predictive value; NPV = negative predictive value; BP I = bipolar I disorder; BP II = bipolar II disorder.

Zimmerman M. *J Affect Disord*. 2021;292:708-713. Zimmerman M, Galione JN. *Harv Rev Psychiatry*. 2011;19(5):219-228.

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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 also has not been studied for its ability to discriminate bipolar disorder from other conditions

RMS = Rapid Mood Screener.

McIntyre RS, et al. *Curr Med Res Opin*. 2021;37:135-144.

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Tools to Assess Mixed Features

Bipolar Depression Rating Scale (BDRS)

- Clinician administered of **current** symptoms

Mini International Neuropsychiatric Interview (MINI)

- Patient self report assessing **current** hypo(manic) symptoms

Clinically Useful Depression Outcome Scale with DSM-5 Mixed (CUDOS-M)

- Patient self report assessing **current** (hypo)manic symptoms

Hypomania Checklist (HCL-32)

- Patient self report screening for **lifetime** (hypo)manic symptoms

BDRS = Bipolar Depression Rating Scale; MINI = Mini International Neuropsychiatric Interview; CUDOS-M = Clinically Useful Depression Outcome Scale with DSM-5 Mixed; HCL = Hypomania Checklist.

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 Sx **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)**.

Sx = symptom; MDE = major depressive episode.

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

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Depressive Episodes in Bipolar Disorder

- Depressive episodes are often the initial presentation of Bipolar Disorder
- Depressive symptoms are the most common reason why patients visit an HCP

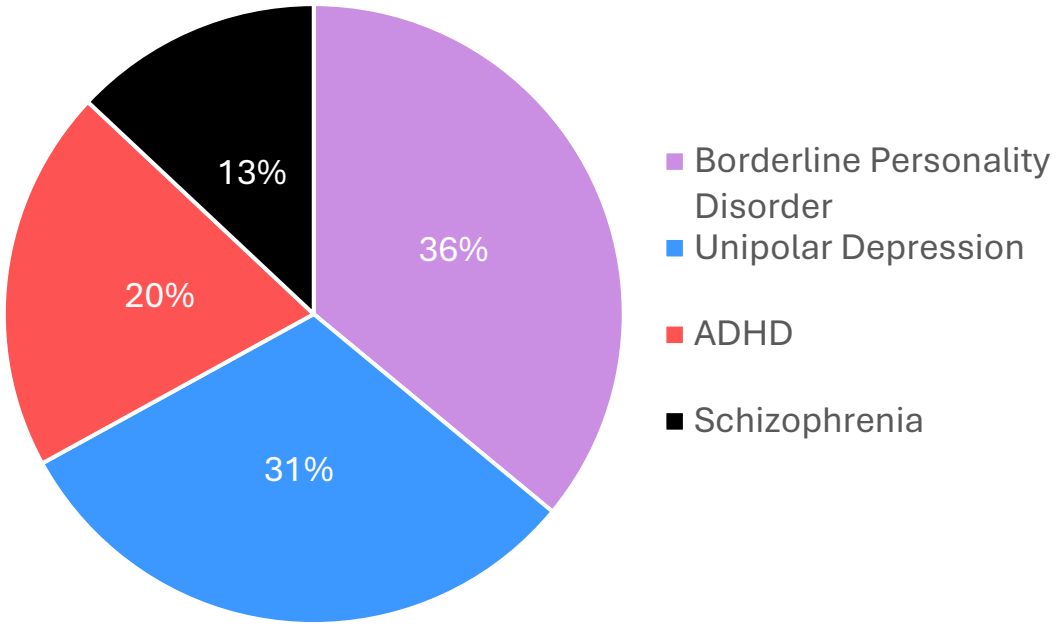
- A 2015 study reported the prevalence of mood types among bipolar I patients experiencing a current mood episode (N=225)
  - 75% of patients were experiencing a bipolar I depressive episode with or without concurrent manic symptoms
  - 25% of patients were experiencing a bipolar I manic/hypomanic episode 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.

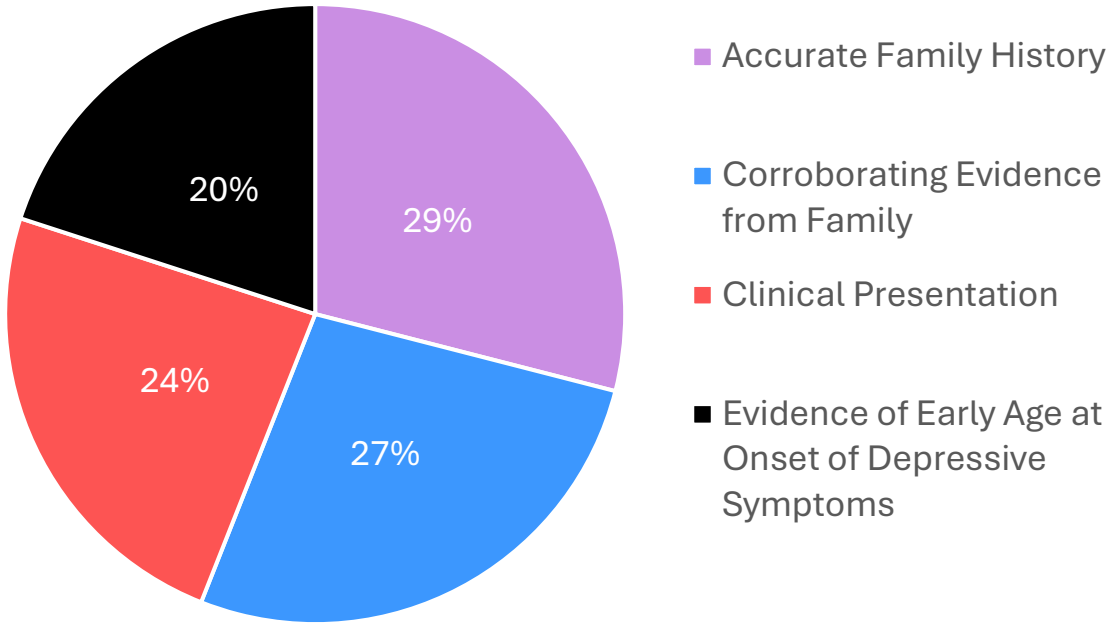
Differentiating Bipolar Disorder from MDD

Disorders Most Difficult to Differentiate From Bipolar Disorder



N = 154

Best Predictors for Achieving Differential Diagnosis between MDD vs BD



N = 168

McIntyre RS, et al. *J Clin Psychiatry*. 2019;80(3):ot18043ah2.

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Key Learning Points

- ✓ Mixed features can be present across mood disorders and can result in more polypharmacy, poorer outcomes, and prognosis
- ✓ 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!

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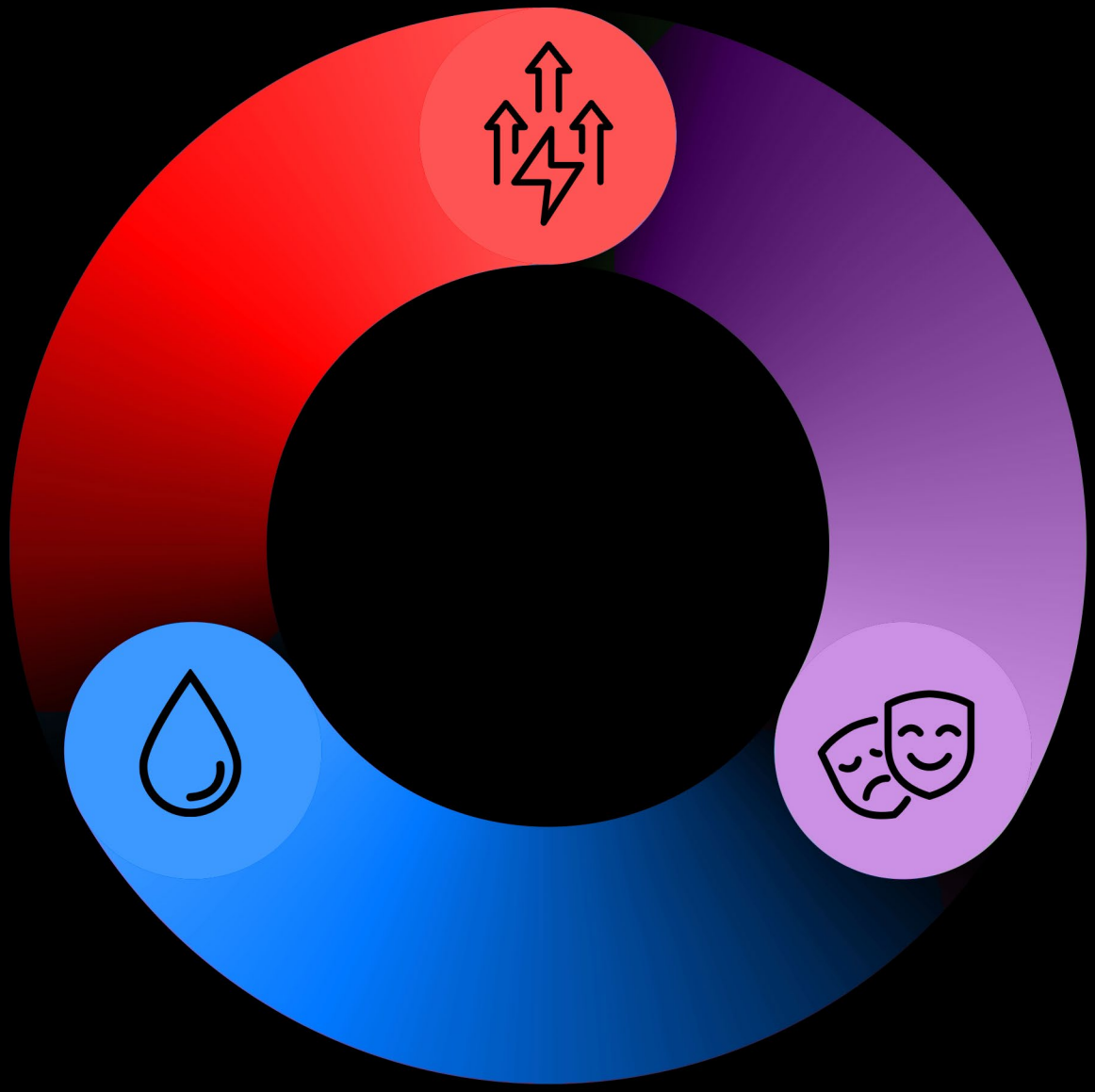
Bringing Treatment of BD Full Circle



Understanding Limitations in the Landscape of Treatment Options in Bipolar Disorder

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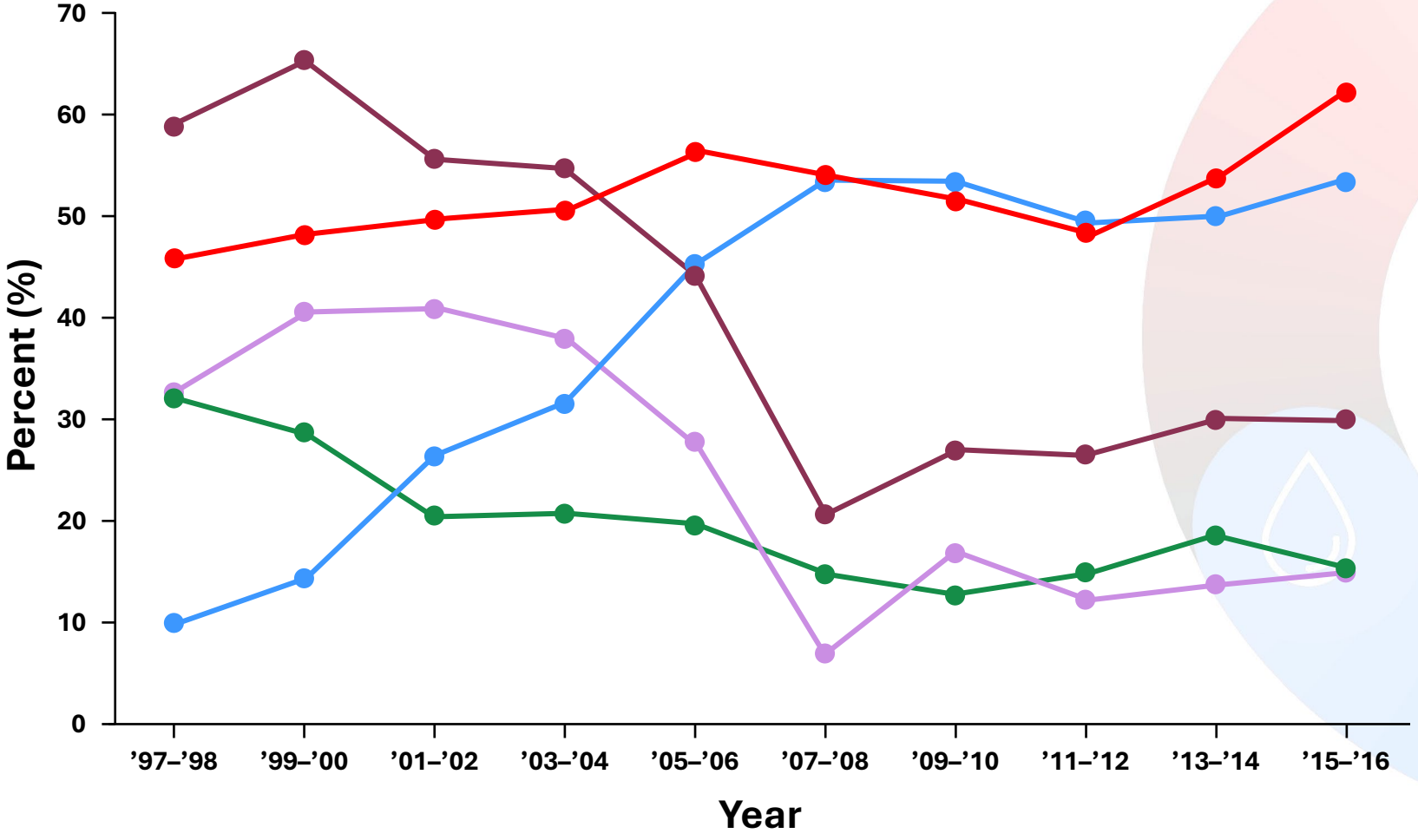
20-Year Trends in the Outpatient Treatment of Bipolar Disorder



- SGAs
- Any Mood Stabilizer
- Lithium
- Non-lithium Antiepileptic Mood Stabilizers
- Antidepressants

Comparing 2015-16 to 1997-98

Lithium scripts fell by almost 50% while Antipsychotic prescriptions nearly tripled

Hot Take!

Antidepressants were prescribed for people with bipolar disorder almost twice as often as lithium in 2015-2016

SGA = second-generation antipsychotic.

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

Mood Stabilizers

Agent	Spectrum of Efficacy	Limitations
Lithium	Mania > depression Pure mania > mixed states Prevention > acute efficacy Reduces suicidal behavior	Renal, thyroid end-organ effects Narrow therapeutic index Weight gain
Valproate	Mania > depression Manic or mixed states Oral loading, wide therapeutic index	Teratogenicity, PCOS Thrombocytopenia No (+) maintenance data
Carbamazepine	Mania > depression Manic or mixed states	Hepatic enzyme induction Leukopenia No maintenance data
Lamotrigine	Prevention of depression, not mania More data in BP I than BP II	Unproven acute efficacy Slow titration to minimize cutaneous reactions

PCOS = polycystic ovary syndrome.

Ghaemi SN. *Clinical Psychopharmacology: Principles and Practice*. Oxford University Press; 2019. Altshuler L, et al. *Am J Psychiatry*. 2003;160(7):1252-1262. El-Mallakh RS, et al. *J Affect Disord*. 2015;184:318-321. Pacchiarotti I, et al. *Am J Psychiatry*. 2013;170(11):1249-62. Kane JM. *J Clin Psychiatry*. 2004;65 Suppl 9:16-20. Correll CU, et al. *JAMA Psychiatry*. 2014;71(12):1350-1363. Gigante AD, et al. *CNS Drugs*. 2012;26(5):403-420. Goldberg JF. *J Clin Psychiatry*. 2024;85(1):23ac15219.

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Evidence from Controlled Trials in Mixed Depressive Episodes of Bipolar Disorder

Medication	Diagnosis	Definition of Mixed	With Mixed Features	Without Mixed Features
Olanzapine OFC	Bipolar I	≥ 2 on 2 YMRS items	Olanzapine NNT=10 OFC NNT=4	Olanzapine NNT=8 OFC NNT=5
Asenapine Olanzapine	Bipolar I	DSM-IV manic	Asenapine significantly >placebo, not olanzapine	n.d.
Lurasidone	Bipolar I	YMRS ≥ 4	NNT=6 ES=0.48	NNT=4 ES=0.48
Cariprazine	Bipolar I	YMRS ≥ 4	1.5 mg NNT=12 3.0 mg NNT=9	1.5 mg NNT=9 3.0 mg NNT=12
Lumateperone	Bipolar I & II	DSM-V Mixed Features	ES=0.52	ES=0.53

n.d. = not determined; ES = effect size; NNT = number needed to treat; OFC = olanzapine-fluoxetine combination; YMRS = Young Mania Rating Scale.

Benazzi F, et al. *J Clinical Psychiatry*. 2009;70:1424. Berk M, et al. *J Clin Psychiatry*. 2015;76:728. McIntyre RS, et al. *J Clin Psychiatry*. 2015;76:398. McIntyre RS, et al. *CNS Spectr*. 2020;25(4):502-510. McIntyre RS, et al. *J Clin Psychiatry*. 2023;84:22m14739.

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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
Brexpiprazole	None	2 (-) trials in acute mania
Cariprazine	Bimodal acute mania and depression efficacy	(-) maintenance data
Iloperidone	Acute mania	No maintenance data
Lumateperone	Efficacy in BD-I or BD-II depression	No data in mania or maintenance
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	Bimodal acute 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; VPA = valproic acid.

Goldberg JF, et al. *Practical Psychopharmacology*. Cambridge University Press; 2021.

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Olanzapine-Samidorphan

Efficacy of Olanzapine Monotherapy in Acute Manic and Mixed Episodes of Bipolar I Disorder

3-Week Acute Pivotal Study

Mean change in YMRS vs placebo = -5.4 (*P*=0.02)

Response rate 49% vs 24%; **NNT=4**

Mean weight change

olanzapine: +3.63 lb
placebo: -0.97 lb

Also 2 positive studies adjunct to Li/VPA

4-Week Acute Pivotal Study

Mean change in YMRS vs placebo = -6.7 (*P*<0.001)

Response rate 65% vs 43%; **NNT=5**

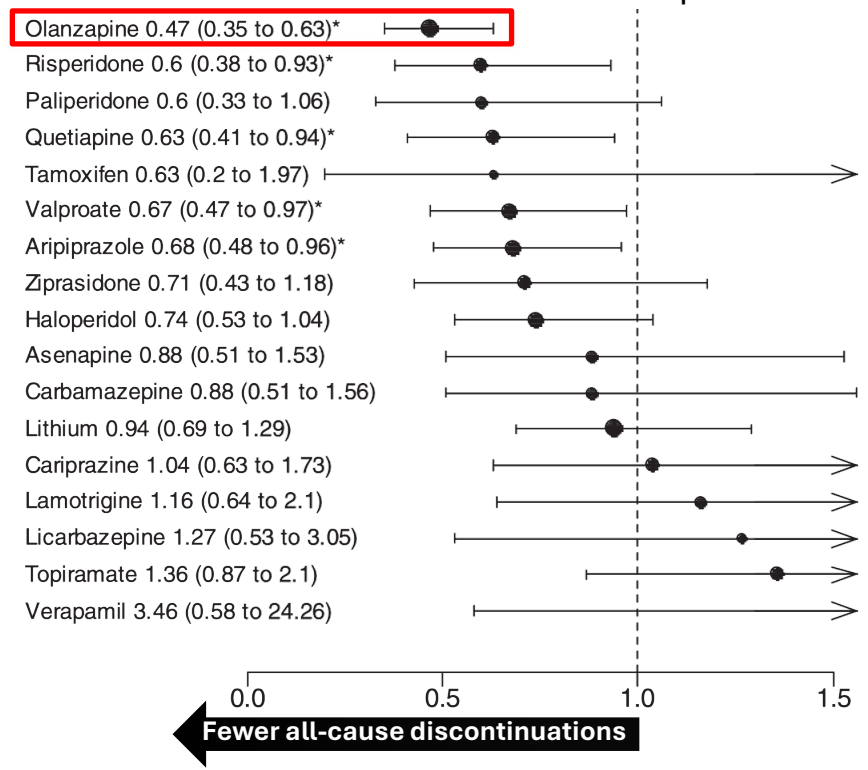
Mean weight change

olanzapine: +4.86 lb
placebo: +0.99 lb

Weight gain, somnolence, dry mouth, and dizziness were common adverse events in both trials;

Pooled D/C due to AE: olanzapine=2% and placebo=2%

Network Meta-Analysis of All-Cause Discontinuation in Acute Manic/Mixed Episodes



Olanzapine monotherapy for acute manic and mixed episodes has efficacy and effectiveness

Hot Take!

D/C = discontinuation; AE = adverse event.

Tohen M, et al. *Am J Psych*. 1999;156(5):702-709. Tohen M, et al. *Arch Gen Psych*. 2000;57(9):841-849. Yildiz, A, et al. *Psychol Med*. 2015;45(2):299-317.

Olanzapine Monotherapy in Maintenance of Bipolar I

Responders to 6-12 weeks of open-label olanzapine were randomized to placebo or continued treatment

Median time to relapse into any mood episode for olanzapine vs placebo: 174 days vs 22 days

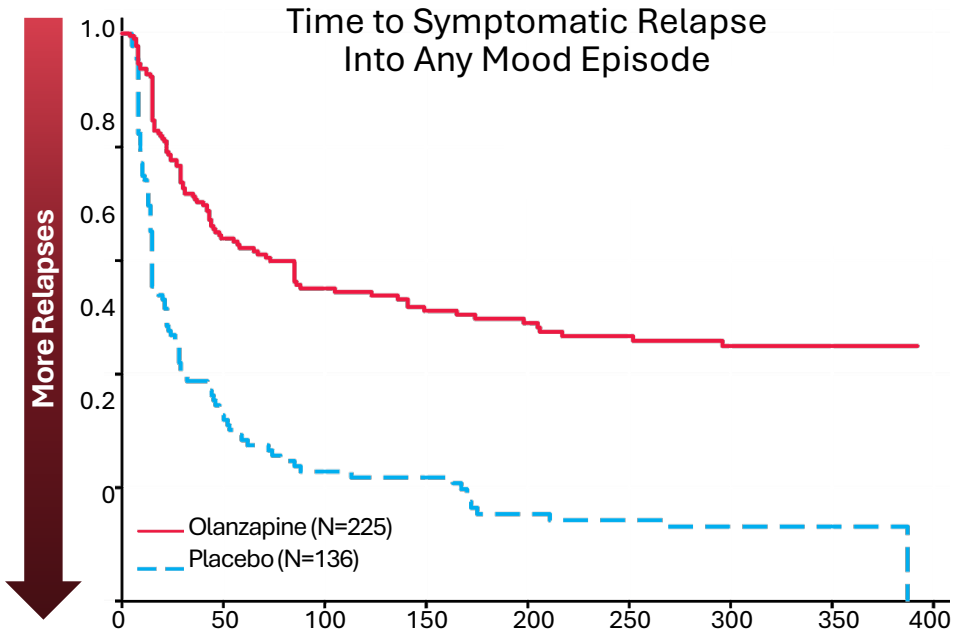
Mean dose 12.5 mg

NNT=3 for relapse prevention

Mean weight change in open-label stabilization: +6.6 lb

In double-blind maintenance: olanzapine +2.2 lb, placebo = -4.4 lb

Discontinuation due to adverse events for those taking olanzapine = 7.6%

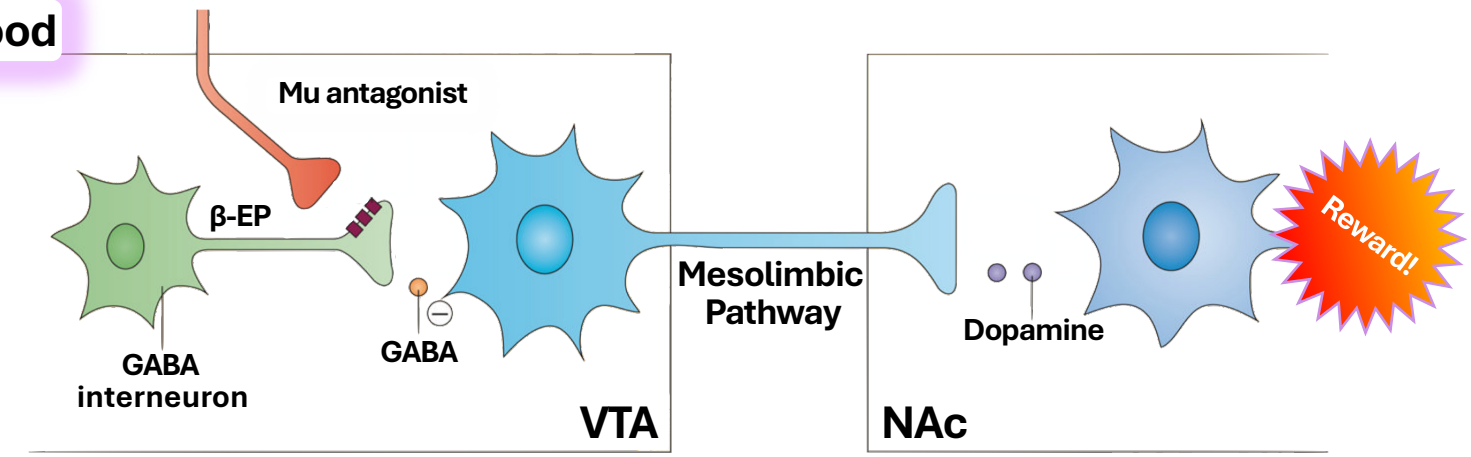


Fun Fact!

Olanzapine has efficacy as monotherapy to prevent relapse into manic, depressive, and mixed episodes

Tohen M, et al. *Am J Psychiatry*. 2006;163(2):247-256. Yatham LN, et al. *Bipolar Disorders*. 2018;20(2):97-170.

The Role of Mu Opioid Receptor Antagonism in Excessive Caloric Consumption



Blocking mu-opioid receptors in the VTA inhibits dopamine release in the NAc, reducing the excessive reward signaling of hedonic eating for highly rewarding foods.

Effects of Opioid Receptor Knockouts in Mouse Models of Metabolism

Mu Knockout Mice
- Reduced weight gain/fat mass despite a high-energy diet
- Protective against insulin resistance in aging mice fed a high-fat diet

Kappa Knockout Mice
- Reduced weight gain/fat mass despite a high-energy diet
- Elevated levels of spontaneous locomotor activity, no increase in thermogenesis

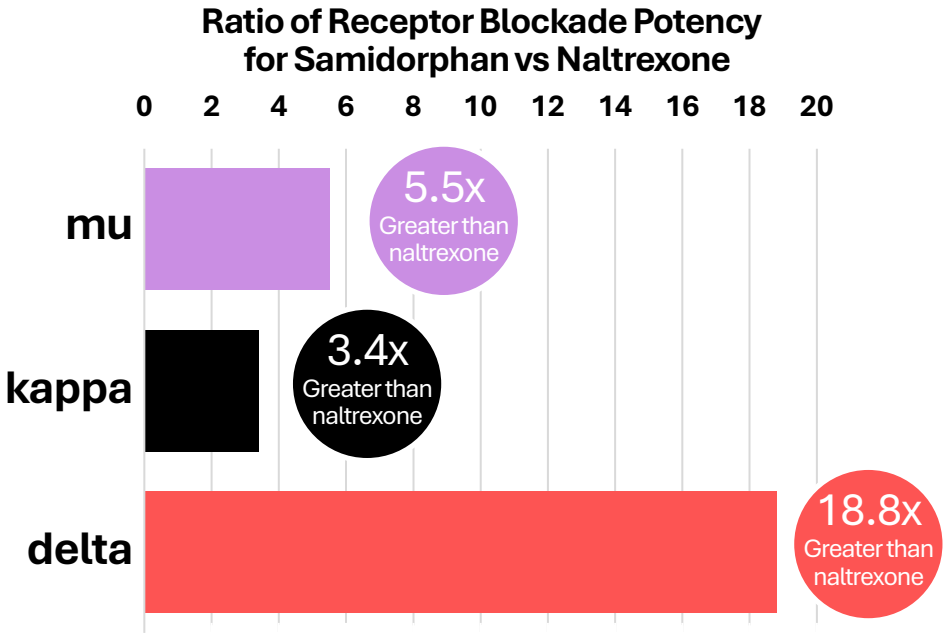
Delta Knockout Mice
- Reduced weight gain per Calorie consumed
- Greater energy expenditure
- Greater thermogenesis in brown adipose tissue

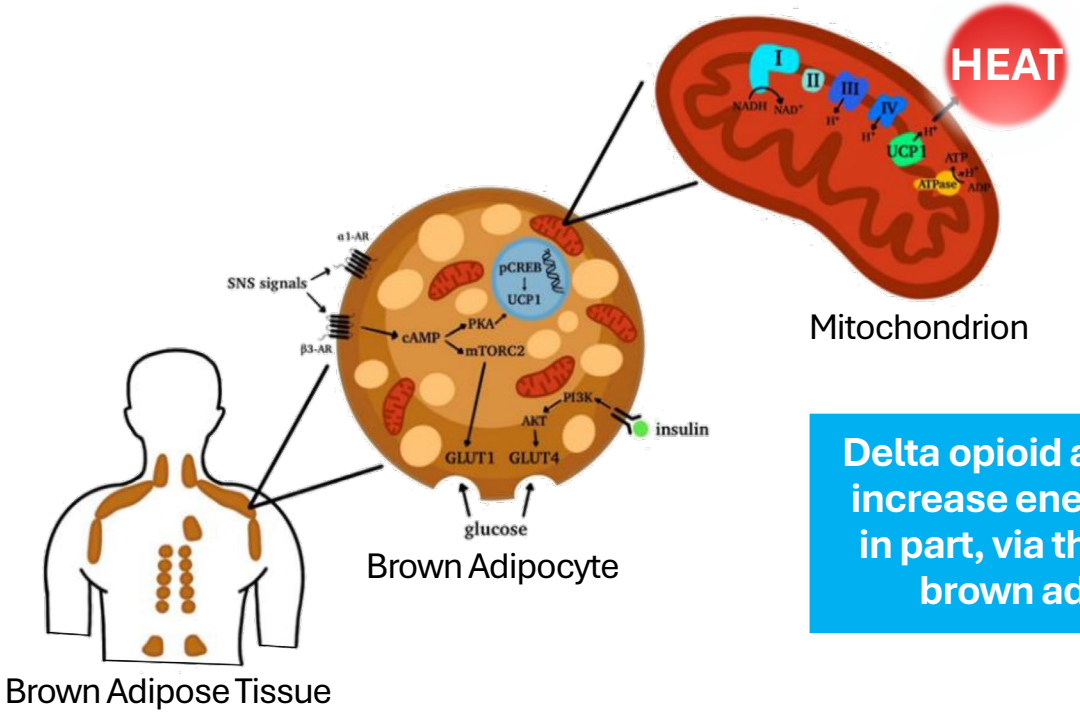
VTA = ventral tegmental area; NAc = nucleus accumbens; β-EP = β-endorphins; GABA = gamma-aminobutyric acid.

McIntyre RS, et al. *CNS Spectrums*. 2023;28(3):288-299. Glass MJ, et al. *Neuropeptides*. 1999;33(5):360-368. Czyzyk TA, et al. *The FASEB Journal*. 2012;26(8):3483. Heilig M, et al. *Nature Reviews Neuroscience*. 201112(11):670-684.

Opioid Receptor Antagonists: Different Medications, Different Results

	Naltrexone	Samidorphan
Half-Life	4 hours	7-9 hours
Oral Bioavailability	5%-40%	69%





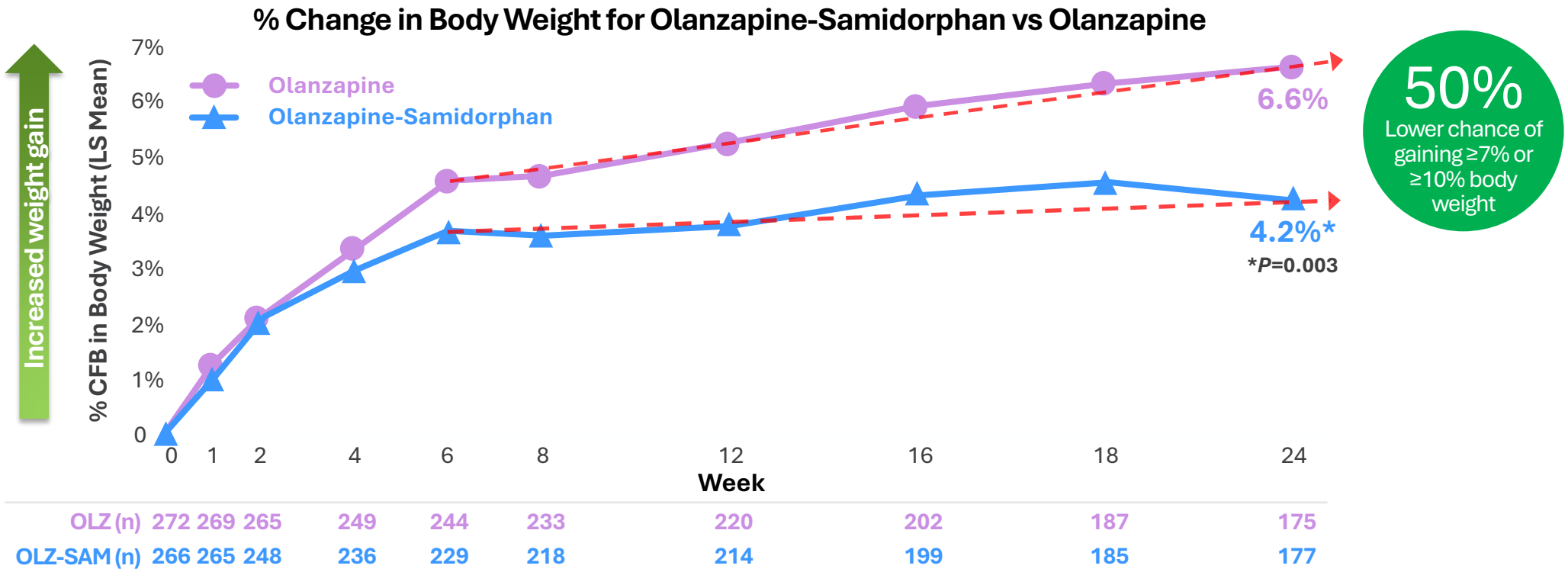
Delta opioid antagonism may increase energy expenditure, in part, via thermogenesis in brown adipose tissue

Hot Take!

Samidorphan and naltrexone have distinct pharmacokinetic and pharmacodynamic properties and are not interchangeable

Tan LA, et al. *Neuropsychiatric Disease and Treatment*. 2022;18:2497-2506. McIntyre RS, et al. *CNS Spectrums*. 2023;28(3):288-299.

OLZ-SAM Had Significantly Less Weight Gain vs OLZ In a 6-mo Head-to-Head Study in Schizophrenia



50%
Lower chance of gaining ≥7% or ≥10% body weight

A previous study demonstrated that samidorphan did not impair the efficacy of olanzapine in schizophrenia

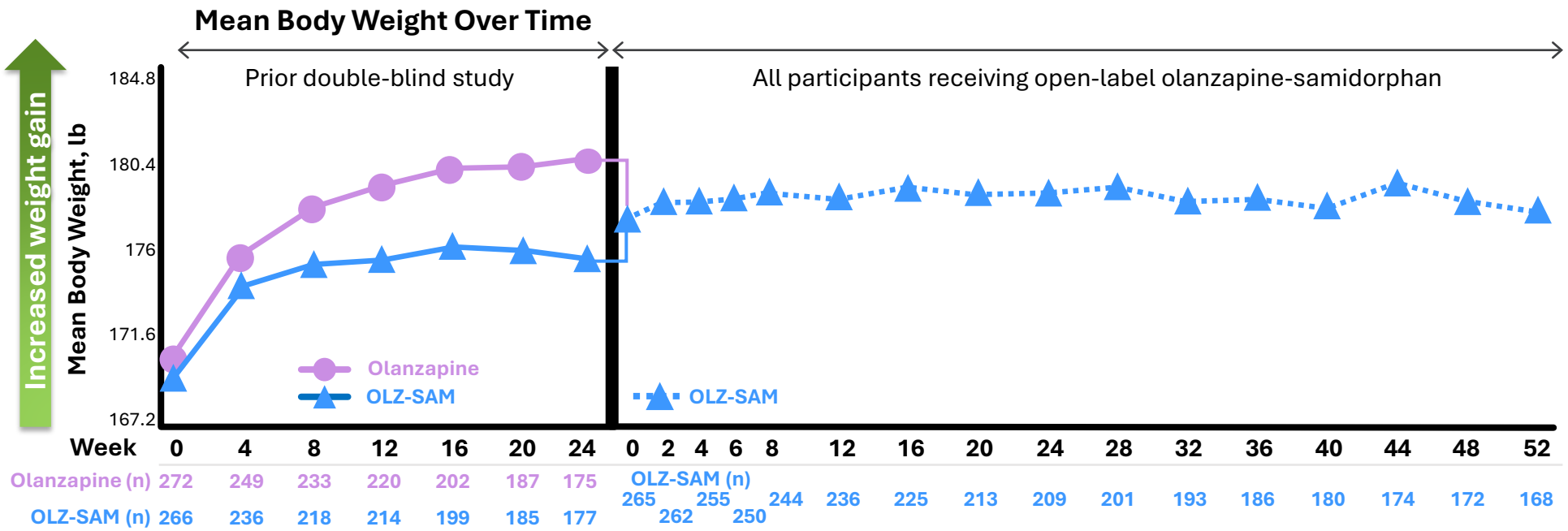
Hot Take!

Olanzapine-samidorphan's mean weight change appears to plateau after ~6 weeks, but olanzapine's does not

OLZ = olanzapine; SAM = samidorphan; CFB = change from baseline; LS = least squares.

Correll CU, et al. *Am J Psychiatry*. 2020;177(12):1168-1178. Potkin SG, et al. *The Journal of Clinical Psychiatry*. 2020;81(2):5960.

OLZ-SAM Weight Remained Stable in a 1-Year Open-Label Study in Schizophrenia



Over the 52-wk open-label period

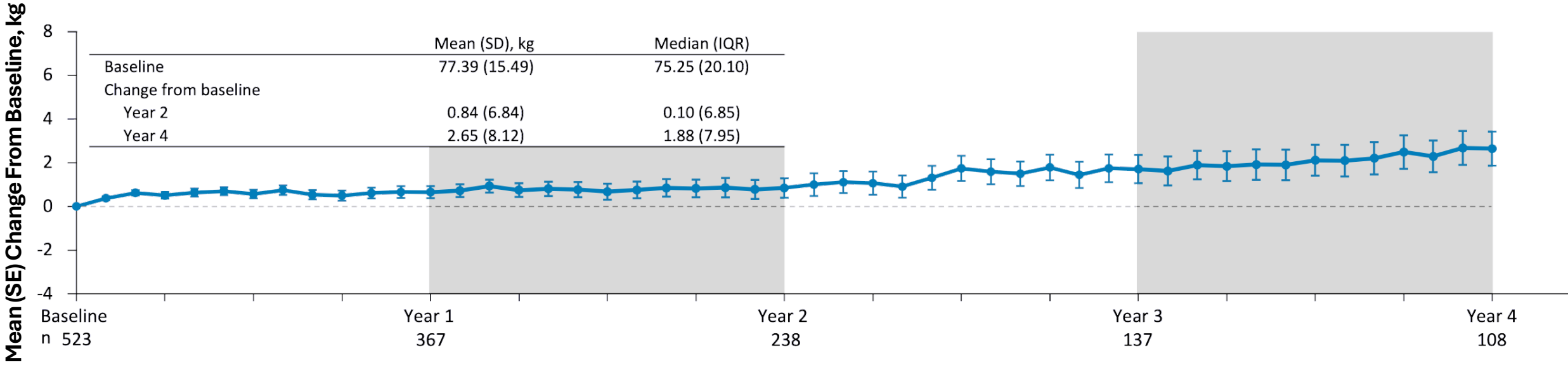
Mean weight and metabolics remained stable

≥7% weight gain: 21.5%
≥7% weight loss: 21.1%

Kahn RS, et al. *Schizophr Res*. 2021;232:45-53. Correll CU, et al. *Am J Psych*. 2020;177(12):1168-1178. Potkin SG, et al. *J Clin Psych*. 2020;81(2):61-64.

Small Weight Changes with Up to 4 Years of Additional Open-Label OLZ-SAM Treatment

Further long-term data from 523 participants with bipolar I or schizophrenia with up to 4 years of additional open-label treatment with olanzapine-samidorphan



Long-term treatment was associated with minimal changes in lipid/glycemic parameters and weight (mean CFB +3.2 lb)

Symptoms remained stable as measured by CGI-S (mean CFB -0.28)

35.9% completed the 4-year treatment period

CGI-S = Clinical Global Impression – Severity; SE = standard error; SD = standard deviation; IQR = interquartile range.

Ballon JS, et al. Long-Term Safety and Efficacy of Olanzapine and Samidorphan: Results of a 4-Year Open-Label Study. Poster Presented at the 37th Psych Congress Annual Meeting, October 29-November 2, 2024, Boston, MA.

Key Learning Points

- ✓ Olanzapine has demonstrated efficacy and effectiveness in acute manic/mixed episodes
- ✓ Olanzapine has efficacy as monotherapy to prevent relapse into manic, depressive, and mixed episodes in patients with an index mixed episode
- ✓ Adding samidorphan to olanzapine mitigates its weight gain, but not its efficacy in schizophrenia or bipolar I disorder

Cariprazine

Cariprazine Receptor Profile

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

Intrinsic Activity (% Agonism of Dopamine)

	Ari	Brex	Car
D_2	60%	45%	30%
D_3	28%	15%	**71%**

Ari = aripiprazole; Brex = brexpiprazole; Car = cariprazine.

Citrome L. *Int J Clin Pract*. 2015;69(11):1211-1220. Kiss B, et al. *Drug Design, Development and Therapy*. 2019;13:3229-3248. Mohr P, et al. *Front Psychiatry*. 2022;12:781946.

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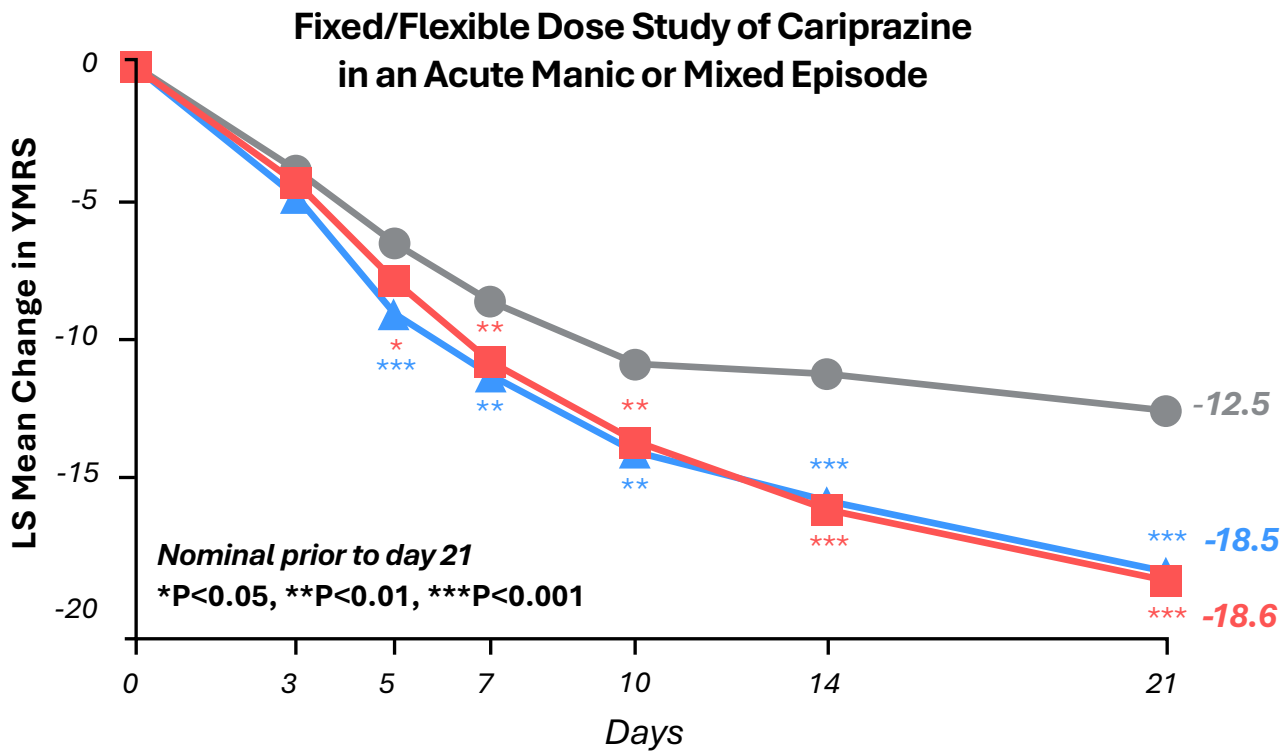
Efficacy of Cariprazine Monotherapy in Acute Manic or Mixed Episodes of Bipolar I Disorder



LS Mean Difference in YMRS vs Placebo at Primary Endpoint

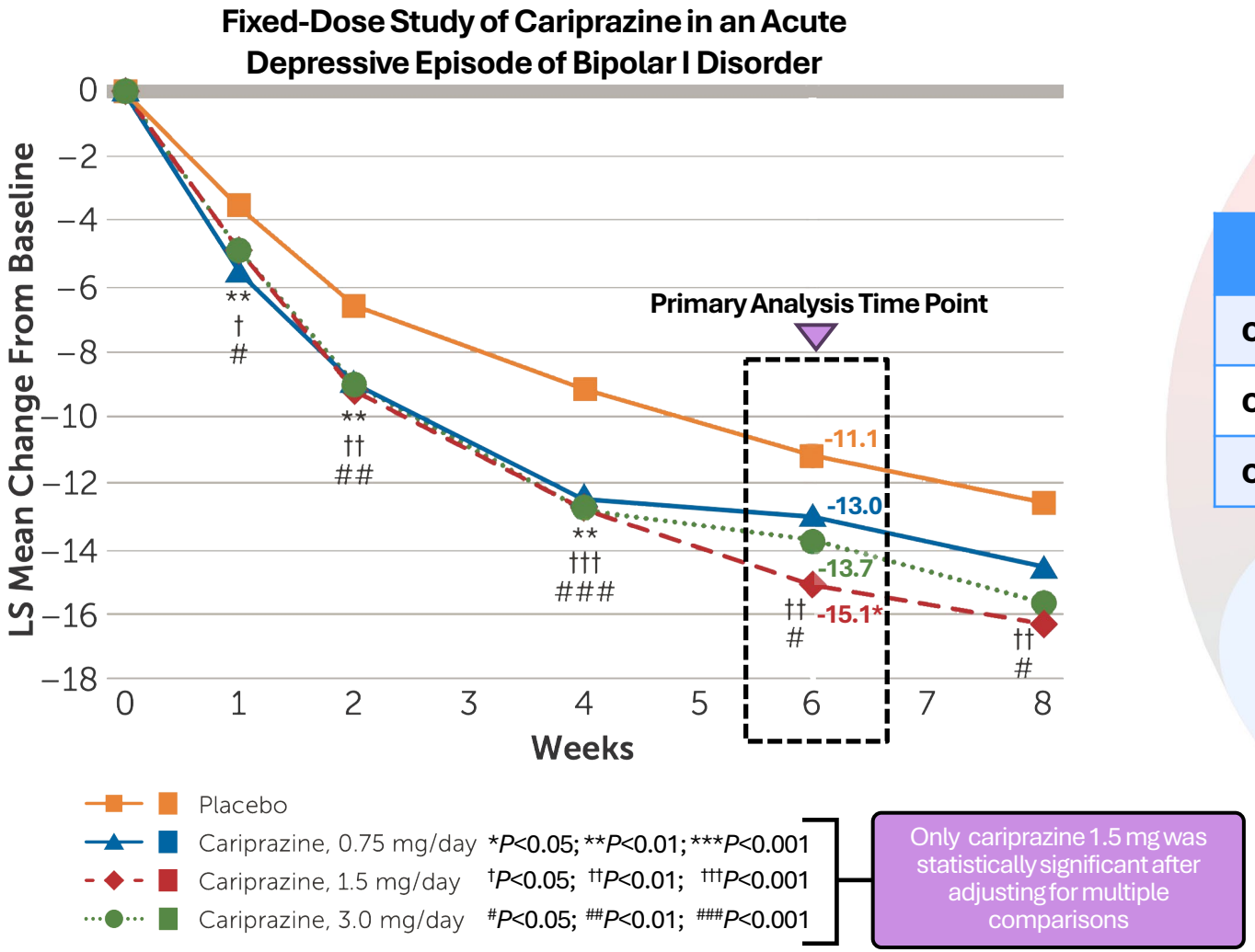
	Study 1	Study 2	Study 3
cariprazine 3-12 mg/d	*n/a*	-6.1***	-4.3***
cariprazine 3-6 mg/d	-6.1***	*n/a*	*n/a*
cariprazine 6-9 mg/d	-5.9***	*n/a*	*n/a*

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.

JG

Calabrese JR, et al. *J Clin Psychiatry*. 2015;76(3):284-292. Durgam S, et al. *Bipolar Disord*. 2015;17(1):63-75. Sachs GS, et al. *J Affect Disord*. 2015;174:296-302.

Phase 3 Studies of Cariprazine in Bipolar I Depression



Only cariprazine 1.5 mg was statistically significant after adjusting for multiple comparisons

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

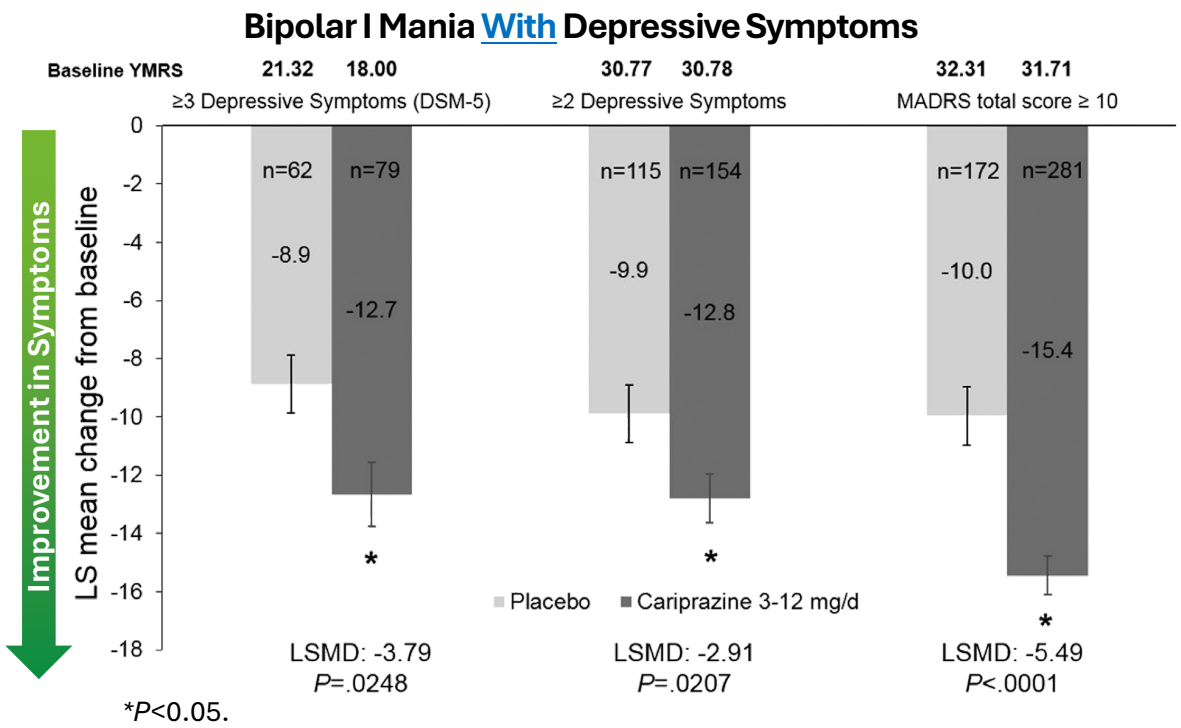
Titration was slower in the Bipolar I Depression studies:
3 mg arms did not reach that dose until after 2 weeks of treatment.

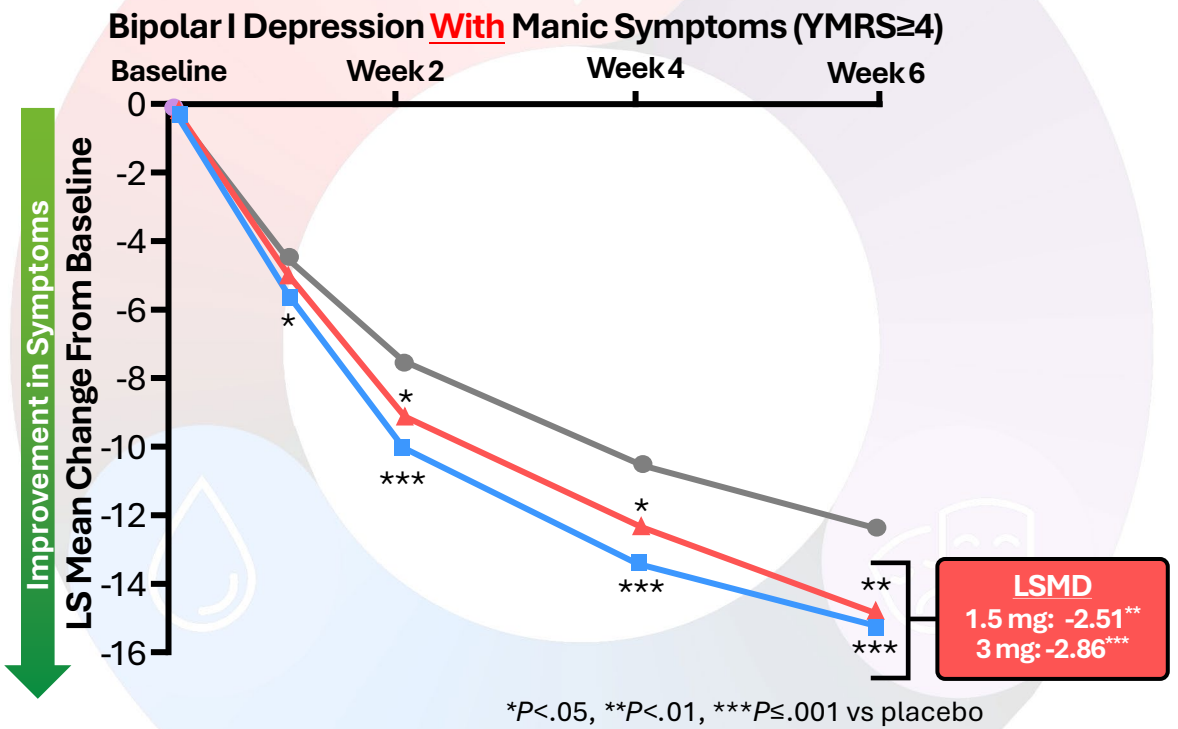
JG

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.

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





LSMD = least squares mean difference.

McIntyre RS, et al. *J Affect Disord*. 2019;257:600-606. McIntyre RS, et al. *CNS Spectr*. 2020;25(4):502-510.

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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.

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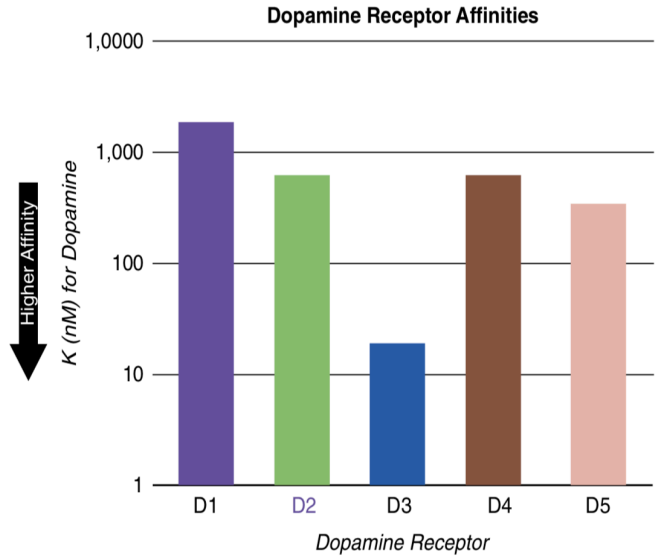
Cariprazine Pharmacokinetics and D_3 Pharmacology

Dopamine has a higher affinity for D_3 than any other dopamine receptor

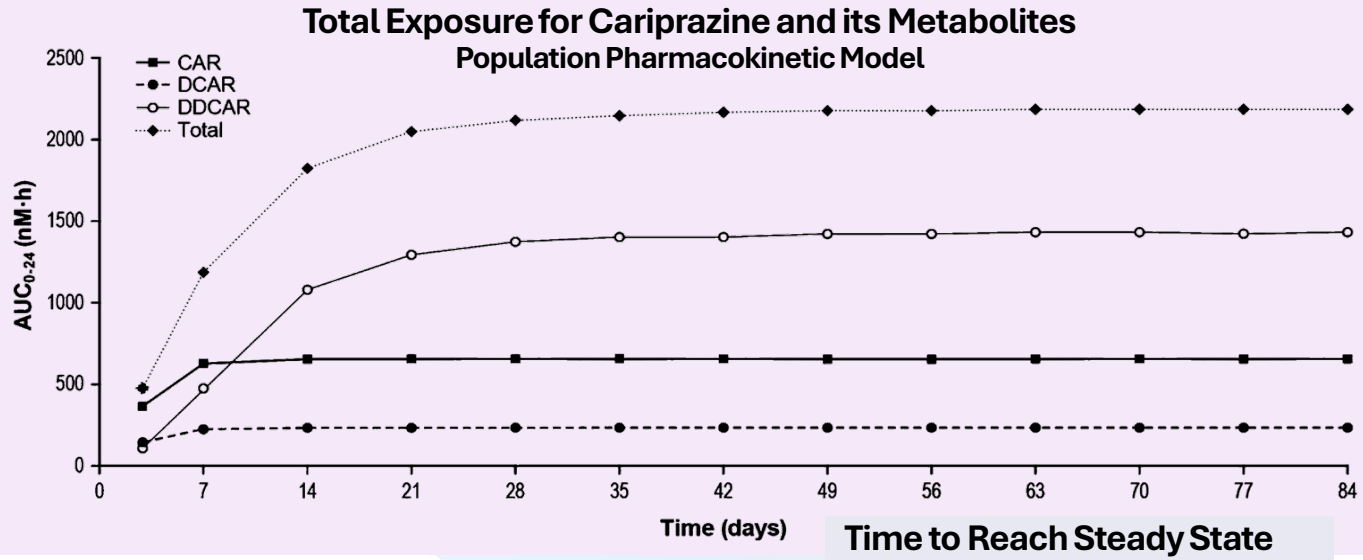
Cariprazine is the only antipsychotic in the US with a higher affinity for D_3 than dopamine itself



The D_3 receptor has a more limited distribution pattern than D_2, 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 ⅔ of the total exposure at steady-state



Time to Reach Steady State

Cariprazine and DCAR: ~1 week

DDCAR: ~3 weeks

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.

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

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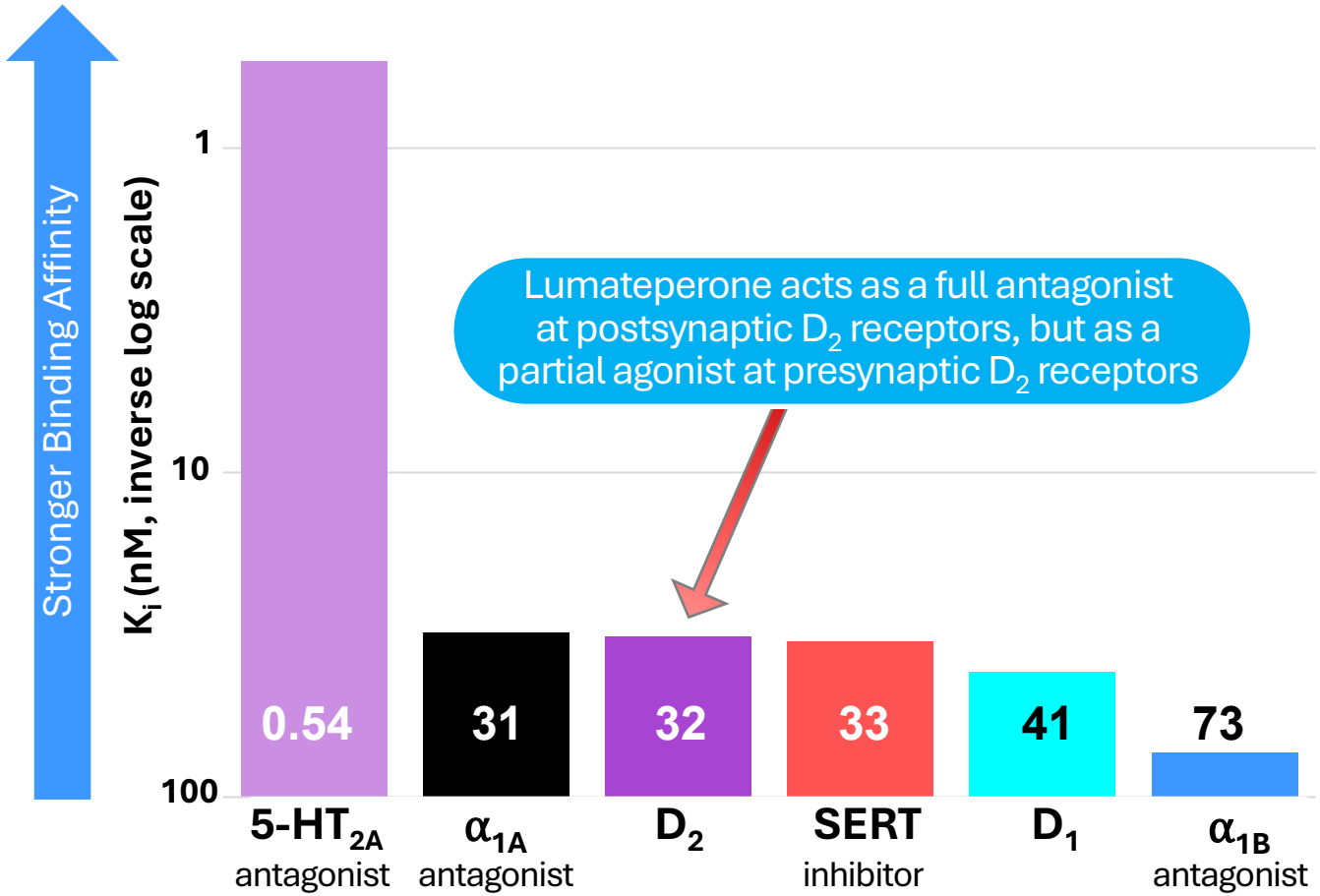
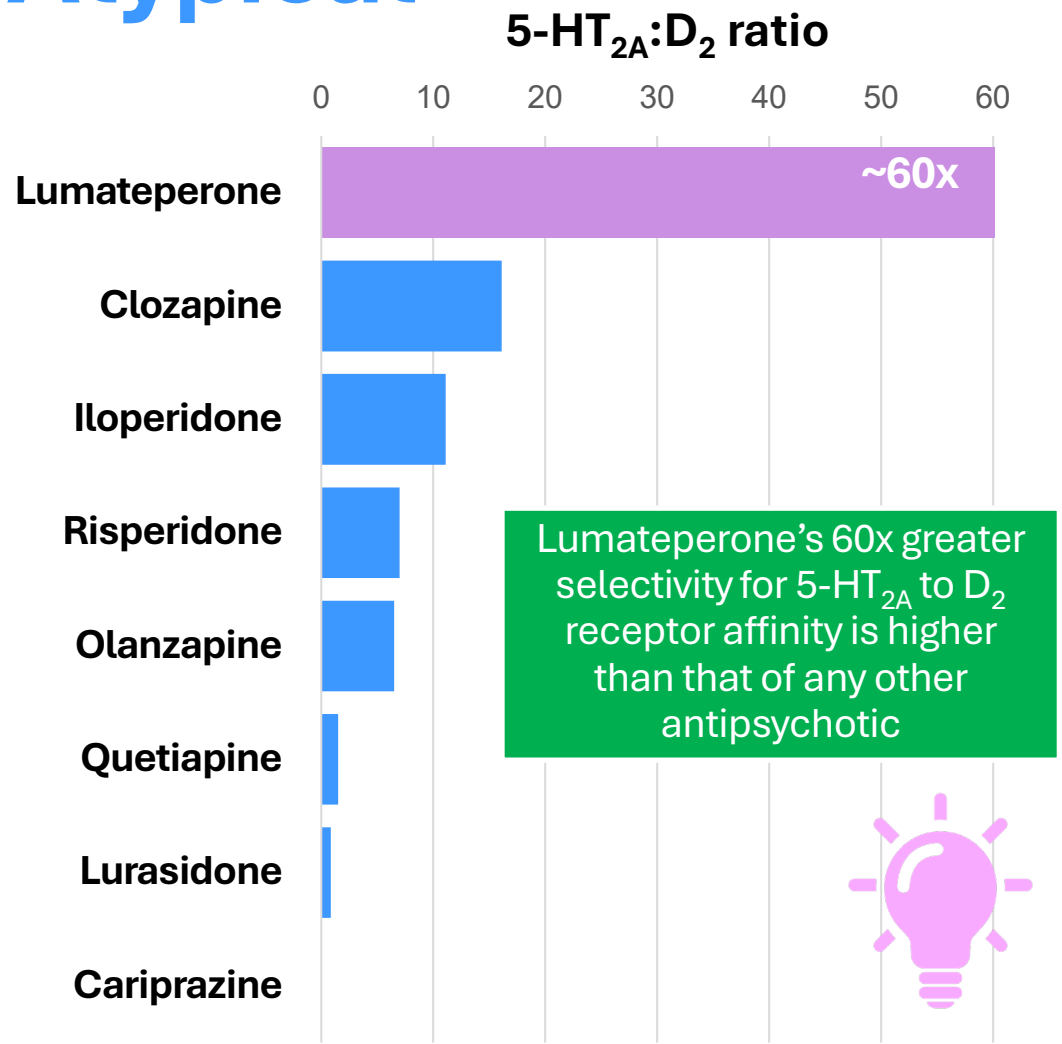
Lumateperone

Lumateperone Receptor Binding: Not Your Typical Atypical



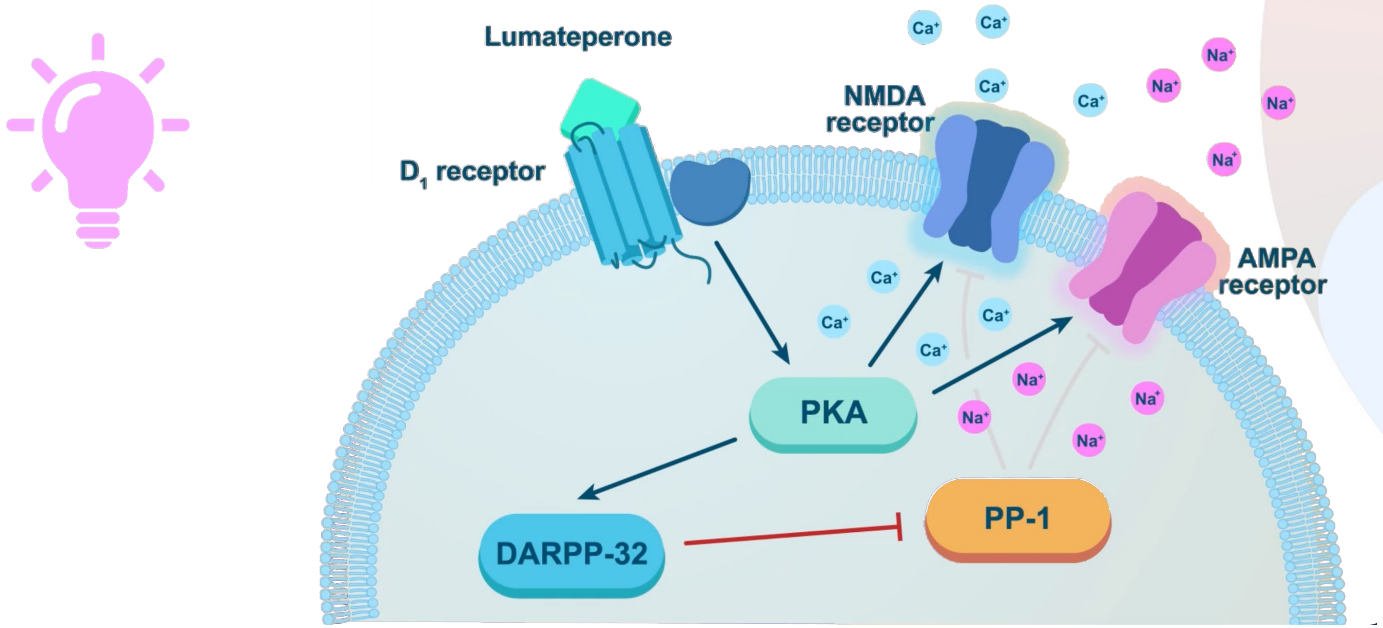


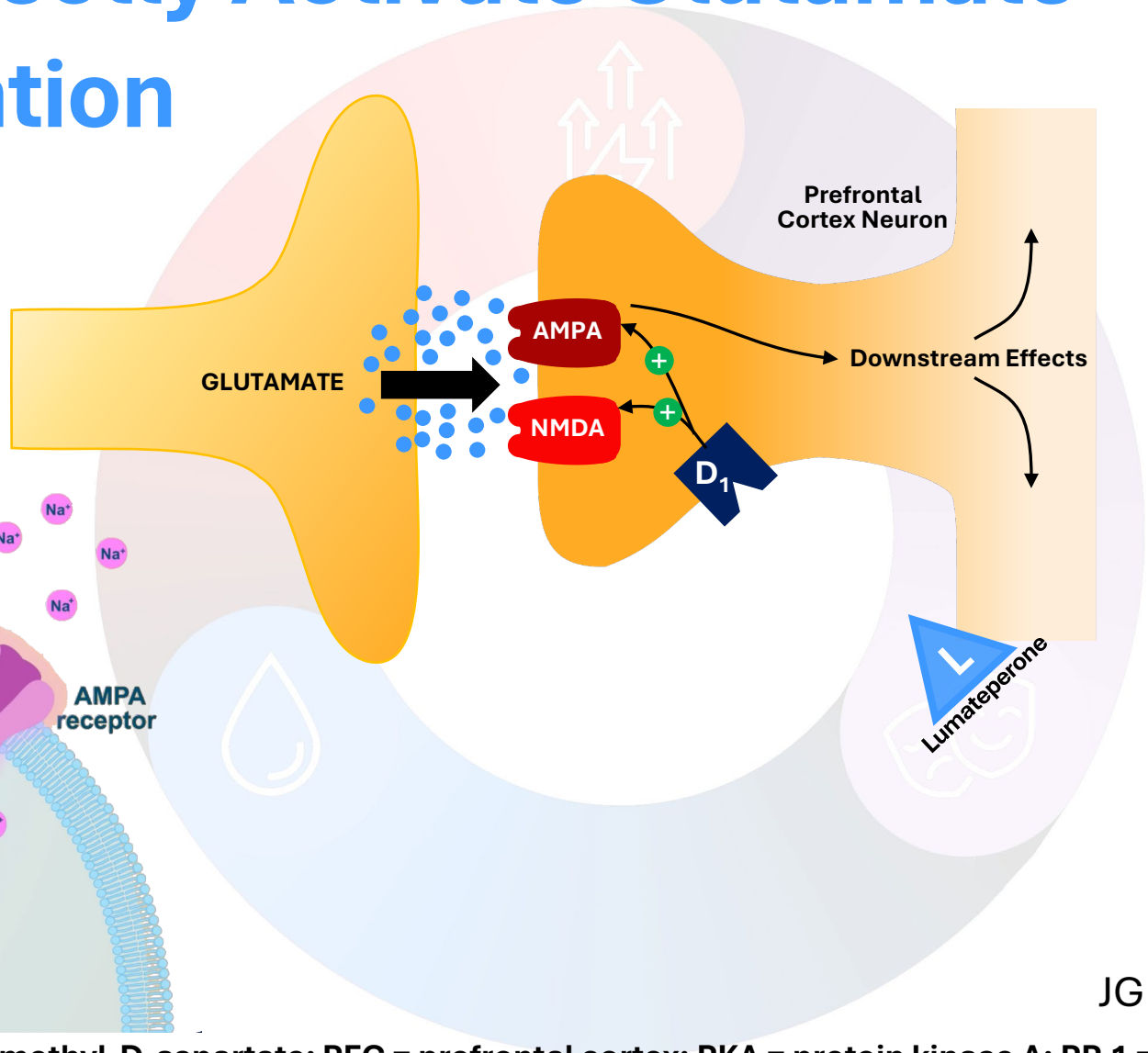
SERT = serotonin reuptake transporter.

Lumateperone Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed May 20, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209500s011lbl.pdf. 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 D_1 Modulation

Preclinical data shows lumateperone indirectly activates both NMDA and AMPA glutamatergic receptors in the PFC via downstream effects from its action on D_1 receptors





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AMPA = α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; NMDA = N-methyl-D-aspartate; PFC = prefrontal cortex; 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.

Lumateperone May Indirectly Activate Glutamate Receptors via D_1 Modulation

Preclinical data shows lumateperone indirectly activates
receptors
fr

Interested in learning more about Lumateperone's MOA?

Scan this QR code to watch a short animated video

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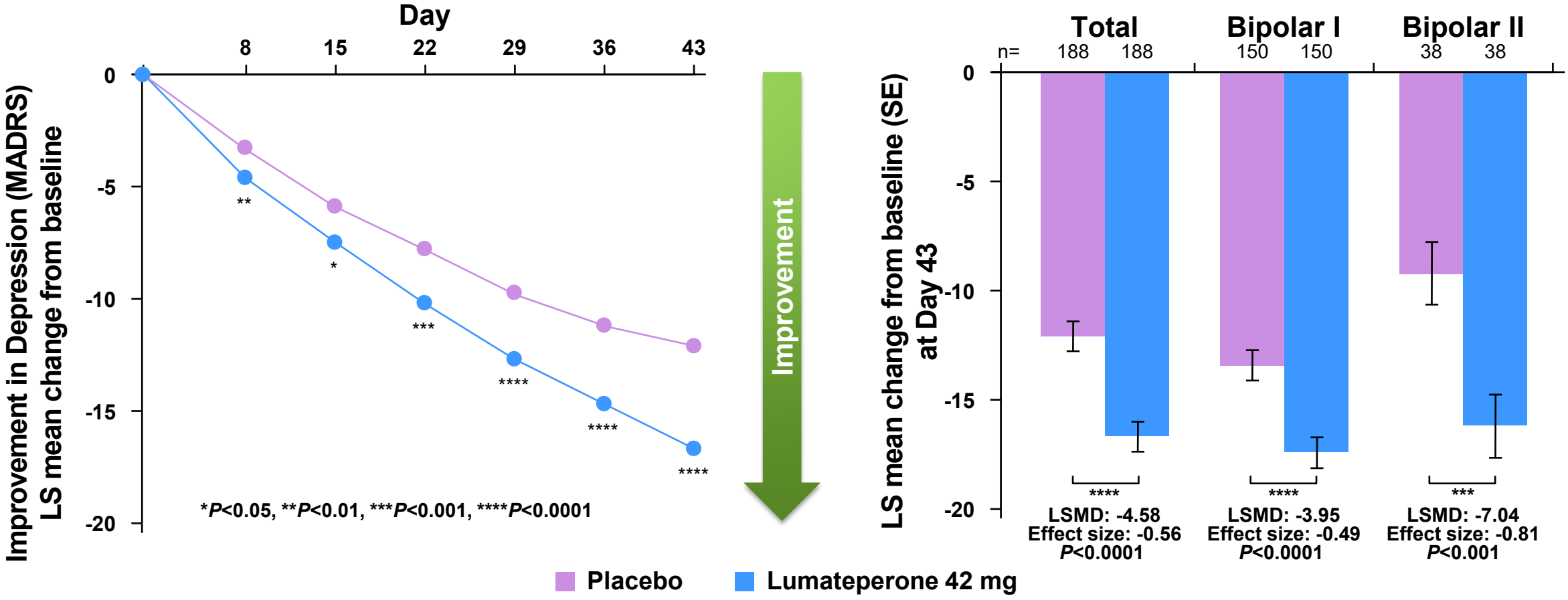
AMPA = α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; NMDA = N-methyl-D-aspartate; PFC = prefrontal cortex; PKA = protein kinase A; PP-1 = protein phosphatase 1; DARPP-32 = dopamine and cyclic adenosine 3',5'-monophosphate-regulated phosphoprotein, 32 kDa.

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.

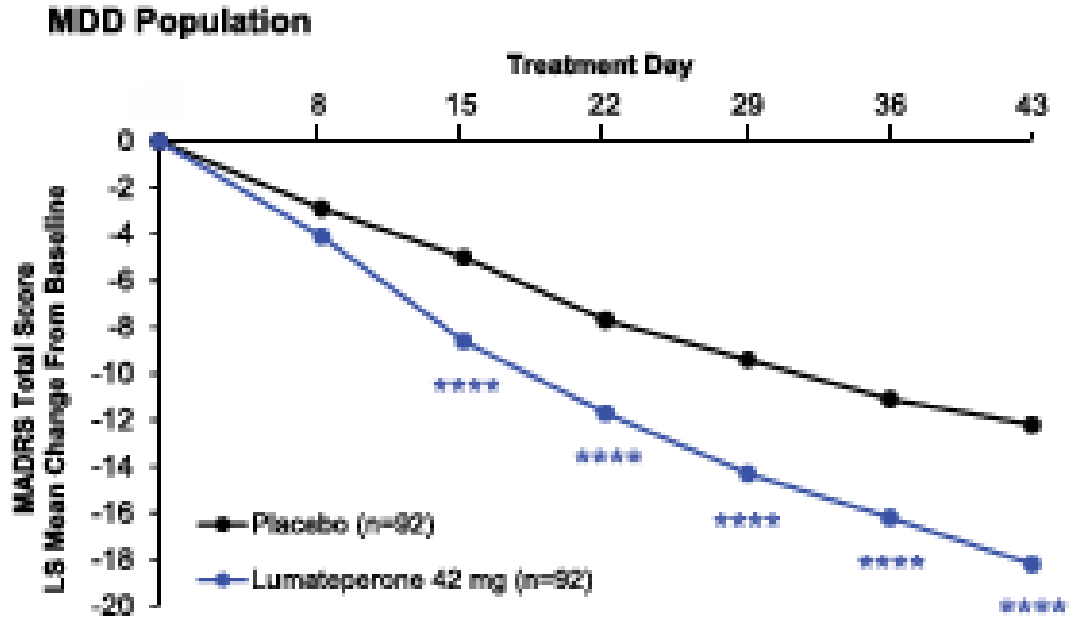
Lumateperone in Bipolar I and Bipolar II Depression

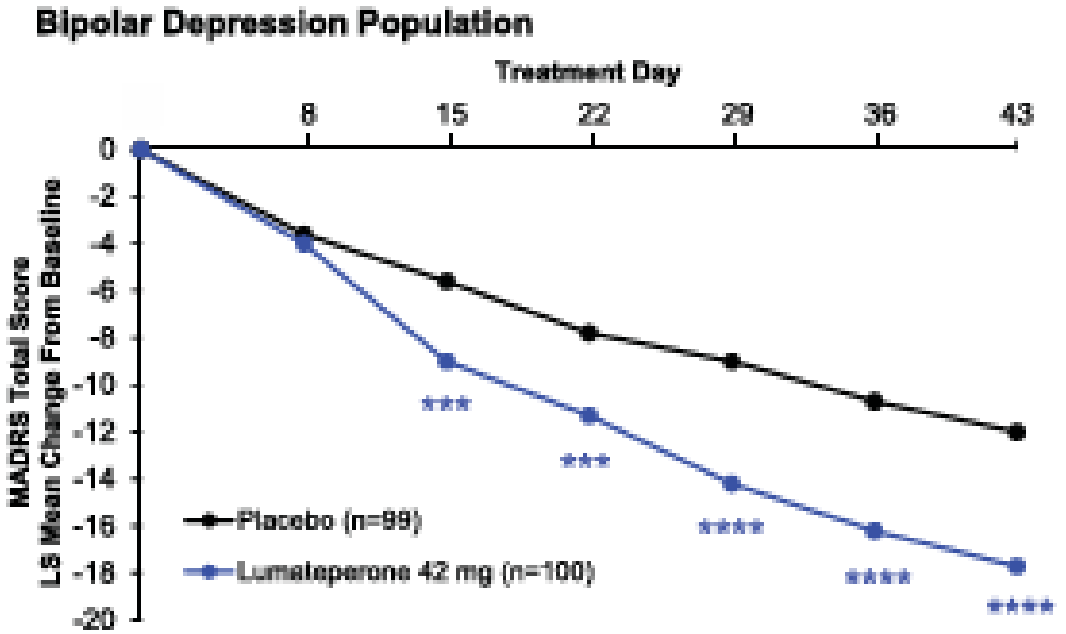


Drug-Placebo differences of >2 points on MADRS are considered clinically relevant

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 Major Depression with Mixed Features and in Bipolar Depression with Mixed Features





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

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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 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

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

Lumateperone Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed May 20, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209500s011lbl.pdf. Mates S, et al. Presented at: American College of Neuropsychopharmacology (ACNP) 2022 Annual Meeting; December 4-7, 2022; Phoenix, AZ.

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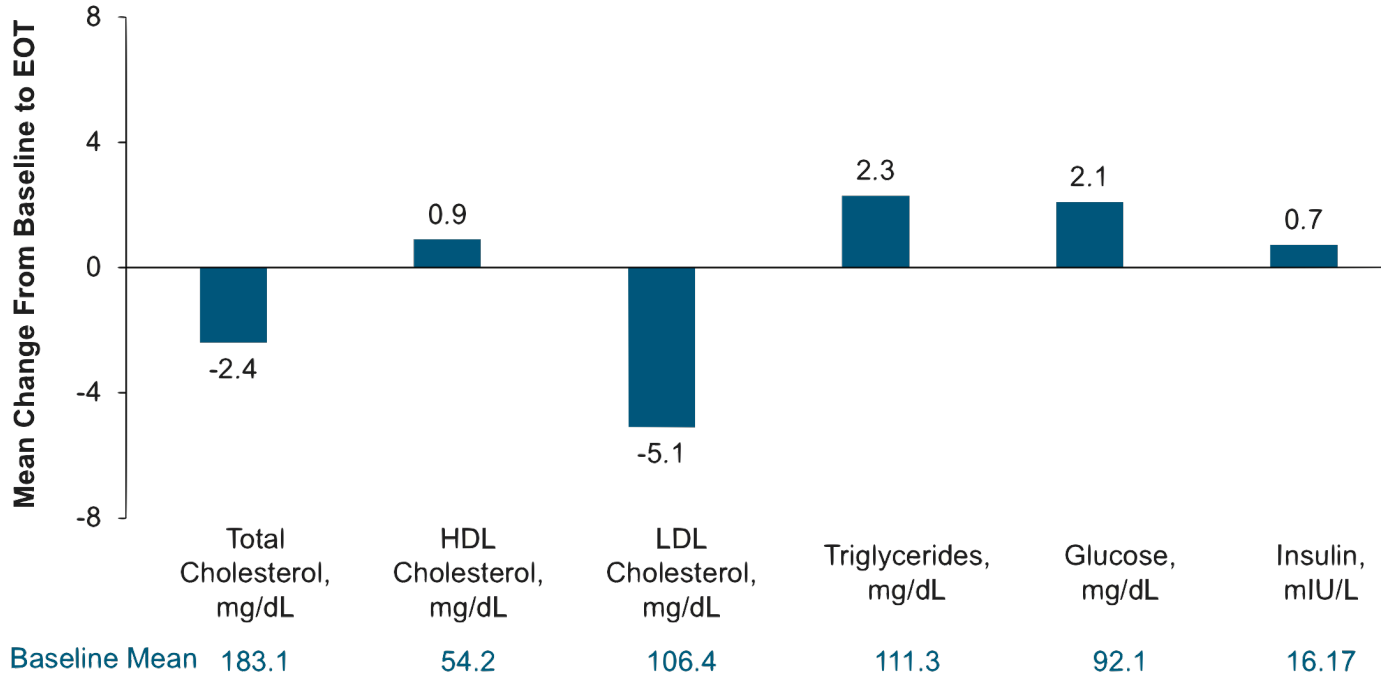
Weight and Metabolic Parameters of Lumateperone Monotherapy in 6-month Open Label Extension

No clinically significant changes from baseline to end of treatment in cardiometabolic laboratory measures

Mean weight change −0.02 lb

3.4% gained ≥7% body weight
6.0% lost ≥7% body weight



Hot Take!

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

EOT = end-of-treatment; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Mates S, et al. Presented at: American College of Neuropsychopharmacology (ACNP) 2022 Annual Meeting; December 4-7, 2022; Phoenix, AZ.

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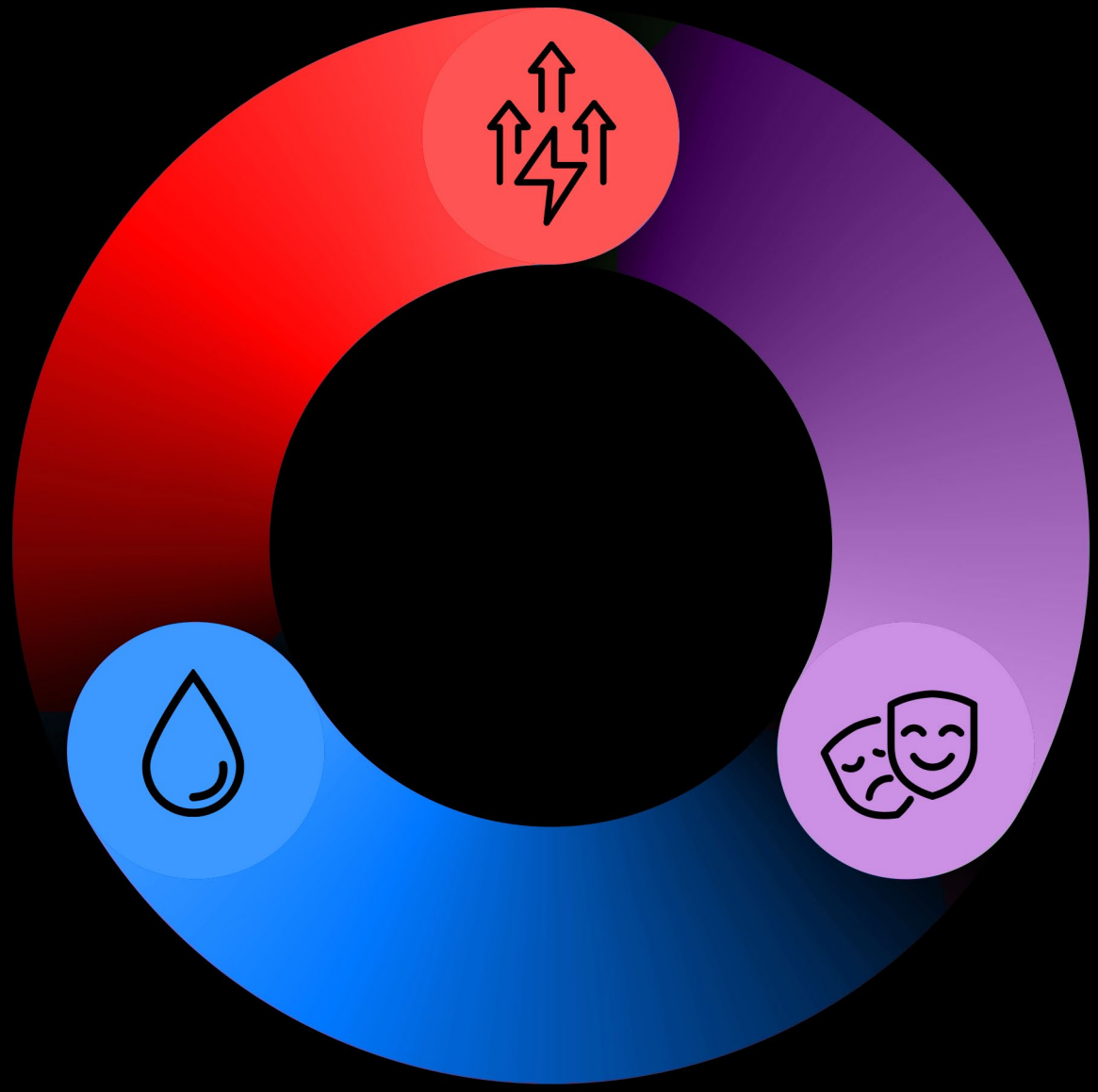
Key Learning Points

- ✓ 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 ($5HT_{2A}$) receptor antagonism**
- ✓ It has not been associated with clinically significant weight gain, **cardiometabolic lab changes**, or movement disorders

JG

Caring for the Whole Patient With BD

Faculty Discussion



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

Goldberg JF, Stahl SM. *Clinical Reasoning and Decision-Making in Psychiatry*. Cambridge Univ Press; 2024.

Positive Relationships Create Results

Elwyn G, et al. *J Gen Intern Med*. 2012;27:1361–1367. Elwyn G, et al. *BMJ*. 2017;359:j4891. Craig Chepke, MD. Personal communication. September 2022.

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.

McIntyre RS, et al. *Hum Psychopharmacol*. 2004;19(6):369-386. Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170.

Practical Take-Aways

- Be vigilant for mixed features in any person presenting with a mood disorder, as their presence may signal a more challenging presentation and can inform our treatment decisions

- From the start of treatment planning, keep in mind that weight gain is a common cause of discontinuation for medications in bipolar disorder
  → *“An ounce of prevention is worth a pound of cure”*

- Remember to prioritize the efficacy of treatments in an evidence-based fashion to help give people with bipolar disorder the best chance to manage their lives!

Q&A