THIS OR THAT?

Understanding the Mechanisms of Action and Clinical Applications of Novel and Emerging Therapies for Bipolar Disorder

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This activity has been supported through an independent educational grant from Intra-Cellular Therapies, Inc.

Faculty Disclosures

- **Dr. Chepke**: Advisory Board—Abbvie, Acadia, Alkermes, Corium, Eisai, Idorsia, Intracellular, Ironshore, Janssen, Jazz, Karuna, Lundbeck, Neurocrine, Noven, Otsuka, Takeda, Teva; Advisory Board (Spouse)—Otsuka; Consultant—AbbVie, Alkermes, Corium, Eisai, Intracellular, Janssen, Jazz, Karuna, Lundbeck, Neurocrine, Noven, Otsuka, Takeda, Teva; Grant Research/Support—Acadia, Axsome, Biohaven, Harmony, Neurocrine, Teva; Speaker's Bureau—AbbVie, Acadia, Alkermes, Eisai, Intracellular, Ironshore, Janssen, Jazz, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sunovion, Takeda, Teva.

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- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Accurately identify BD, differentiating among its various symptom domains and BD1 vs BD2
- Evaluate the mechanisms of action, safety and efficacy data, and clinical indications associated with novel and emerging pharmacotherapies for BD1 and BD2
- Implement patient-centered strategies to select and monitor treatment

Quiz Show

Throughout the presentation, participate in polling to see how your knowledge stacks up against your peers!

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Differentiating Between BD1, BD2, and Other Psychiatric Disorders

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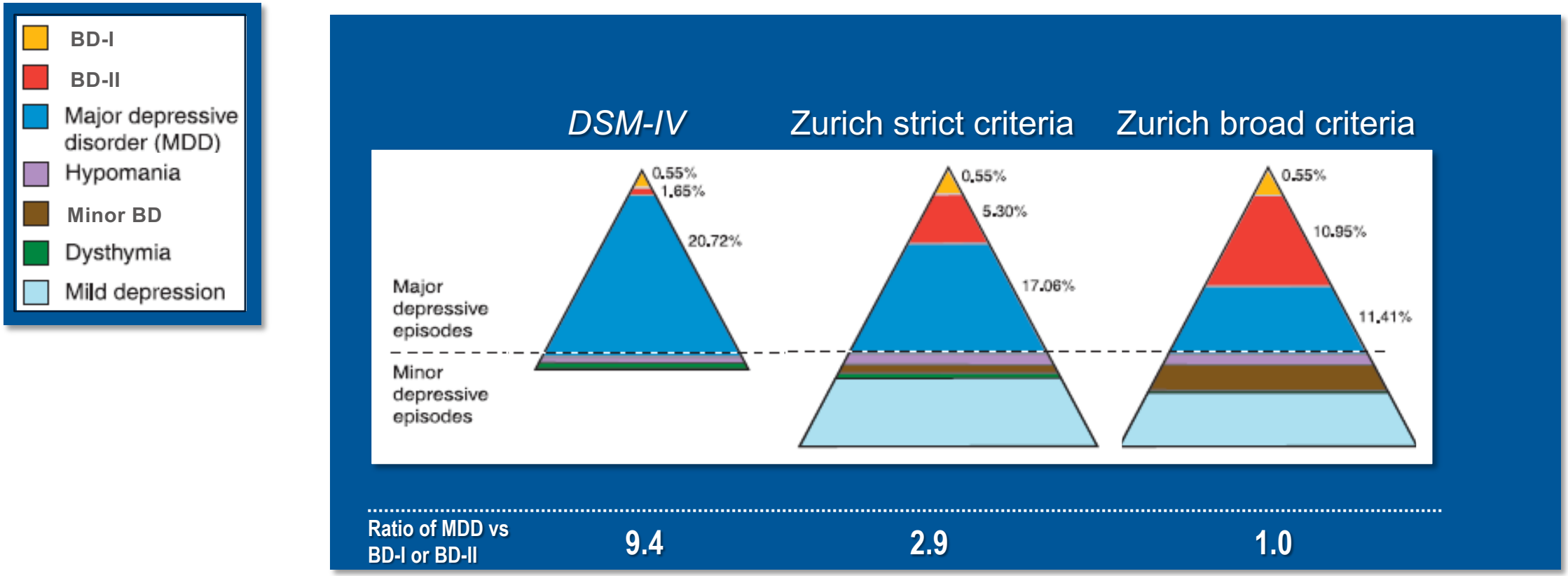
Bipolar Disorders Are Common—Both BD-I and BD-II Disorders



Prevalence of MDD vs BD-II based upon 3 different sets of criteria: *DSM-IV,* Zurich strict, and Zurich broad as used in Angst J, et al. *Eur Neuropsychopharmacol*. 2003;13(Suppl 2):S43-S50.

Angst J, et al. *Bipolar Disord*. 2005;7(Suppl 4):4-12.

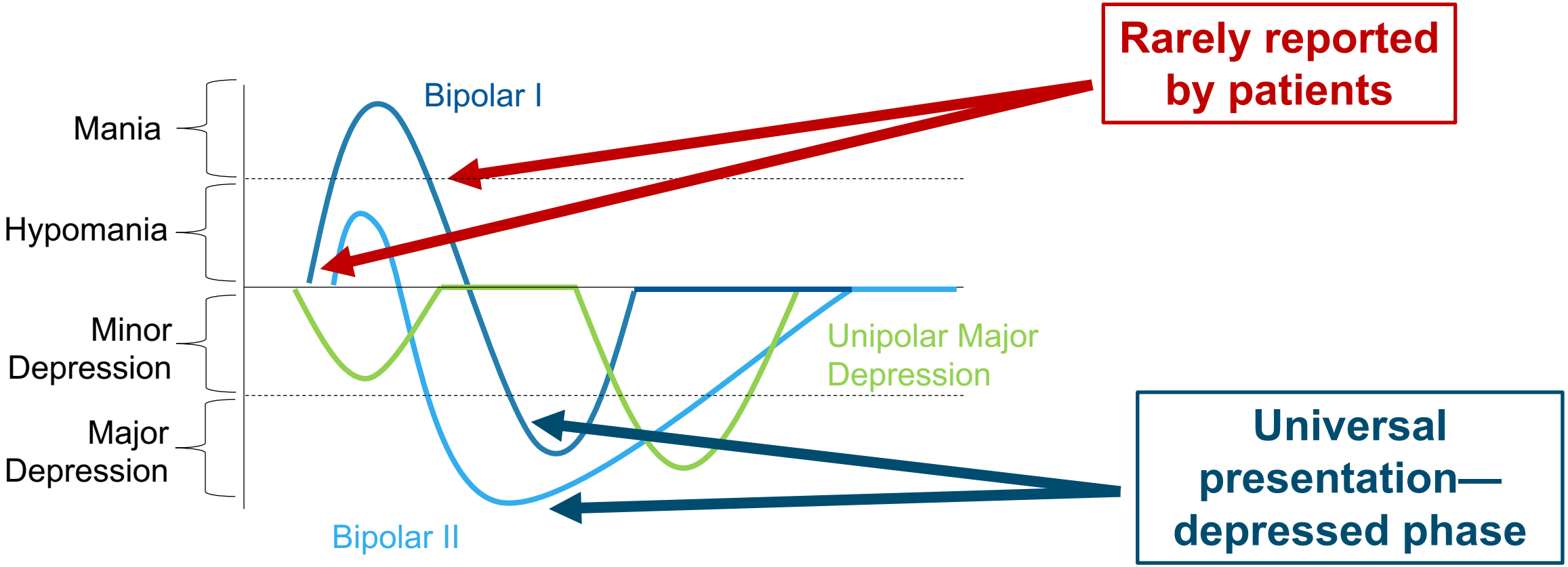
Difference Between Bipolar I and II:

Examining the Difference Between Manic and Hypomanic Episodes

- Abnormally and persistently elevated, expansive, or irritable mood and abnormally or persistently increased goal-directed activity
- Lasting at least 7 days, most of the day, nearly every day (unless hospitalized)
- 3 or more of the following; 4 if irritable:
  - Inflated self esteem or grandiosity
  - Decreased need for sleep
  - More talkative than usual
  - Flight of ideas or racing thoughts
  - Distractibility
  - Increase in goal-directed activity or psychomotor agitation
  - Activities with painful consequences
  - Marked impairment, hospitalization needed, or psychosis
  - Not due to substance or other medical condition

- Abnormally and persistently elevated, expansive, or irritable mood and abnormally or persistently increased goal-directed activity
- At least 4 days, most of the day, nearly every day
- 3 or more of the following; 4 if irritable:
  - Inflated self esteem or grandiosity
  - Decreased need for sleep
  - More talkative than usual
  - Flight of ideas or racing thoughts
  - Distractibility
  - Increase in goal-directed activity or psychomotor agitation
  - Activities with painful consequences
  - Unequivocal change in functioning; observable by others
  - No marked impairment, hospitalization needed, or psychosis
  - Not due to substance or other medical condition

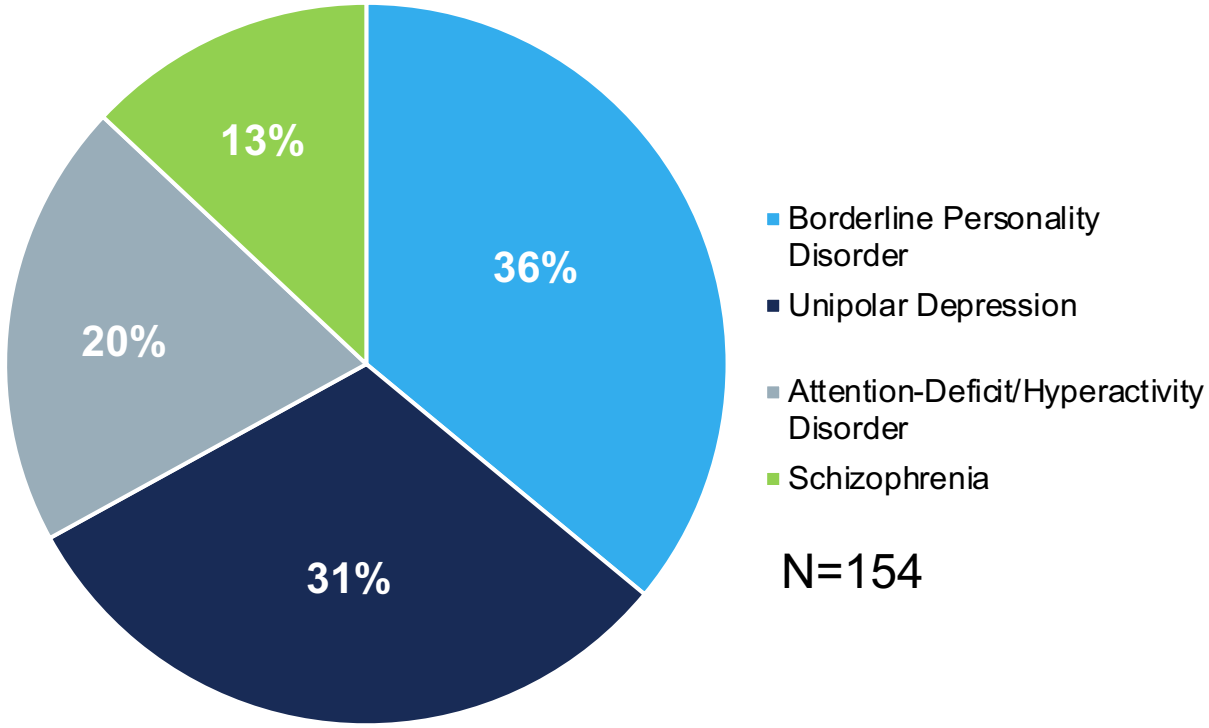
Bipolar I and II Patients Typically Present in the Depressed Phase



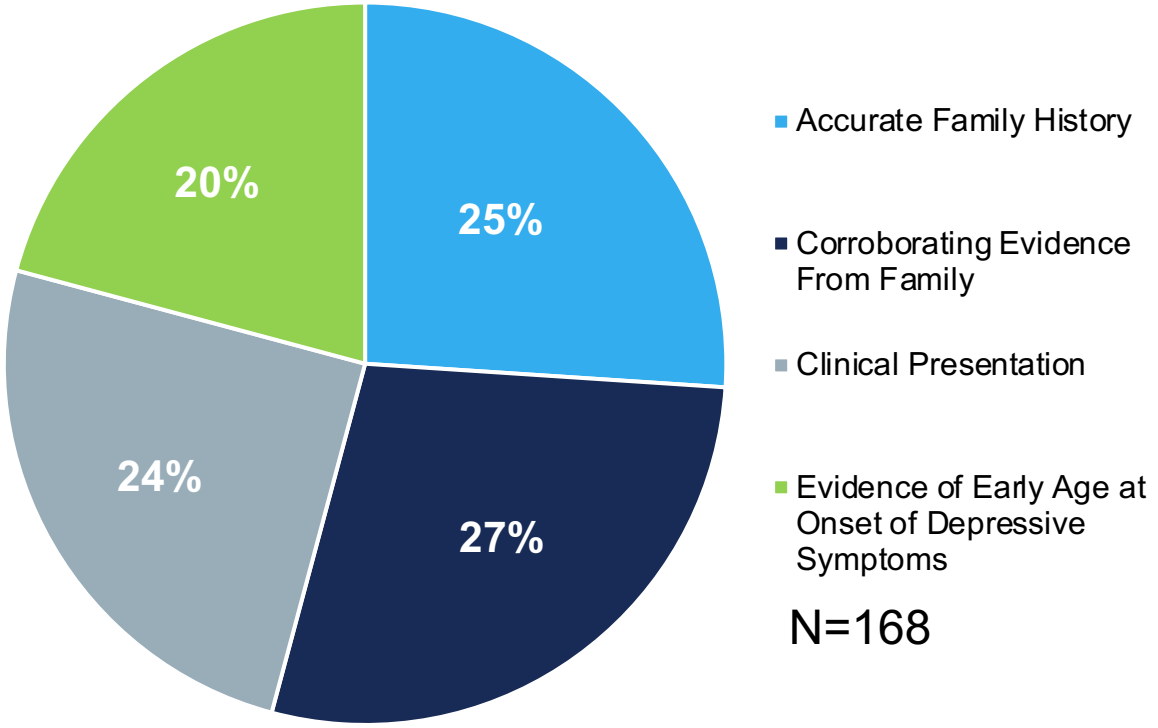
Gitlin M, et al. *Int J Bipolar Disord.* 2020;8:5.

Bipolar Disorder Is Often Complex to Diagnose—and Tips on Differentiating BD from MDD

Disorders Most Difficult to Differentiate from Bipolar Disorder



Best Predictors for Achieving Differential Diagnosis between MDD vs. BD



Results of a survey of majority psychiatry clinicians.

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

How many adult patients diagnosed with ADHD also have Bipolar Disorder?

A 10%

B 15%

C 20%

D 30%

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Results

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How many adult patients diagnosed with ADHD also have Bipolar Disorder?

A 10%

B 15%

C 20%

D 30%

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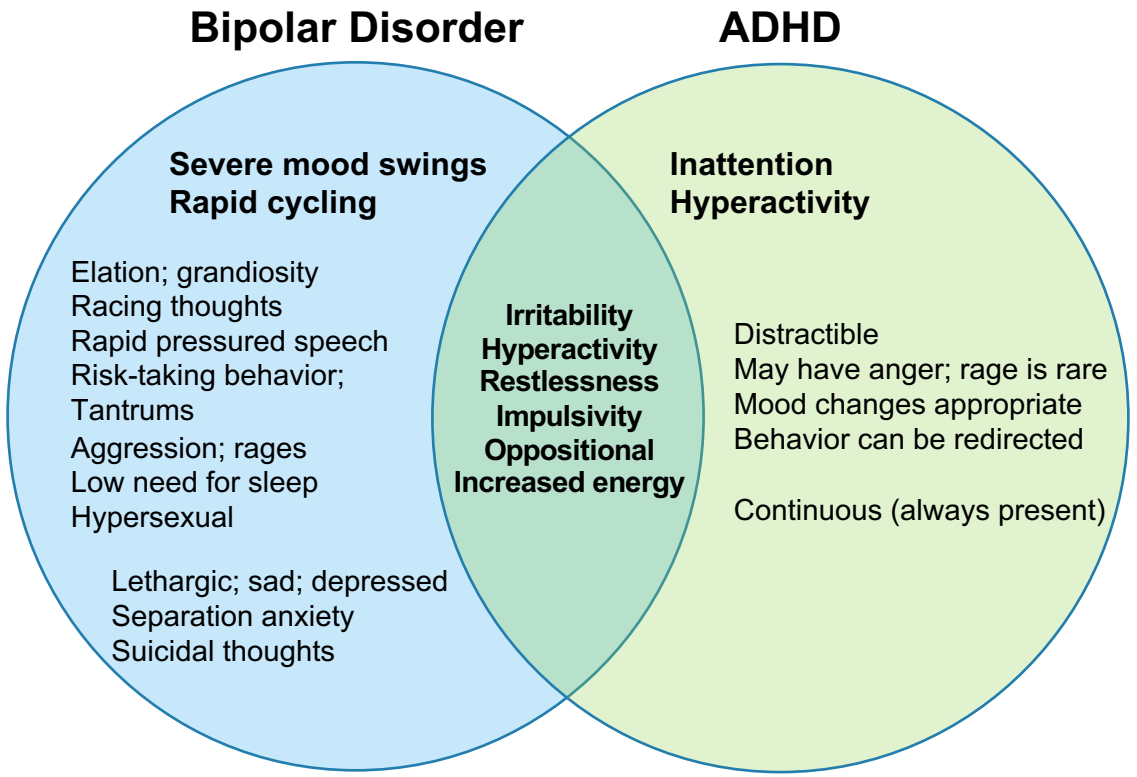
An Important Differential Diagnosis—Bipolar Disorder vs. ADHD (or both?)

Adult ADHD and bipolar disorder have multiple overlapping symptoms, but there are differences in prevalence:

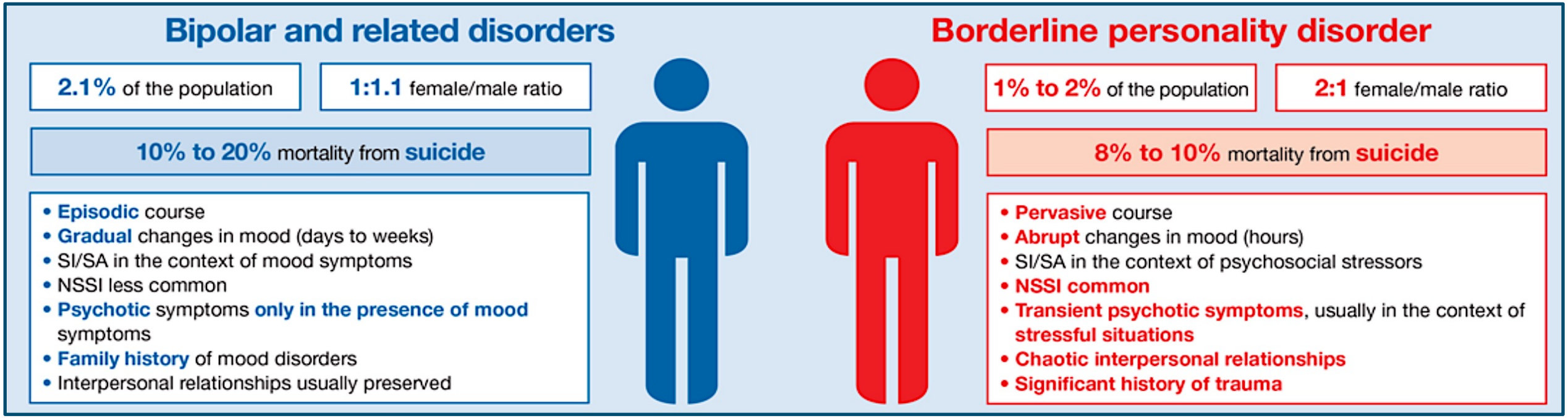
- ADHD affects 4.4% of versus 1.4% for bipolar disorder
- Onset of symptoms—usually before age 7 years in ADHD versus after age 12 years in bipolar disorder
- Disease course (chronic in ADHD versus cyclical in bipolar disorder)
- Mood symptoms (absent in ADHD but always present in bipolar disorder)
- Approximately 20% of adult patients with ADHD also have bipolar disorder, while 10%-20% of patients with bipolar disorder have adult ADHD



ADHD = attention-deficit hyperactivity disorder.

Brus MJ, et al. *J Psychiatr Pract*. 2014;20(6):428-37.

BD vs BPD: A Complex but Important Differential Diagnosis



Bayes A, et al. *Curr Psychiatry Rep.* 2019;21(12):125.

What testing scale can be used to screen for bipolar disorder in people presenting with depressive episodes?

A PHQ-9

B RMS

C MDQ

D HAM-D

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Results

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What testing scale can be used to screen for bipolar disorder in people presenting with depressive episodes?

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New Screener: Rapid Mood Screener

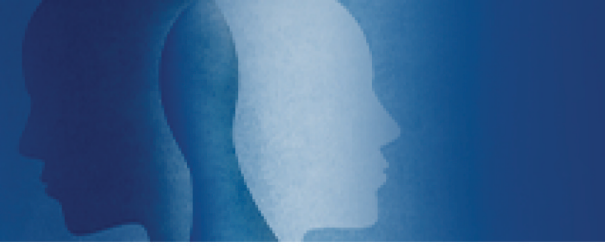
The Rapid Mood Screener

1	Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?	Y	N
2	Did you have problems with depression before the age of 18?	Y	N
3	Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	Y	N
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?	Y	N
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?	Y	N
6	Have you ever had a period of at least 1 week during which you needed much less sleep than usual?	Y	N

- Released in 2021
- Differentiates bipolar I disorder from MDD in patients with depressive symptoms
- Provides guidance on whether a more comprehensive assessment for bipolar I disorder is warranted.

McIntyre RS, et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. *Curr Med Res Opin*. 2021;37(1):135-144. doi: 10.1080/03007995.2020.1860358. Epub 2021 Jan 6. PMID: 33300813.

Strategies to Accurately Identify BP-I Depression and BP-II Depression



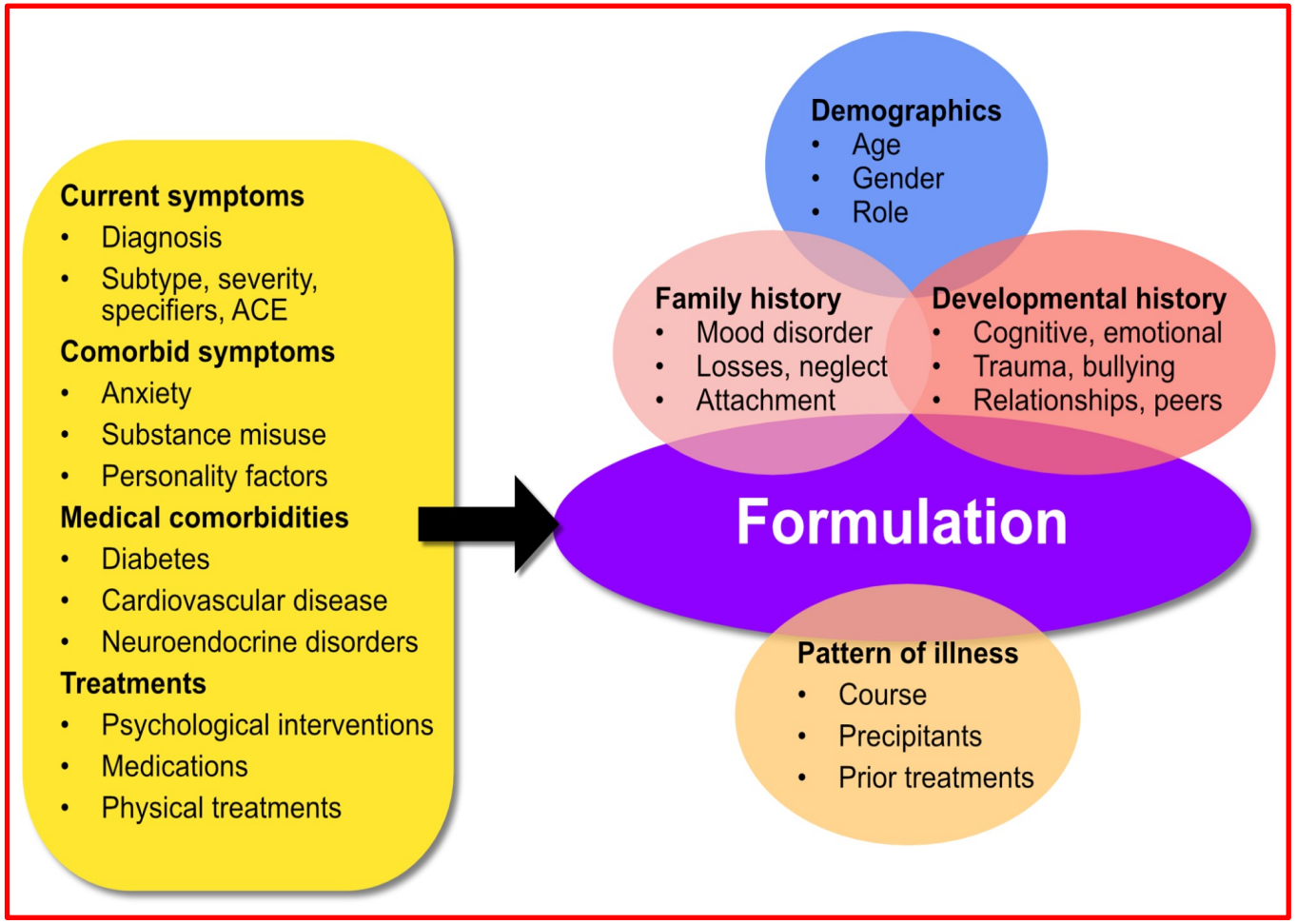
- Never make a diagnosis of major depression without proactively assessing for mania/hypomania in past/currently
- Acquire collateral information from family/friends
- If patient presents with irritability, distractibility, insomnia, substance misuse (amongst other) symptoms, proactively look for bipolar disorder

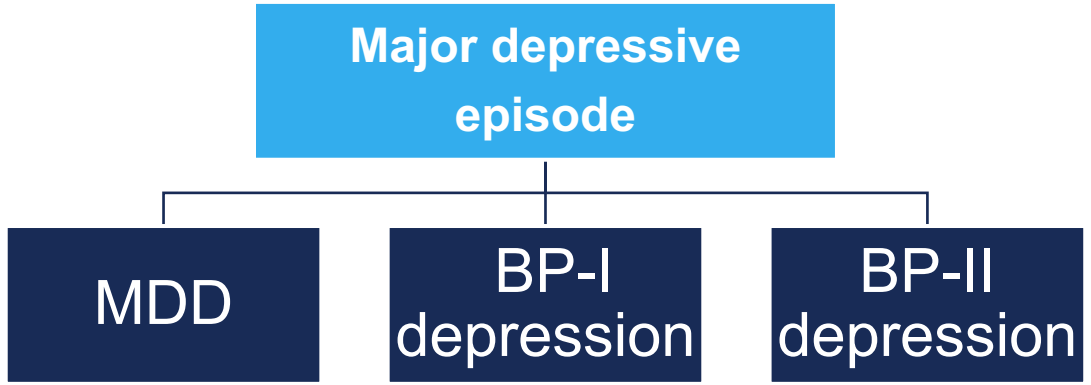
- Use screening instruments such as the Rapid Mood Screener (RMS)
- Look for family history—BD is a highly genetic disorder
- Early onset, multiple episodes of depression, poor response to antidepressants (amongst others) are all markers of accurate bipolar disorder
- Watch out for hypomanic episodes! They are tricky to detect, yet it's crucial to look for them to establish an accurate dx of bipolar DO type II

Dx = diagnosis; DO = disorder.

Phillips ML, et al. *Lancet*. 2013;381(9878):1663-71.

Getting to A Final Diagnosis—Utilizing Multiple Sets Of Information to Arrive at the Correct Dx/Dxs





Mahli GS, et al. *Aust N Z J Psychiatry.* 2021;55(1):7-117.

Illuminating the Importance of Mechanisms of Action in the Treatment of Bipolar Depression

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Medication Trials in Acute Bipolar Depression

Monotherapy

Agent vs PBO	Primary Outcome
Lithium	Negative
Lamotrigine	All 5 negative
Aripiprazole	2 Negative
Olanzapine	Positive
Ziprasidone	Negative
Quetiapine	All 5 positive
Paroxetine	Negative
Lurasidone	Positive
Cariprazine	3 positive / 1 negative
Lumateperone	1 positive / 1 negative
	12 out of 26 positive

Augmentation

Agent	Primary Outcome
Paroxetine + lithium vs lithium	Negative
Paroxetine or bupropion + MS vs MS+PBO	Negative
Olanzapine+fluoxetine vs PBO vs olanzapine	Positive
Lamotrigine + Li vs placebo + Li	Positive
(Ar)modafinil vs placebo	2 positive / 1 negative
Levetiracetam	Negative
Ziprasidone	Negative
Agomelatine	Negative
Lurasidone	1 positive / 1 negative
Lumateperone	Positive
	6 out of 13 positive

Many medications effective in mania are not effective in bipolar depression

MS = mood stabilizer; Li = Lithium; PBO = placebo.

Yatham LN, et al.. *Supplement to Current Psychiatry*. 2019;18(10):S5-S8. D'Souza. *CNS Spectr*. 2021;26:150.

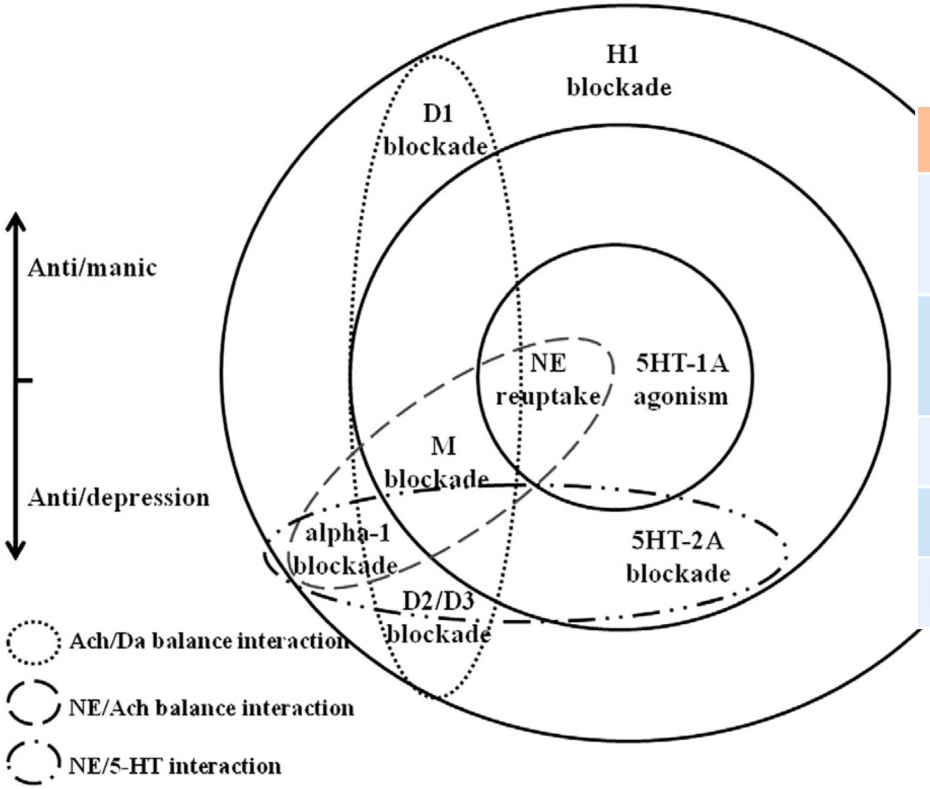
Medications with FDA Approvals for Bipolar Depression

	2003	2006	2013	2019	2021	
	Olanzapine/ Fluoxetine	Quetiapine (IR and XR)	Lurasidone	Cariprazine	Lumateperone	Total Options
Has FDA Approval in Bipolar Depression	✓	✓	✓	✓	✓	5

FDA = US Food and Drug Administration.

Lumateperone. Prescribing information. Intra-Cellular Therapies; 2021. Quetiapine. Prescribing information. AstraZeneca; 2021. Quetiapine XR. Prescribing Information. AstraZeneca; 2020. Olanzapine/fluoxetine. Prescribing information. Eli Lilly, Inc; 2021. Lurasidone. Prescribing information. Sunovion Pharmaceuticals Inc; 2019. Cariprazine. Prescribing information. AbbVie plc; 2019.

Receptor Targets for Bipolar Depression: Looking for a Tie that Binds



	D1	D2	D3	5-HT$_{1A}$	5-HT$_{2A}$	α1	H$_1$/M$_1$	SERT	NET
Receptor Affinities (k_i, nM)									
Olanzapine-Fluoxetine	56.6	30.8	38.1	2063-2720	4.0	19	High	High	-
Quetiapine *norquetiapine*	1096 *99.8*	437 *489*	394 -	320-432 *191*	96-101 *2.9*	22 *46.4*	High *High*	- -	- *Mod*
Lurasidone	262	0.66	15.7	6.75	2.03	47.9	Low	-	-
Cariprazine	1000	0.49	0.09	2.6	18.8	155	Low	-	-
Lumateperone	41	32	-	1480	0.54	31-73	Low	Mod	-

Fountoulakis, KN, et. al. *Journal of affective disorders. 2012;*138(3): 222-238. Goldberg JF, et al. *Practical Psychopharmacology.* Cambridge University Press; 2021:17-19. Quetiapine XR. Prescribing Information. AstraZeneca; 2020. Li P, et al. *Journal of Medicinal Chemistry.* 2014;57(6):2670-2682. Snyder, GL, et al. *Psychopharmacology*. 2015;232(3): 605-621.

Name That Mechanism!

Which receptor effect is believed to be in part responsible for the antidepressant effect of mirtazapine, nefazodone, trazodone, TCAs, and some atypical antipsychotics?

A 5-HT_{1A} partial agonism

B 5-HT_{2A} antagonism

C D_2 partial agonism

D D_3 partial agonism

Hint: This receptor effect may also be partially responsible for mitigating the motor adverse effect of antipsychotics...

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Name That Mechanism!

Which commonly used (off-label) medication is believed to exert its psychiatric effects through α1 antagonism?

A Propranolol

B Gabapentin

C Benztropine

D Prazosin

Hint: Its most common psychiatric use is in PTSD

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Potential Receptor Effects in Depressive States: An Ensemble Cast

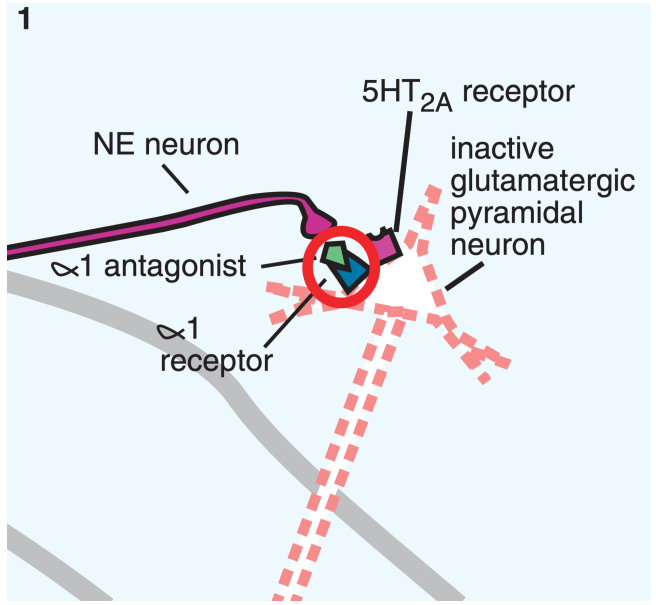
Receptor Activity	Potential Effects
5-HT_{1A} partial agonism	Increases dopamine in medial PFC; anxiolytic & antidepressant action
5-HT_{2A} antagonism	Increases DA in PFC: enhanced attention, working memory; antidepressant effect
5-HT_3 antagonism	Indirectly facilitates release of acetylcholine, dopamine, and norepinephrine
5-HT_7 antagonism	Enhances serotonin and glutamate release; antidepressant & procognitive effects
SERT reuptake inhibition	Possible antidepressant action
α1 antagonism	Similar to, and synergistic with, 5-HT_{2A} antagonism
α2 antagonism	Enhances release of monoamines
NET reuptake inhibition	Possible antidepressant action
D_1 modulation	Postsynaptic crosstalk may indirectly increase glutamatergic signaling
D_3 partial agonism	Increased signaling in reward pathway

DA = dopamine; PFC = prefrontal cortex; SERT = serotonin reuptake transporter; NET = norepinephrine reuptake transporter.

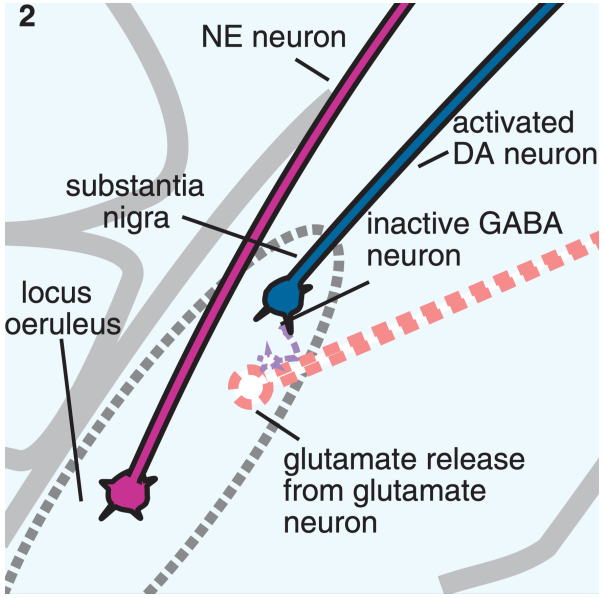
Goldberg JF, et al. *Practical Psychopharmacology.* Cambridge University Press. 2021:17-19. Stahl, SM. Stahl's Essential Psychopharmacology. Cambridge University Press, 2021.

Serotonin, Norepinephrine, and Dopamine: A Polyamorous Relationship

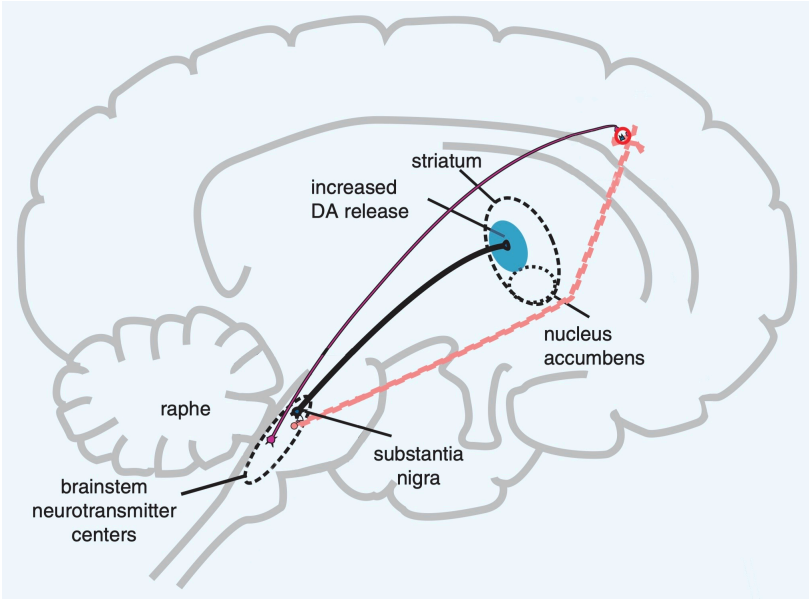
5-HT_{2A} and/or α_1 antagonism inactivates glutamate neurons



...which inactivates GABA neurons



...which activates dopamine neurons in multiple areas of the brain



Modulation of striatal and cortical dopamine neurotransmission by serotonin and norepinephrine may contribute to an antidepressant response.

Stahl, SM. *CNS Spectrums*. 2013;18(6):285-288. Auclair A, et al. *European Journal of Neuroscience*. 2004;20(11):3073-3084. El Mansari M, et al. *CNS Neuroscience & Therapeutics*. 2010;16(3):e1-e17.

Medications Are Not One Size Fits All in Bipolar Disorder: Especially BP I vs. BP II

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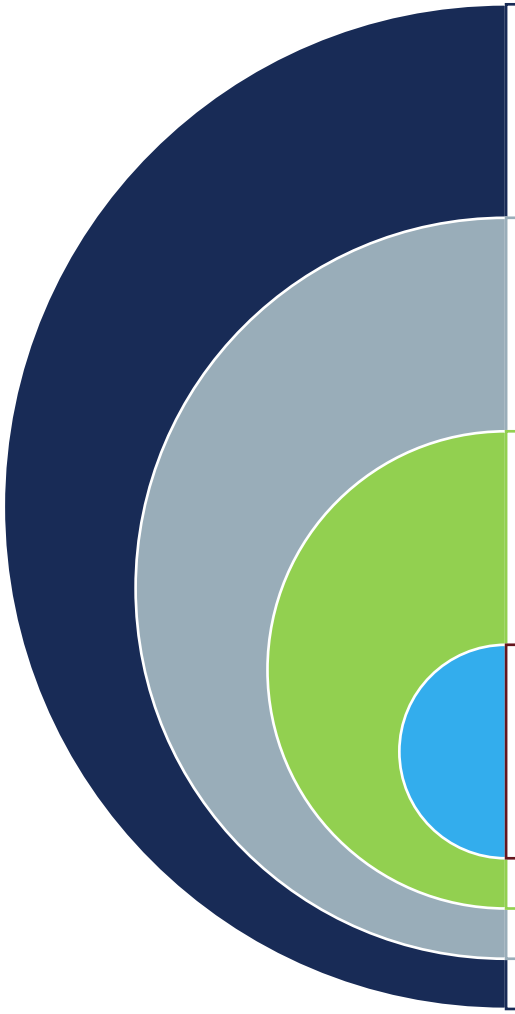
Use of Bipolar I Medications in Bipolar II: Caveat Emptor

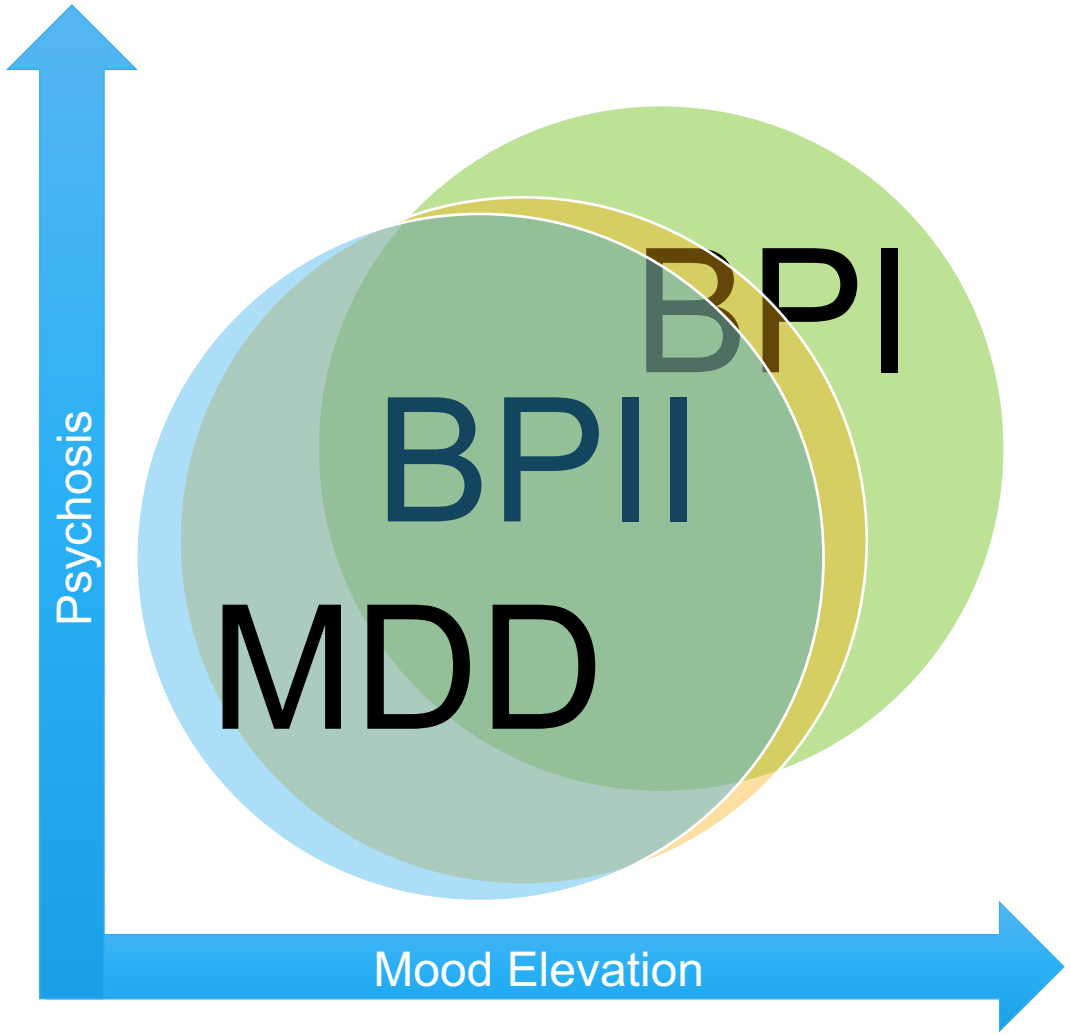


Modafinil	Response rate • 50% in BP-I • 14% in BP-II
Lamotrigine	Response Rate • BP-I RR=1.24, 95% CI 1.04–1.46 • BP-II RR=1.15 95% CI 0.90–1.47 (nonsignificant)
Quetiapine	Superiority to placebo • 5 of 5 trials in BP-I • 3 of 5 trials in BP-II
Cariprazine	Phase 2 study in BP-I and BP-II depression • Primary endpoint negative • Subsequent phase 3 trials in BP-I all positive

Yatham LN, et al. *International Clinical Psychopharmacology*. 2020;35(3):14. Geddes JR, et al. *British Journal of Psychiatry*. 2009;194(1):4-9. Yatham LN, et al. *Bipolar Disorders*. 2018;20(2):97-170. Frye, MA, et al. *American Journal of Psychiatry*. 2007;164(8):1242-1249.

How Different are Bipolar I and Bipolar II?

	Bipolar I	Bipolar II	MDD
Depressive	31.9%	50.3%	59%
Manic or Hypomanic	9.3%	1.3%	0%
Cycling/Mixed	5.9%	2.3%	-
Asymptomatic	52.9%	46.1%	41%
Percent of symptomatic time spent in depression	**68%**	**93%**	**100%**



Judd LL, et al. *Archives of General Psychiatry*. 1998;55(8):694-700. Judd LL, et al. *Archives of General Psychiatry*. 2002;59(6):530-537. Judd, LL, et al. *Archives of General Psychiatry*. 2003;60(3):261-269.

Latest Updates in Treatment Innovations

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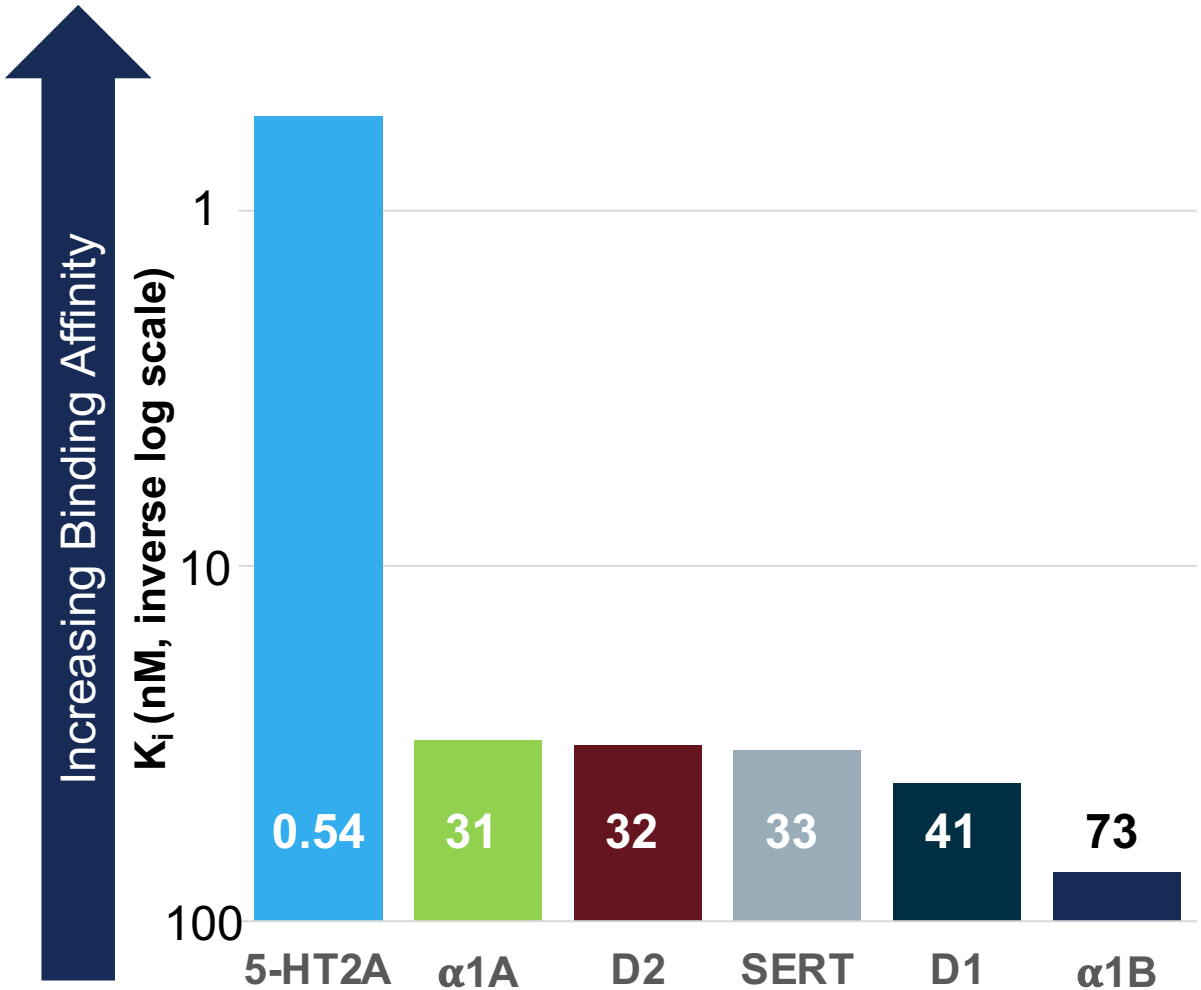
FDA-Approved Treatments for Bipolar Depression: Some Needs are More Unmet than Others

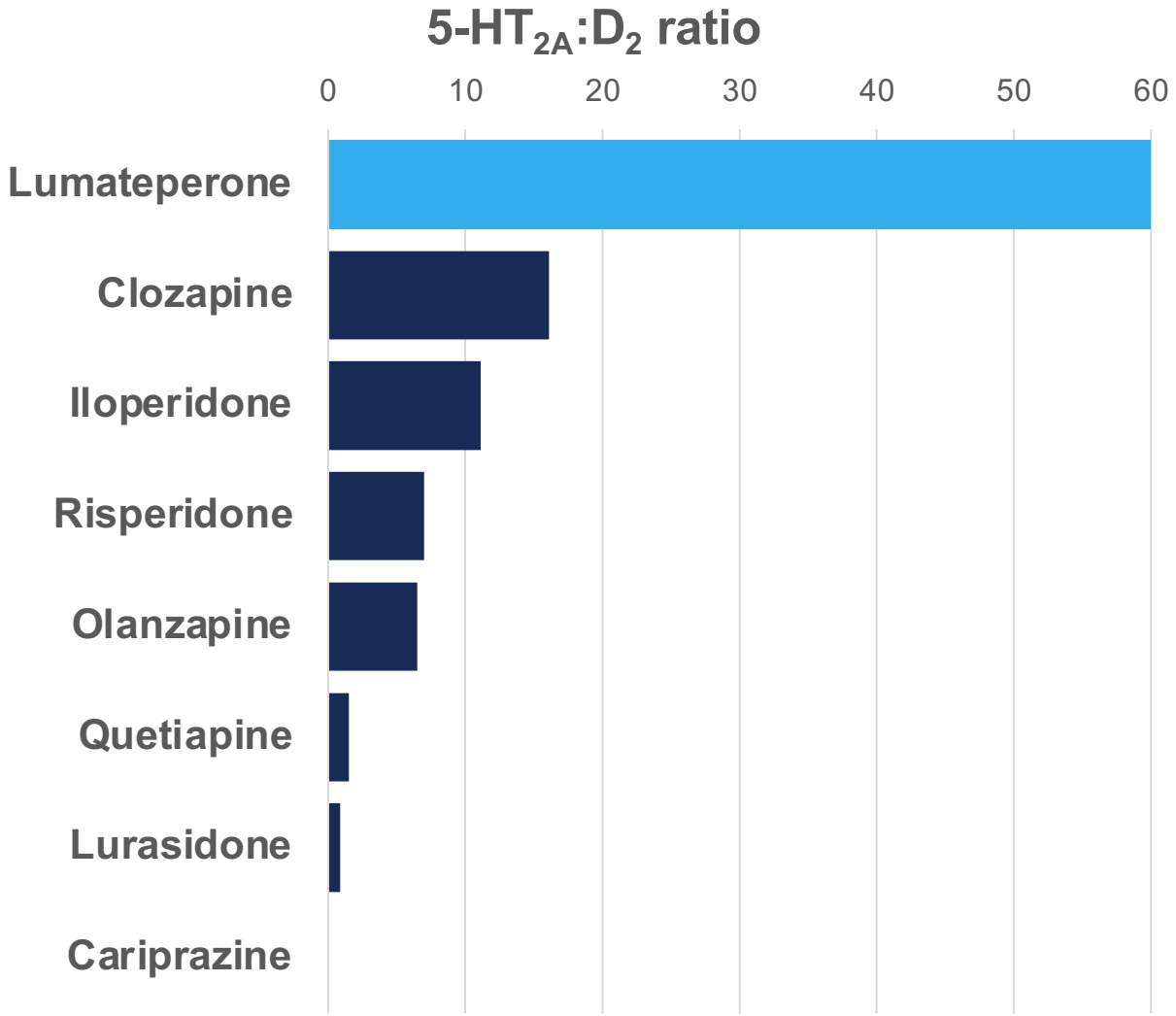
		2003	2006	2013	2019	2021	
		Olanzapine/ Fluoxetine	Quetiapine (IR and XR)	Lurasidone	Cariprazine	Lumateperone	Total Options
Bipolar I	Monotherapy	✓	✓	✓	✓	✓	5
	Adjunct to Lithium or Valproate			✓		✓	2
Bipolar II	Monotherapy		✓			✓	2
	Adjunct to Lithium or Valproate					✓	1

FDA = US Food and Drug Administration.

Lumateperone. Prescribing information. Intra-Cellular Therapies; 2021. Quetiapine. Prescribing information. AstraZeneca; 2021. Quetiapine XR. Prescribing Information. AstraZeneca; 2020. Olanzapine/fluoxetine. Prescribing information. Eli Lilly, Inc; 2021. Lurasidone. Prescribing information. Sunovion Pharmaceuticals Inc; 2019. Cariprazine. Prescribing information. AbbVie plc; 2019.

Lumateperone Receptor Binding



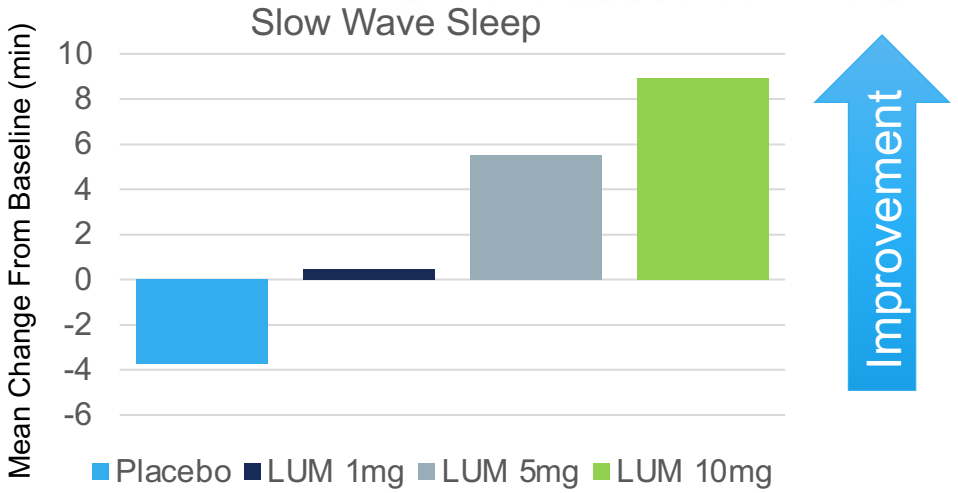


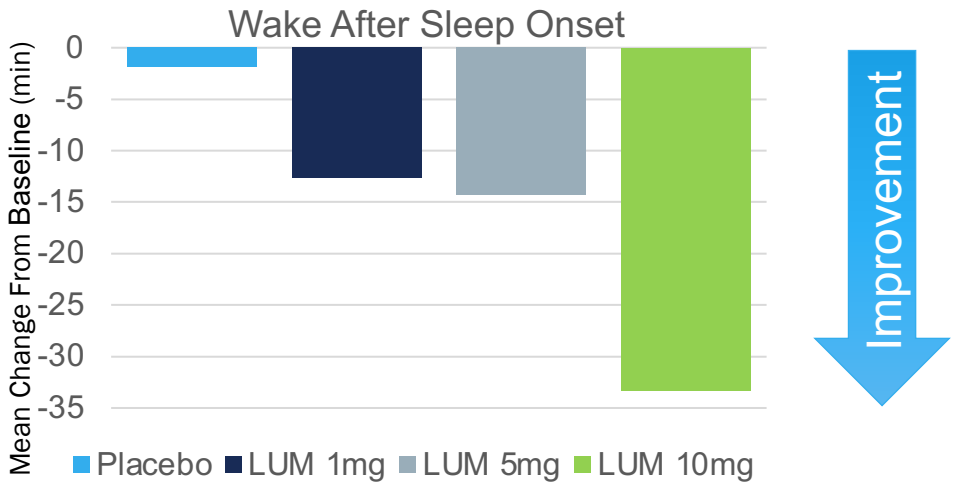
Caplyta. Prescribing information. Intra-Cellular Therapies; 2021. Li P, et al. *Journal of Medicinal Chemistry.* 2014;57(6):2670-2682. Kantrowitz JT. *CNS Drugs. 2020;*34(9):947-959.

5-HT_{2A} Antagonism and Sleep

Potential Effects of 5-HT_{2A} Antagonism	
Positive Effects on Sleep	**Potential Adverse Effects**
Increased Slow Wave Sleep	Dizziness/hypotension
Decreased wake after sleep onset	Fatigue
Decreased arousals/awakenings	Headache
Improved sleep maintenance	Nausea/vomiting
Improved sleep efficiency	Constipation

Low-dose lumateperone improved sleep parameters in patients with insomnia disorder



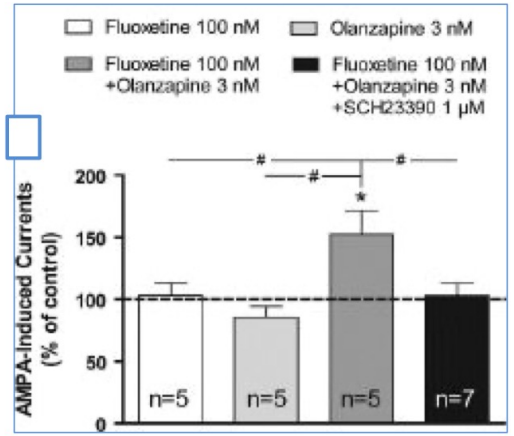


LUM = lumateperone.

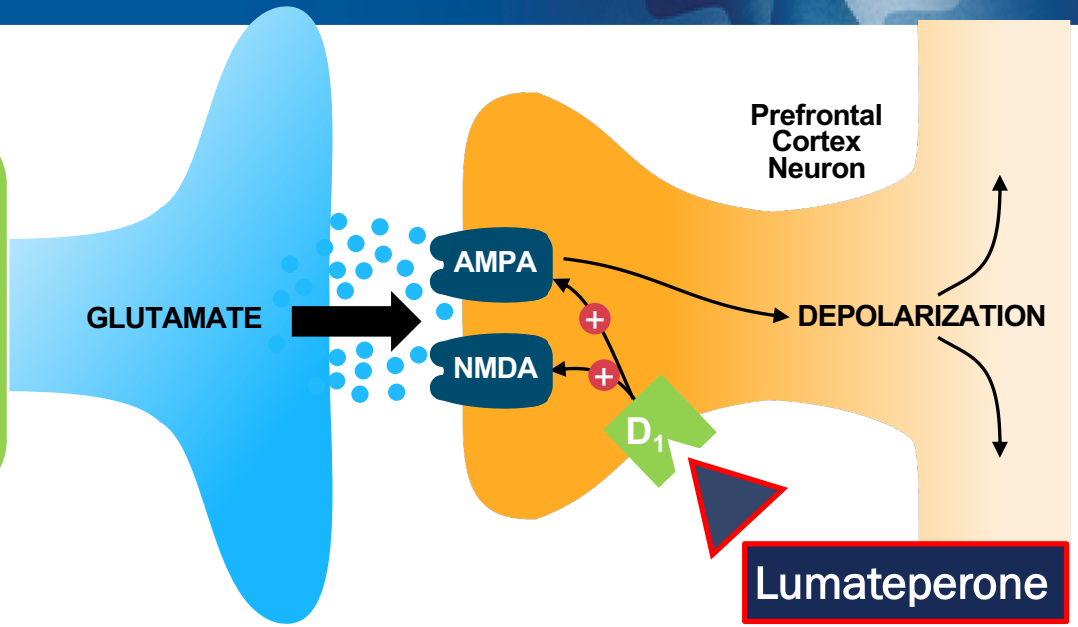
Vanover KE, et al. European Neuropsychopharmacology. 2017;27:S660-S661. Vanover KE, et al. Nature and Science of Sleep.2010;2:139.

D_1 Indirect Modulation of Glutamate Function

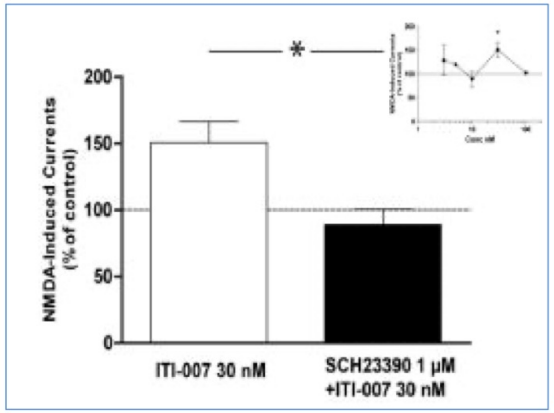
Olanzapine enhances AMPA currents only when combined with fluoxetine

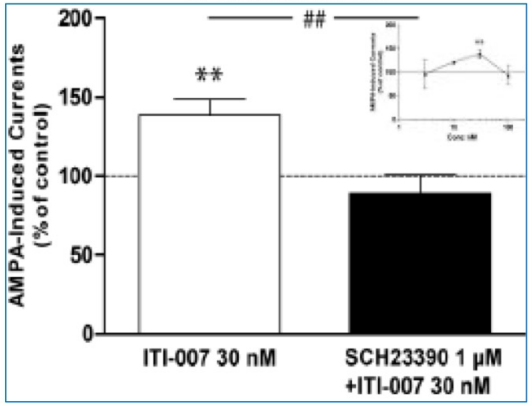


Preclinical data shows lumateperone indirectly activates both NMDA and AMPA glutamatergic function in the PFC via its D_1 receptor binding



Lumateperone monotherapy enhances NMDA and AMPA-induced currents



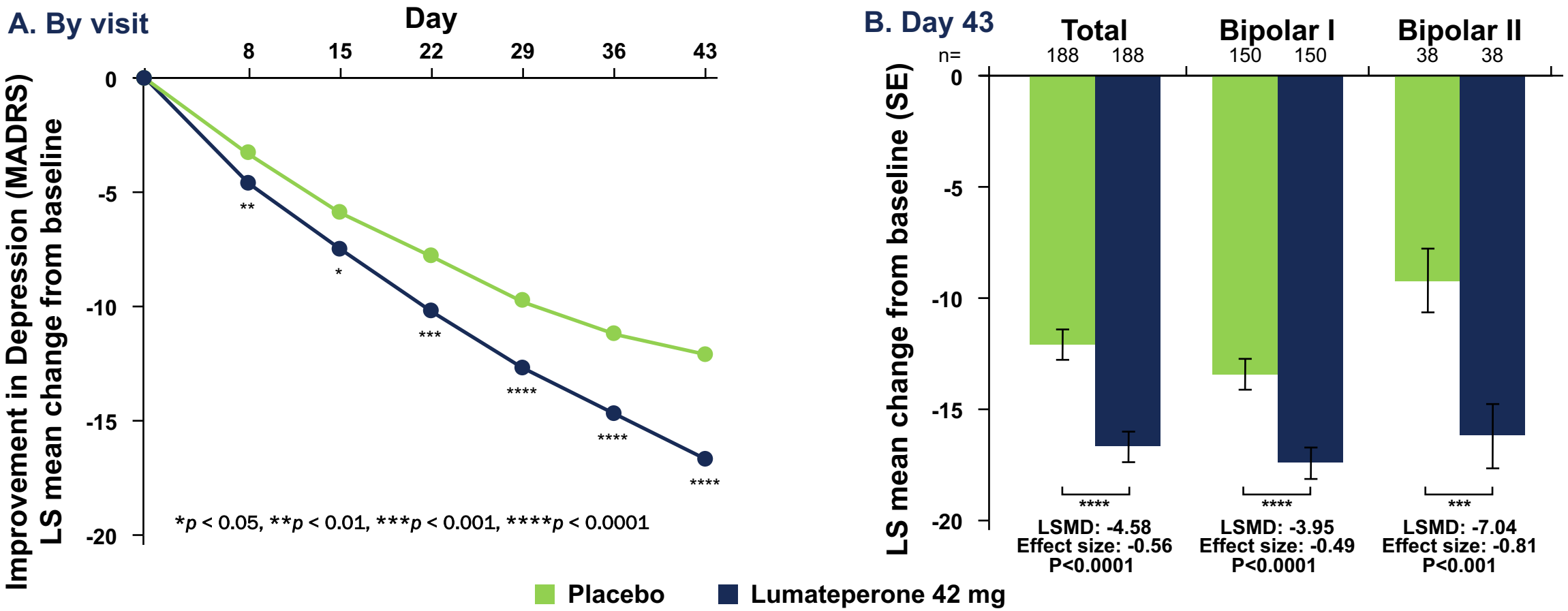


	D1	D2	D3	5-HT$_{1A}$	5-HT$_{2A}$	α1	SERT
Olanzapine-Fluoxetine	56.6	30.8	38.1	2063-2720	4.0	19	High
Lumateperone	41	32	-	1480	0.54	31-73	Mod.

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartate; PFC = Prefrontal Cortex.

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

Lumateperone in Bipolar I and II Depression: Monotherapy

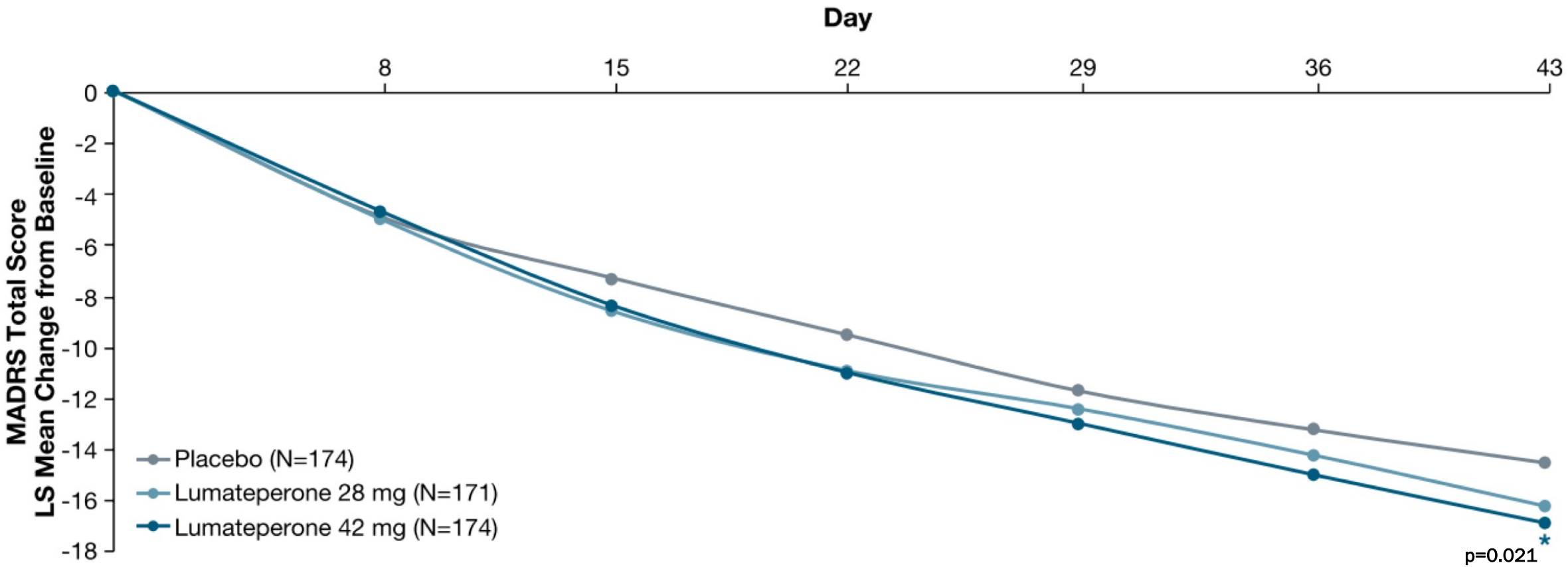


Drug-Placebo differences of 3-4 points on MADRS are considered clinically relevant

MADRS = Montgomery Åsberg Depression Rating Scale; SE = standard error.

Durgam, S. Poster presented at: ACNP Annual Meeting; December 6-9, 2020; virtual. Montgomery, SA. *European Neuropsychopharmacology. 1994;*4(3):283-284.

Lumateperone in Bipolar I and II Depression: Adjunct to Lithium or Valproate



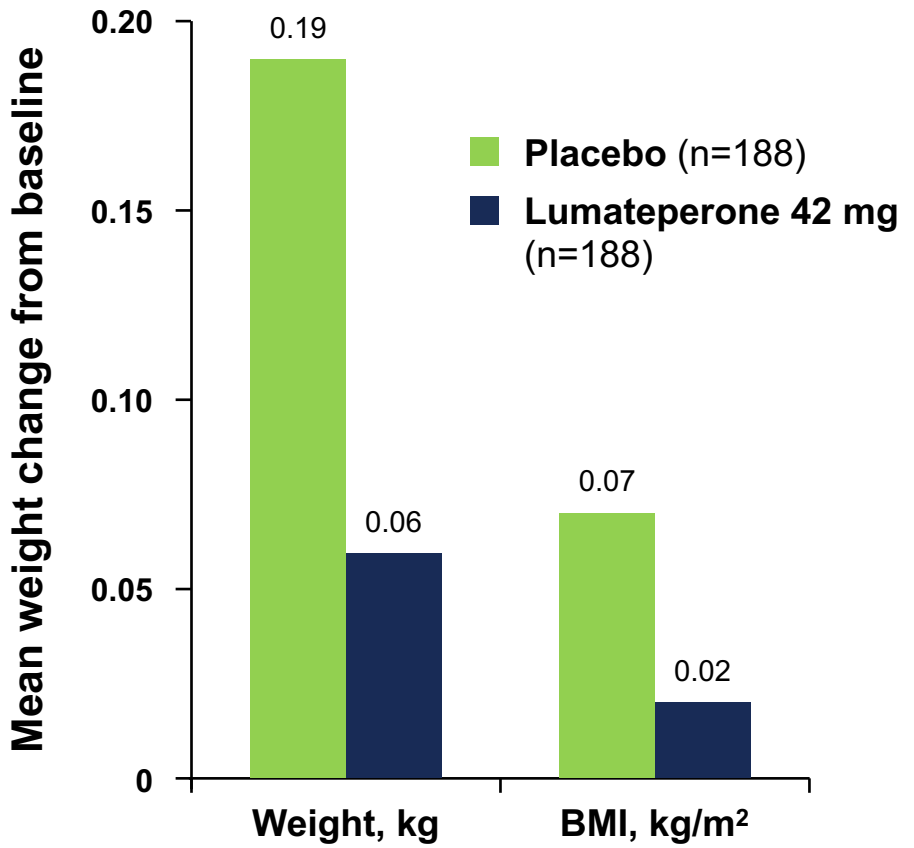
SE = standard error.

Yatham, L. Poster presented at: APA Annual Meeting; May 1-3, 2021; virtual.

Tolerability of Lumateperone Across Acute Bipolar Depression Trials

Proportion of patients (%) with:	6-week monotherapy trials		Adjunctive therapy with 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%

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



0 patients with > 7% weight gain

Caplyta. Prescribing information. Intra-Cellular Therapies; 2021. Posters presented at: APA Annual Meeting; May 1-3, 2021; virtual.

Considerations for Selecting and Monitoring Treatment

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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

e.g., antimanic efficacy less relevant in BD-II than it is in BD-I

Past treatment responses, past adverse reactions

e.g., meds with high risk for akathisia are less favorable for patients with past history of akathisia

Presence of comorbid disorders

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

McIntyre RS, et. al. *Human Psychopharmacology: Clinical and Experimental. 2004;*19(6):369-386. Yatham LN, et al. *Bipolar Disorders*. 2018;20(2):97-170.

Which of the following medications both have a MODERATE movement disorder risk?

A Quetiapine & Olanzapine

B Quetiapine & Lurasidone

C Lurasidone & Olanzapine

D Lurasidone & Cariprazine

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Scan the QR code to participate!

Results

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Which of the following medications both have a MODERATE movement disorder risk?

A Quetiapine & Olanzapine

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C Lurasidone & Olanzapine

D Lurasidone & Cariprazine

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Which of the following medications has a HIGH weight and metabolic risk?

A Quetiapine & Olanzapine

B Quetiapine & Lurasidone

C Lurasidone & Olanzapine

D Lurasidone & Cariprazine

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Results

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Which of the following medications both have a HIGH weight and metabolic risk?

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Considerations for Monitoring Treatment

	Olanzapine/ Fluoxetine	Quetiapine (IR and XR)	Lurasidone	Cariprazine	Lumateperone
Weight & Metabolic Risks	**High**	**High**	**Low**	**Low**	**Low**
Movement Disorder Risks	**Low**	**Low**	**Moderate**	**Moderate**	**Low**

Early onset of weight gain or metabolic changes are usually a harbinger of further problems

Early movement disorders (akathisia, dystonia, DIP) are risk factors for later development of TD

Both must be monitored closely in the short and long term!

As patients transition from acute treatment to long-term maintenance, tolerability and treatment satisfaction are key factors in adherence!

DIP = drug-induced Parkinsonism; TD = tardive dyskinesia.

Olanzapine/fluoxetine PI. Eli Lilly, Inc; 2021. Quetiapine PI. AstraZeneca; 2021. Quetiapine XR PI. AstraZeneca; 2020. Lurasidone PI. Sunovion Pharmaceuticals Inc; 2019. Cariprazine PI. AbbVie plc; 2019. Lumateperone PI. Intra-Cellular Therapies; 2021.

Bates JA, et al. *The Primary Care Companion for CNS Disorders.* 2010; 12(5):26157.

Strategies for Optimizing Patient-Centered Treatment Plans

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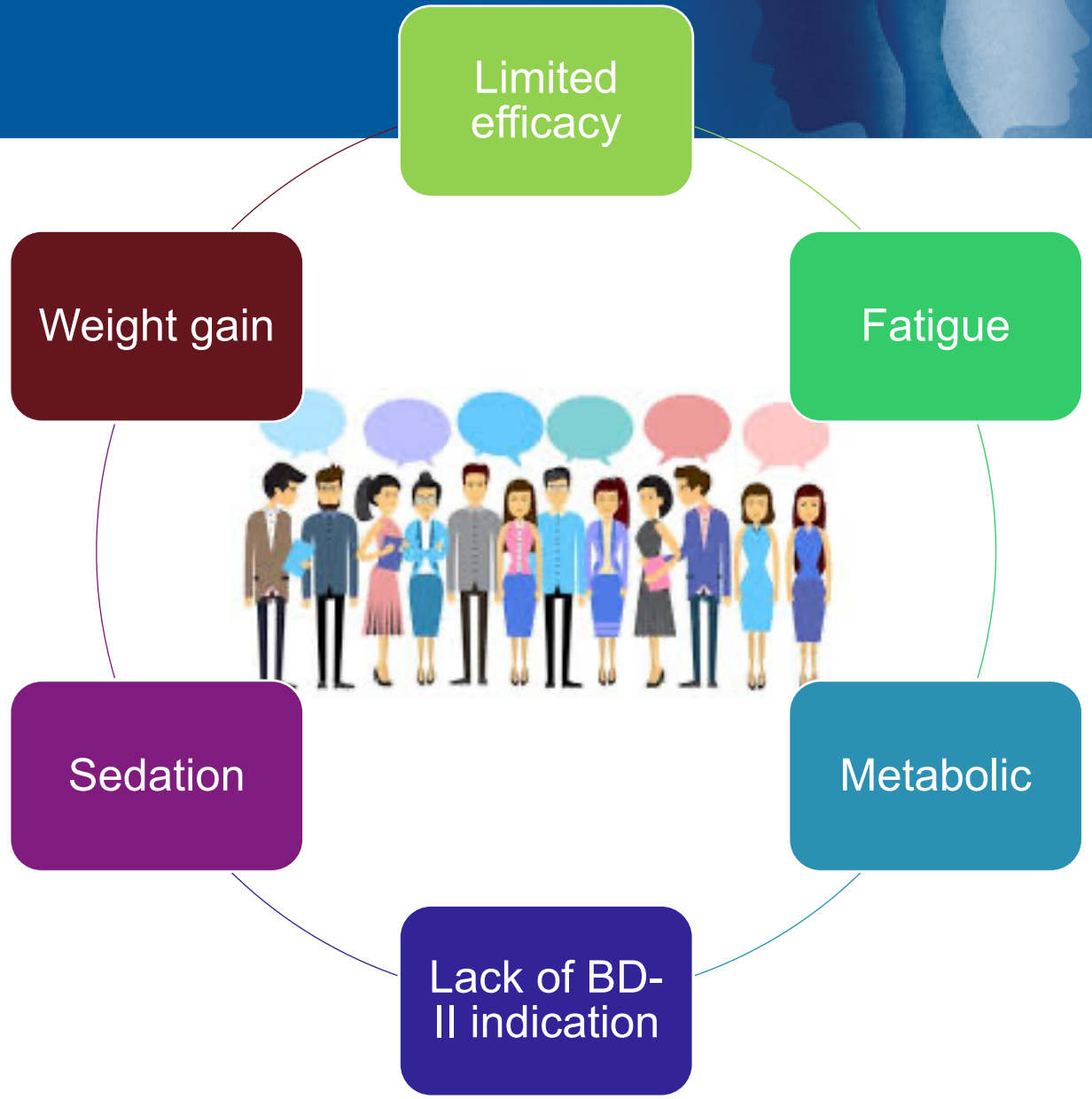
Strategies for Optimizing Patient-Centered Treatment Plans

- Oral Med vs Injection
  - Onset of Action
  - Frequency
  - Where does the patient go to get the injection?
  - What location on the body is the injection administered?
  - Fiscal Obtainability
  - Home Delivery vs Pick Up
  - Half Life of Medication

In Conclusion…

The six major unmet needs with current pharmacotherapy of bipolar disorder



Rosenblat JD, et al. *J Affect Disord.* 2019;243:116-120.

Meet Vanessa

Talking with Patients About the Potential for Novel Medications To Address Adverse Effects

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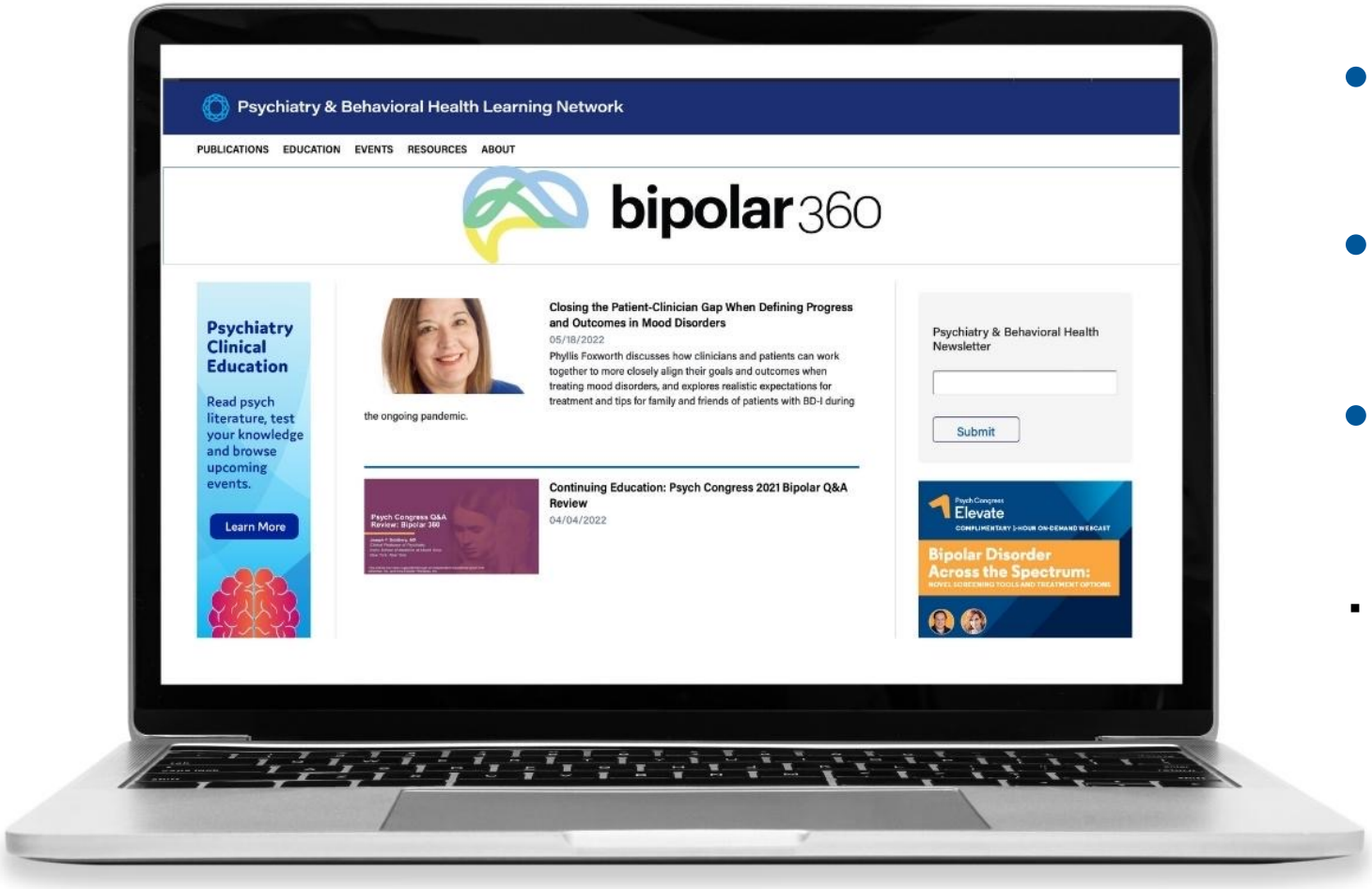

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