BIPOLAR 360

Psych Congress REGIONALS | ONLINE SERIES

Looking Beyond D2: Mechanisms of Action and Clinical Applications of Novel Therapies for Bipolar I and Bipolar II Disorder

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Faculty Disclosure

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

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- **Vanessa Joy Walker** has no financial relationships to disclose relating to the subject matter of this presentation

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- This activity has been independently reviewed for balance

CME = continuing medical education.

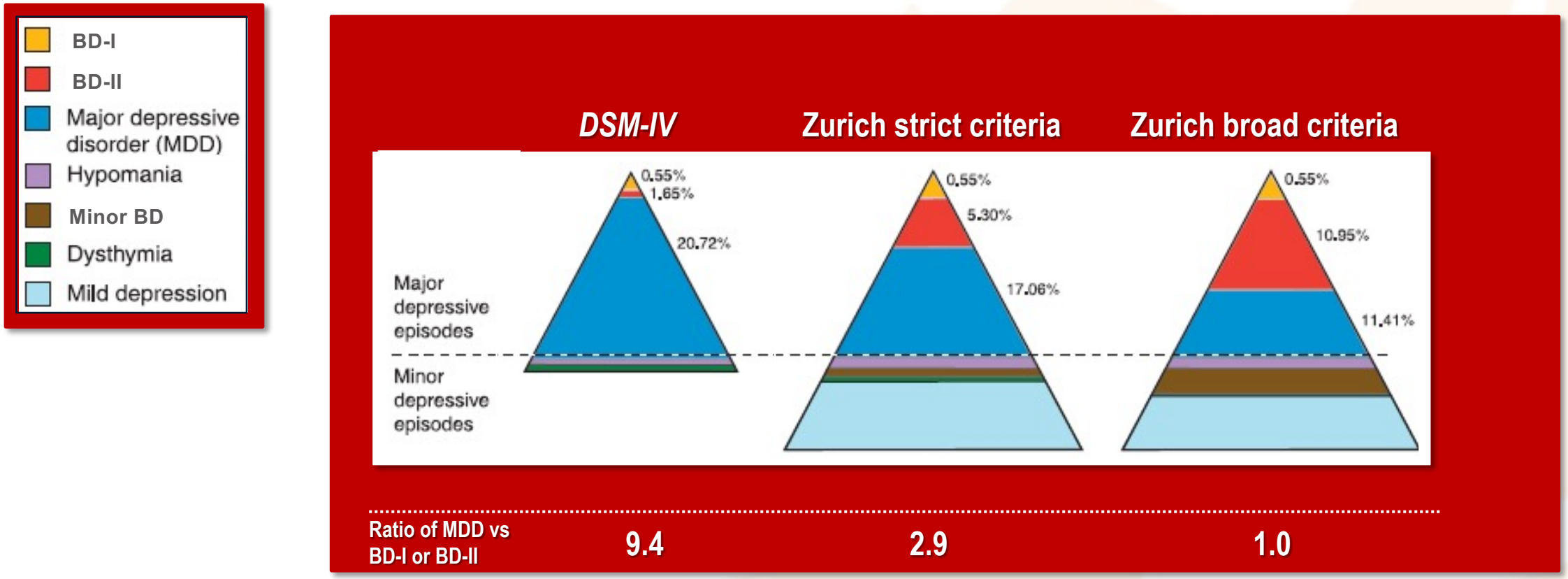
Learning Objectives

- 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
- Assess patient characteristics, comorbidities, and preferences in order to optimize personalized/patient-centered treatment plans
- Implement effective multidisciplinary strategies to monitor treatment and address adverse effects and/or comorbidities, including obesity, dyslipidemia, and EPS

BD = bipolar disorder; EPS = extrapyramidal symptoms.

Differentiating between BD1, BD2, and Other Psychiatric Disorders and Obstacles to BD Identification: Strategies to Identify and Assess BD and Its Symptom Domains

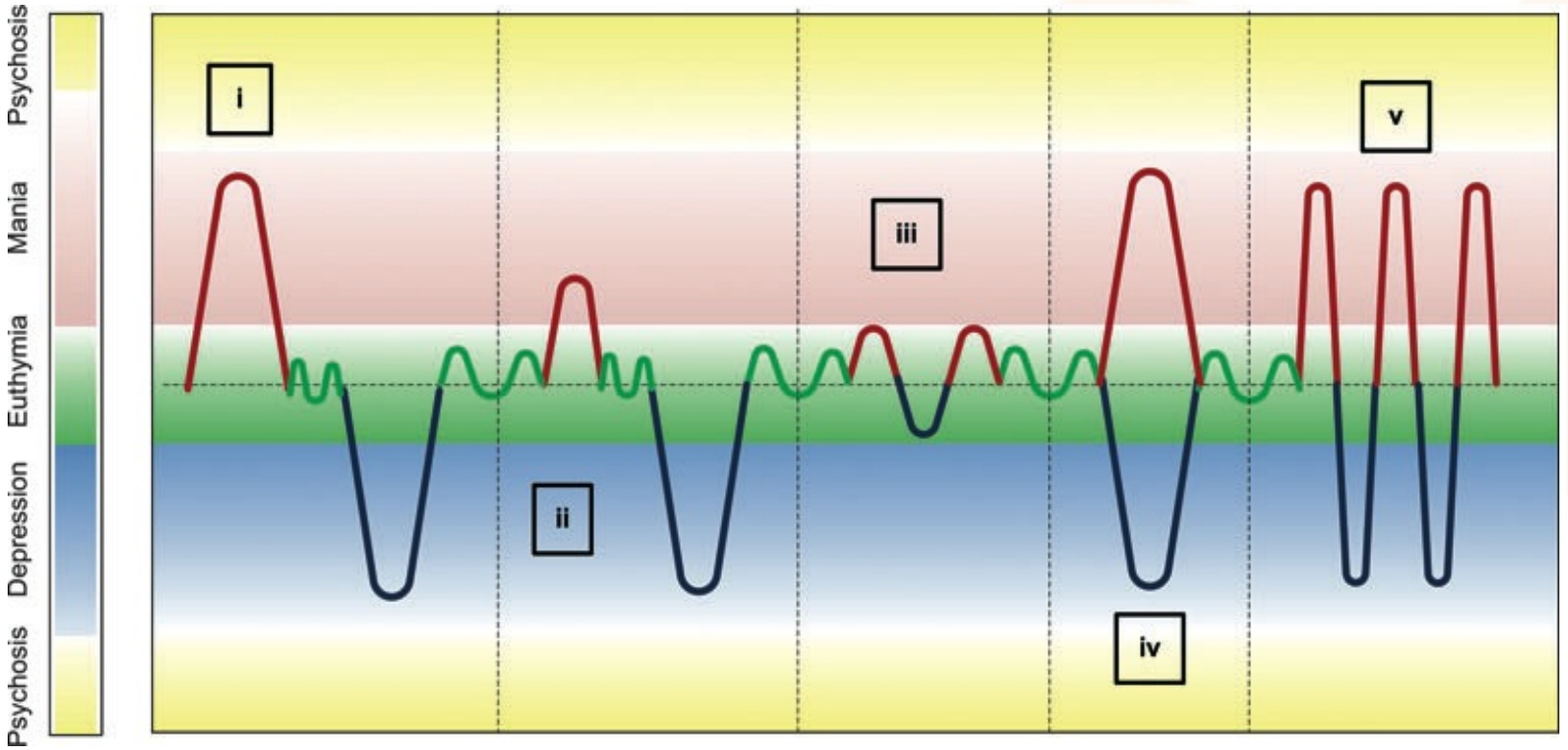
Bipolar Disorders Are Common—Both BD-I and BD-II Disorders



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.

Bipolar Disorder and the Vast Variety of Presentations

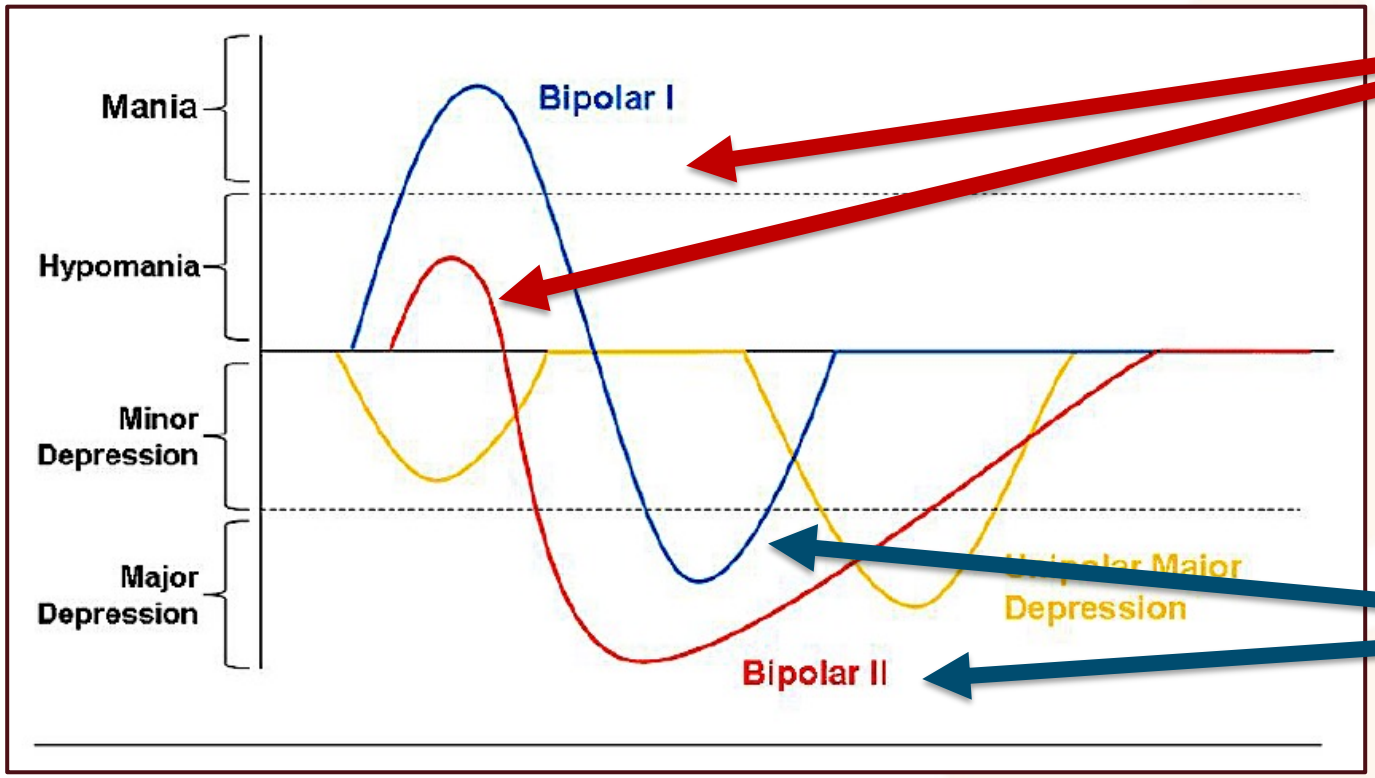


The core patterns of BD

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

Malhi GS, et al. *Bipolar Disord*. 2012;14(Suppl 2):66-89.

Bipolar I and II Patients Typically Present in the Depressed Phase

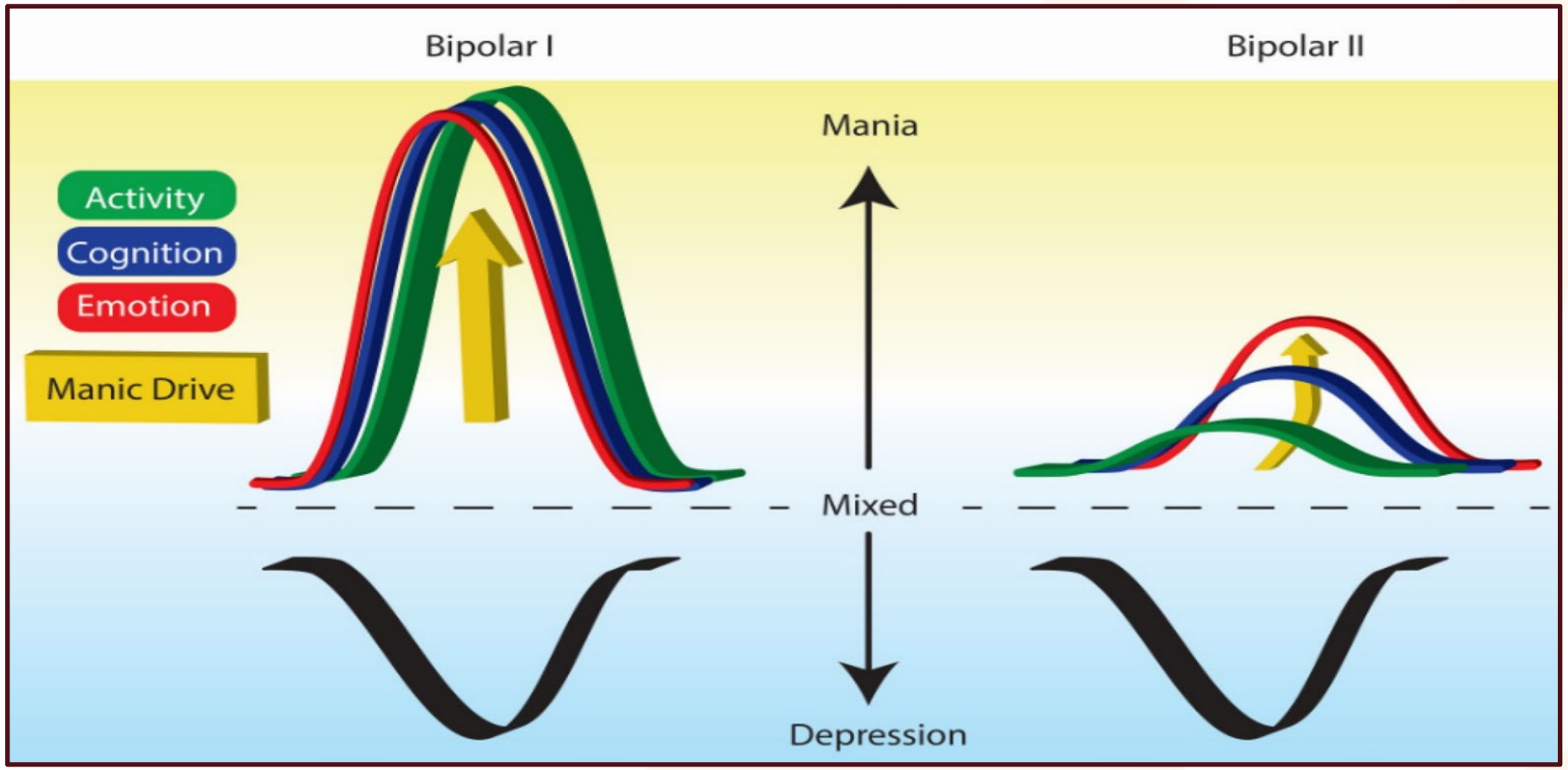


Rarely reported by patients

Universal presentation—depressed phase

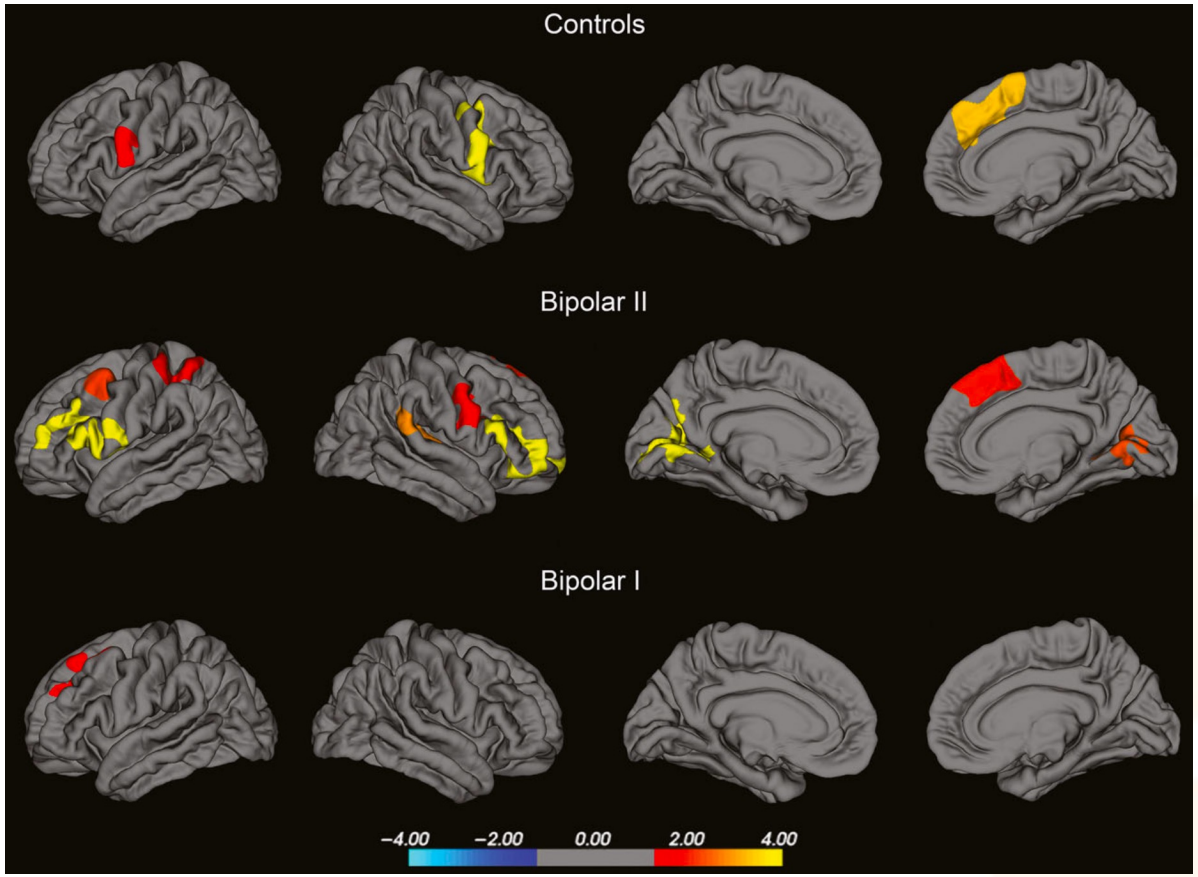
Gitlin M, et al. *Int J Bipolar Disord.* 2020;8:5.

Looking at Bipolar Disorder I and II Though the Lens of ACE Model

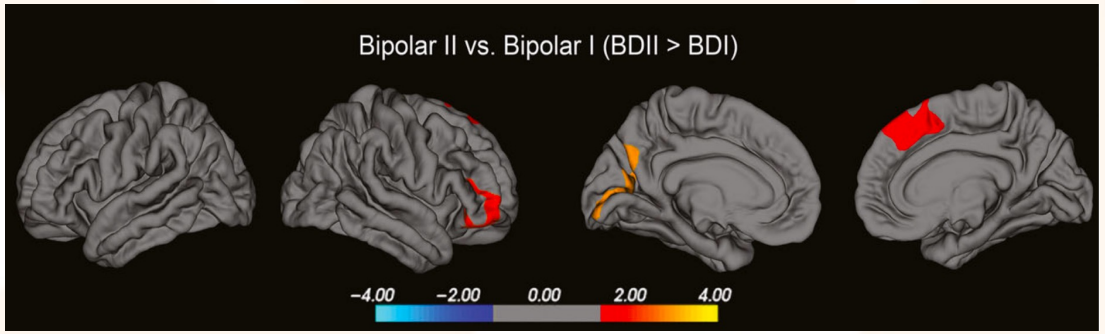


ACE = activity, cognition, and emotion.
Gitlin M, et al. *Int J Bipolar Disord.* 2020;8:5.

Is Bipolar Type II a Distinct Disorder? Neurobiologic Evidence Says "Yes"



49 patients with BD-I, 28 patients with BD-II, and 83 controls; two modalities combined (neuroimaging and neuropsychological testing)



Findings:

- **Focal associations between executive function and cortical thickness in the medial PFC in bipolar II patients and controls, but not in bipolar I disorder**
- **In bipolar II patients, additional correlations in lateral prefrontal and occipital regions between neuroimaging and neuropsych testing**

PFC = prefrontal cortex.

Abé C, et al. *Acta Psychiatr Scand.* 2018;138(4):325-335.

Difference Between Bipolar I and II:

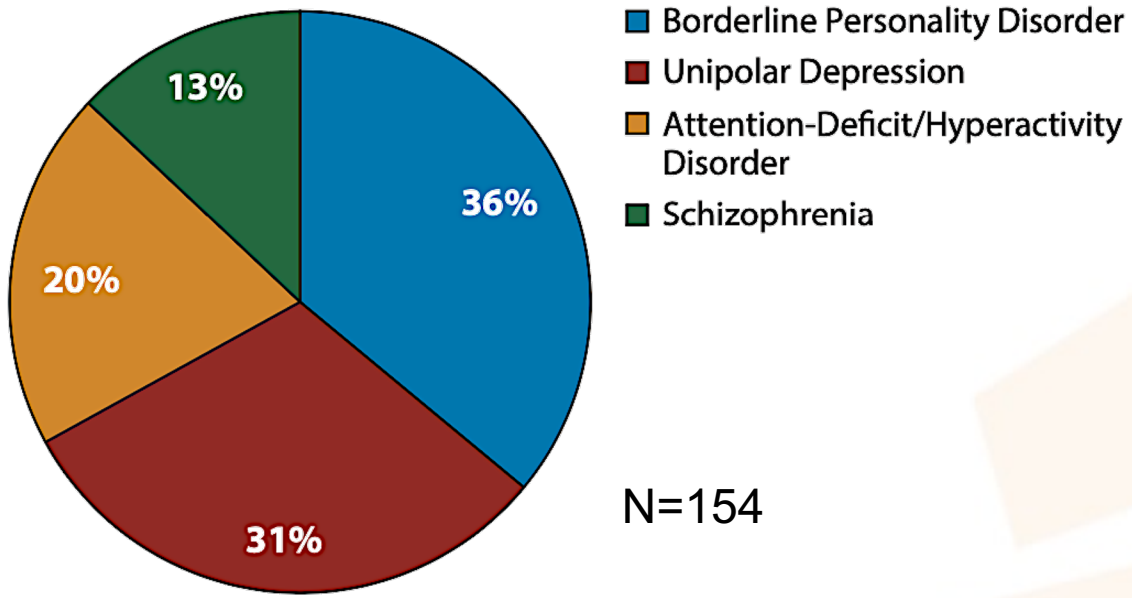
Examining the Difference Between Manic and Hypomanic Episodes

- 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

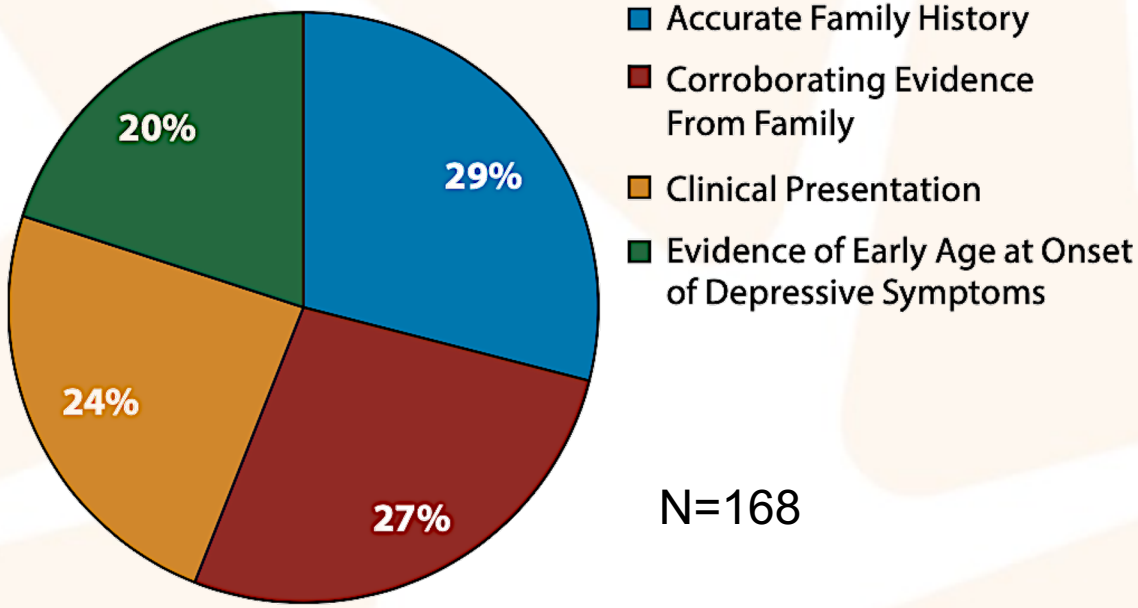
Bipolar Disorder Is Often Complex to Diagnose—and Tips on Differentiating BD from MDD

Disorders Most Difficult to Differentiate from Bipolar Disorder



N=154

Best Predictors for Achieving Differential Diagnosis between MDD vs. BD



N=168

Results of a survey of majority psychiatry clinicians.

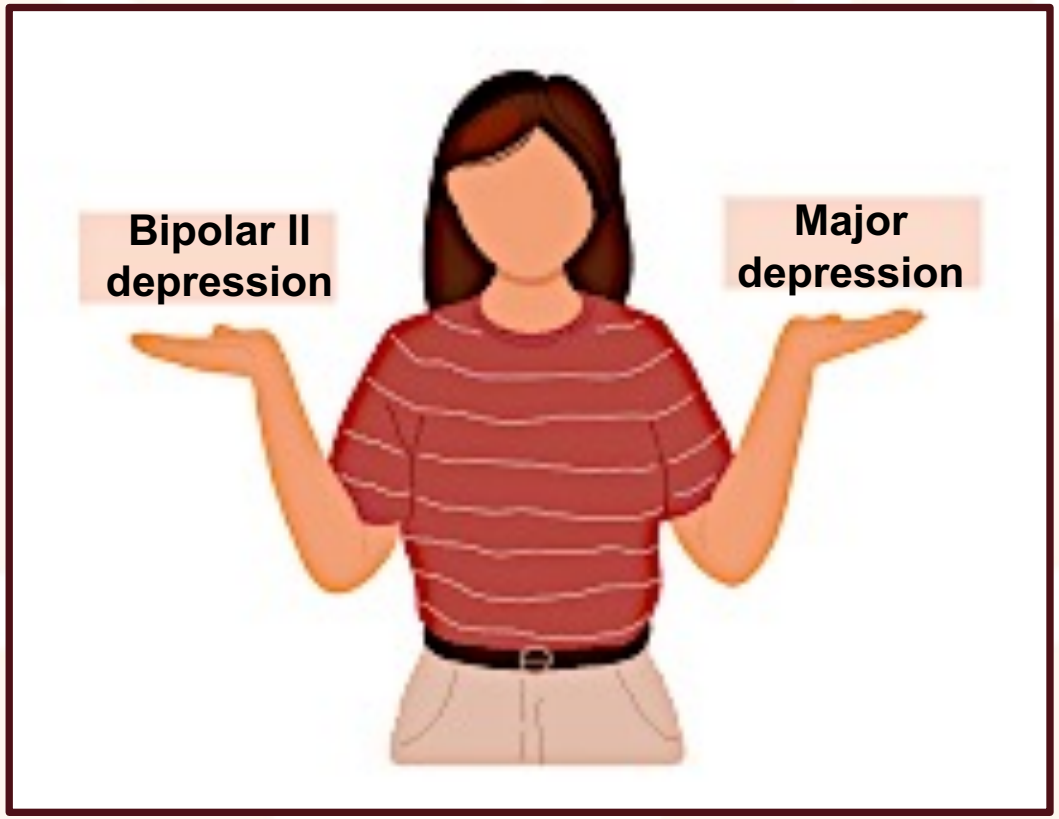
McIntyre RS, et al. *J Clin Psychiatry.* 2019;80(3):ot18043ah2.

“Is This Major Depression or Bipolar II Depression?”
Some Risk Factors

The following prodromal elements increase the risk what we are seeing is bipolar II depression vs major depression

Patients with BD-II, as compared to major depression, experienced:

- **Experience both insomnia and hypersomnia during the depressive episode (p=.04)**
- **More likely to have experienced > 5 previous mood episodes 61 % vs 12% (p<.0001)**
- **Earlier age of onset (p=.003)**

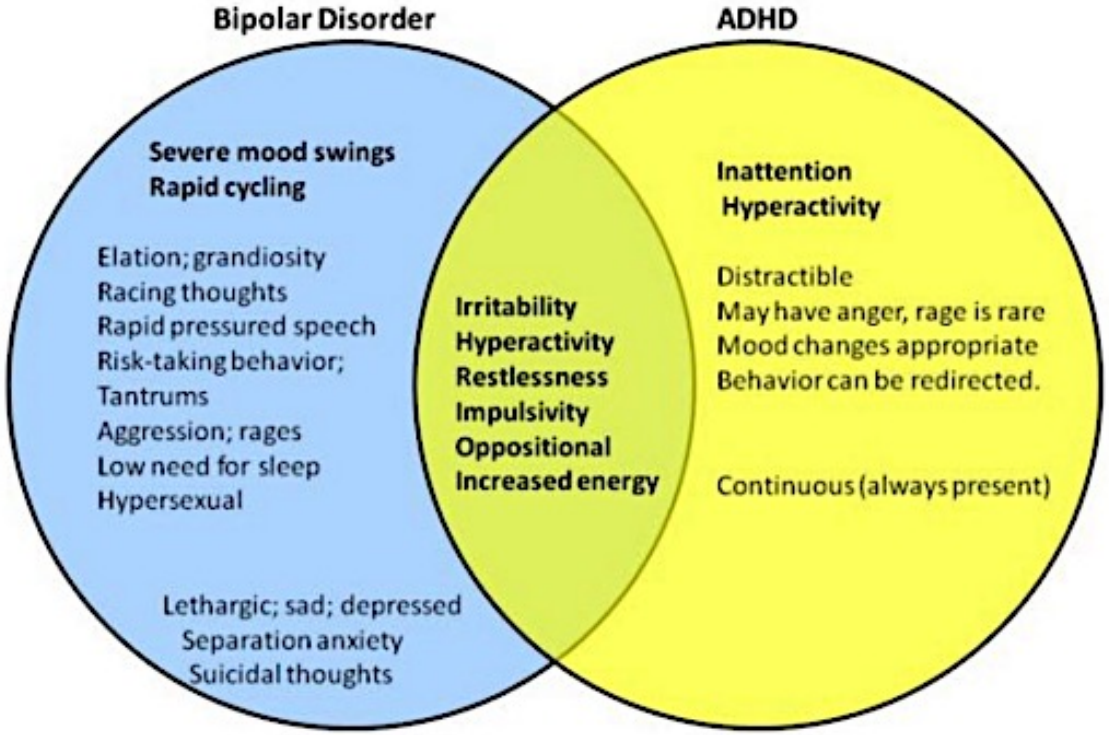


Rastelli CPB, et al. *J Affect Disord*. 2013;150(3):1120-1124.

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:

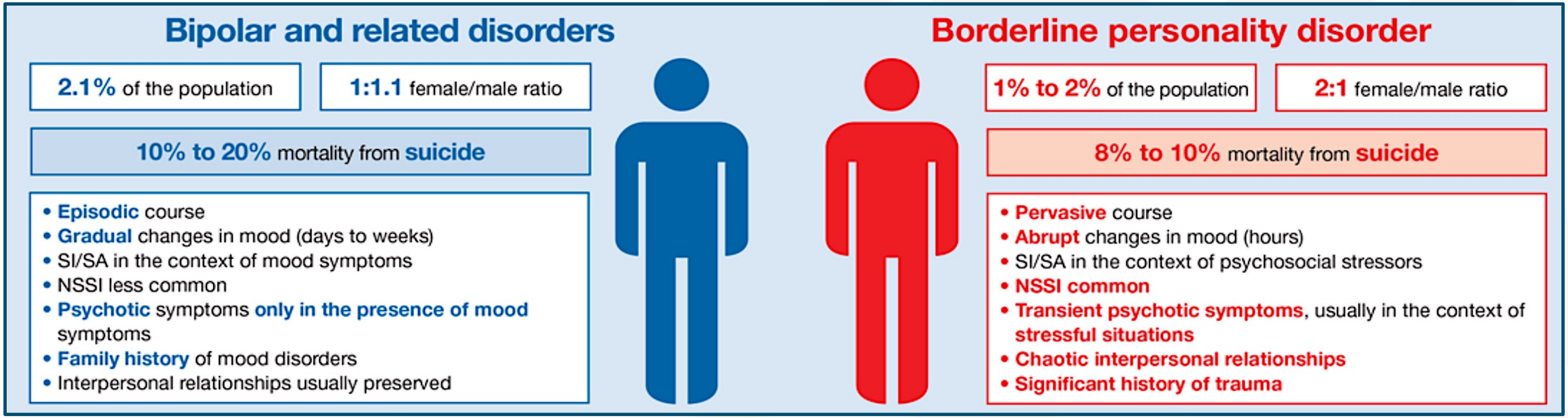
- ADHD affects 4.4% of versus 1.4% for bipolar disorder
- Onset of symptoms—usually before age 7 years in ADHD versus after age 12 years in bipolar disorder
- Disease course (chronic in ADHD versus cyclical in bipolar disorder)
- Mood symptoms (absent in ADHD but always present in bipolar disorder)
- 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.

Identifying Bipolar Depression: Screening and Diagnostic Considerations

- Evaluate all patients with major depression for manic, hypomanic, and subthreshold symptoms
  - Ask about mood changes immediately before or after prior depressive episodes
  - Ask about prior periods of enhanced function
  - Ask about temporal relationship with antidepressants
- Consider screening tools
  - Mood Disorder Questionnaire (MDQ)
  - Bipolar Spectrum Diagnostic Scale (BSDS)
- Obtain collateral history from a significant other
  - Relationship challenges between patient and significant others can complicate obtaining collateral information

Berk M, et al. *Bipolar Disord*. 2007;9:571-579. Hirschfeld RM, et al. *Am J Psychiatry*. 2000;157:1873-1875.

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

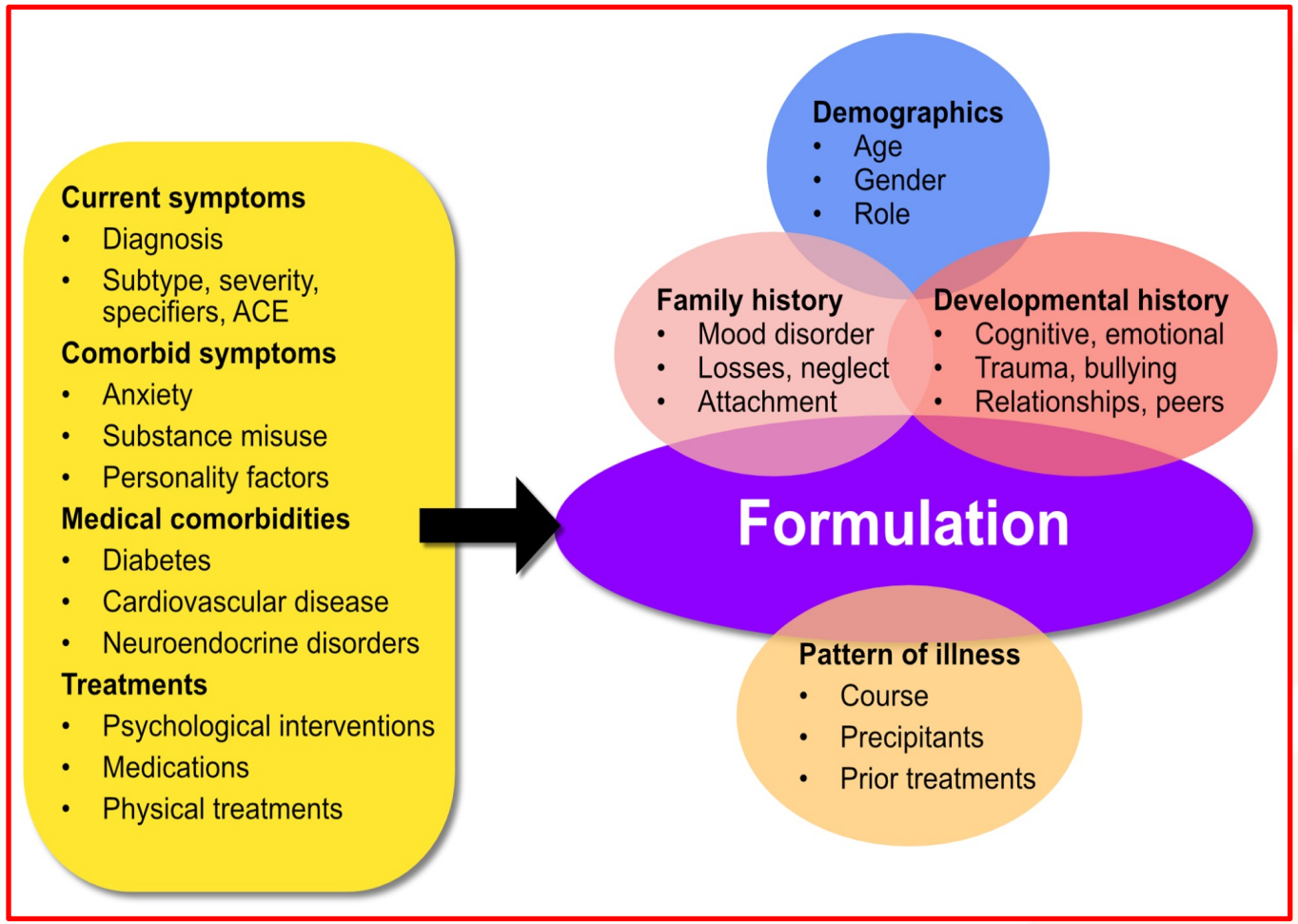
- Never make a diagnosis of major depression without proactively assessing for mania/hypomania in past/currently
- Acquire collateral information from family/friends
- If patient presents with irritability, distractibility, insomnia, substance misuse (amongst other) symptoms, proactively look for bipolar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

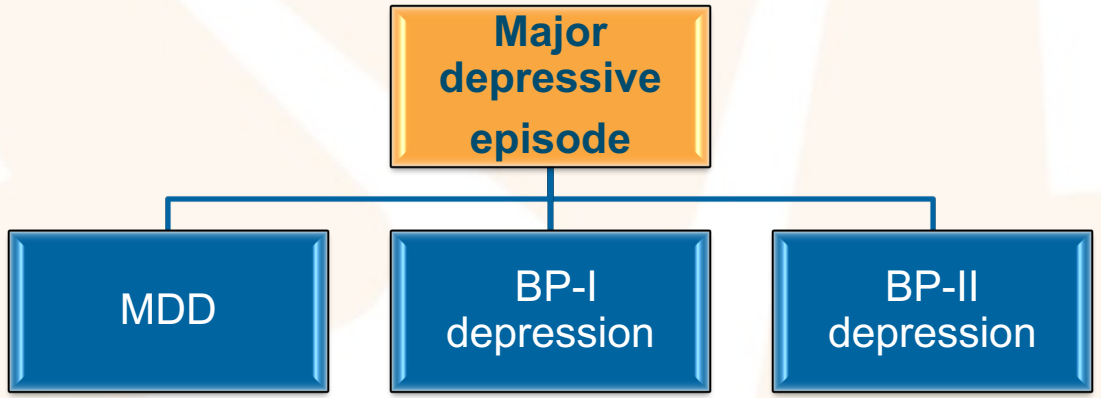
- Use screening instruments such as the MDQ
- Look for family history—BD is a highly genetic disorder
- Early onset, multiple episodes of depression, poor response to antidepressants (amongst others) are all markers of accurate bipolar disorder
- Watch out for hypomanic episodes! They are tricky to detect, 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 to the Correct Dx/Dxs.





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

Limitations Associated with Traditional Treatments

There are Many Treatment Options…But Many Patients with BP-I and BP-II Depression Are Not Getting Optimum Outcomes with Efficacy and Tolerability.

CANMAT Guidelines: Bipolar Psychopharmacology Options in 2016—The 2022 Portfolio Is Even Bigger

	Level of evidence by phase of treatment					Considerations for treatment selection			
		Maintenance				Acute		Maintenance	
	Acute depression	Prevention of any mood episode	Prevention of depression	Prevention of mania	Acute mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns
First-line treatments									
Quetiapine	●	●	●	●	●	+	++	++	++
Lurasidone + Li/DVP	●	◐[a]	◐[b]	◔[c]	n.d.	+	++	++[d]	++/+
Lithium	◔	●	●	●	●	+	+	++	++
Lamotrigine	◔	●	●	◔	■	++	–	–	–
Lurasidone	◔	◔	◔	◔	n.d.	–	+	–	+
Lamotrigine (adj)	◔	◔	◔	◔	◪	++	+	++	++
Second-line treatments									
Divalproex	◔	●	◔	◐	●	–	+	++[d]	+
SSRIs/bupropion (adj)	●	n.d.	◔	n.d.	n.d.	–	+	–	+
ECT	◔	◔	◔	◔	◐	+	++	+	++
Cariprazine	●	n.d.	n.d.	n.d.	●	–	+	–	–
Olanzapine-fluoxetine	◔	n.d.	n.d.	n.d.	n.d.	+	++	+++	+

CANMAT = Canadian Network for Mood and Anxiety Treatments.
Yatham LN, et al. *Bipolar Disorders.* 2018;20:97-170.

Adverse Events Cause Discontinuations—the High Burden of Side Effects in BD

Adverse effects that cause discontinuation of medications Answer options	Depression group $N = 316$ Response percent	Bipolar group $N = 384$ Response percent	P value
Weight gain	43.7%	56.9%	<0.001
Feeling lethargic/sleepiness	36.7%	49.7%	<0.001
Blunted emotions	35.4%	31.0%	0.218
Anxiety	34.2%	43.7%	0.010
Suicidal thoughts	27.8%	38.5%	0.003
Sexual dysfunction	27.5%	33.8%	0.073
Shaking/trembling	26.6%	43.1%	<0.001
Dry mouth	26.3%	22.0%	0.185
Irritability	24.4%	35.7%	0.001
Insomnia	23.7%	33.8%	0.004
Gastrointestinal issues	23.7%	26.4%	0.413
Headaches/blurred vision	21.8%	29.7%	0.018
Loss of balance/dizziness	21.8%	33.5%	<0.001
Other	17.4%	21.2%	0.206
Impact on pregnancy/nursing	4.1%	5.5%	0.392

DBSA = Depression and Bipolar Support Alliance.
Rosenblat JD, et al. *J Affect Disord.* 2019;243:116-120.

DBSA survey. 896 participants completed the survey; 49.9% unipolar depression and 50.1% bipolar depression

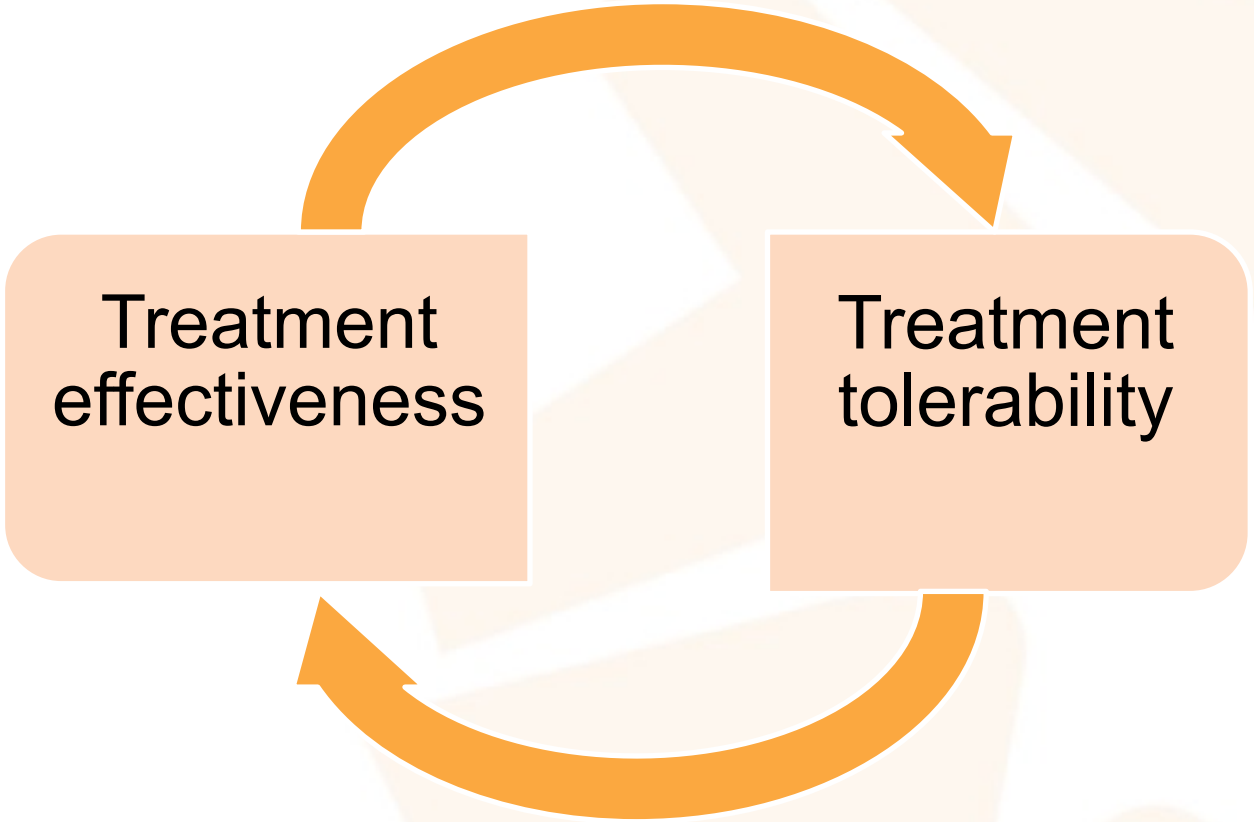
Current pharmacotherapy of bipolar disorder is sub-optimum in terms of tolerability.

Top side effects

- **Weight gain**
- **Lethargy**
- **Sleepiness**
- **Blunted emotions**
- **Anxiety**
- **Etc.**

The Top 2 Patient-Desired Goals in The Treatment of Bipolar Disorder

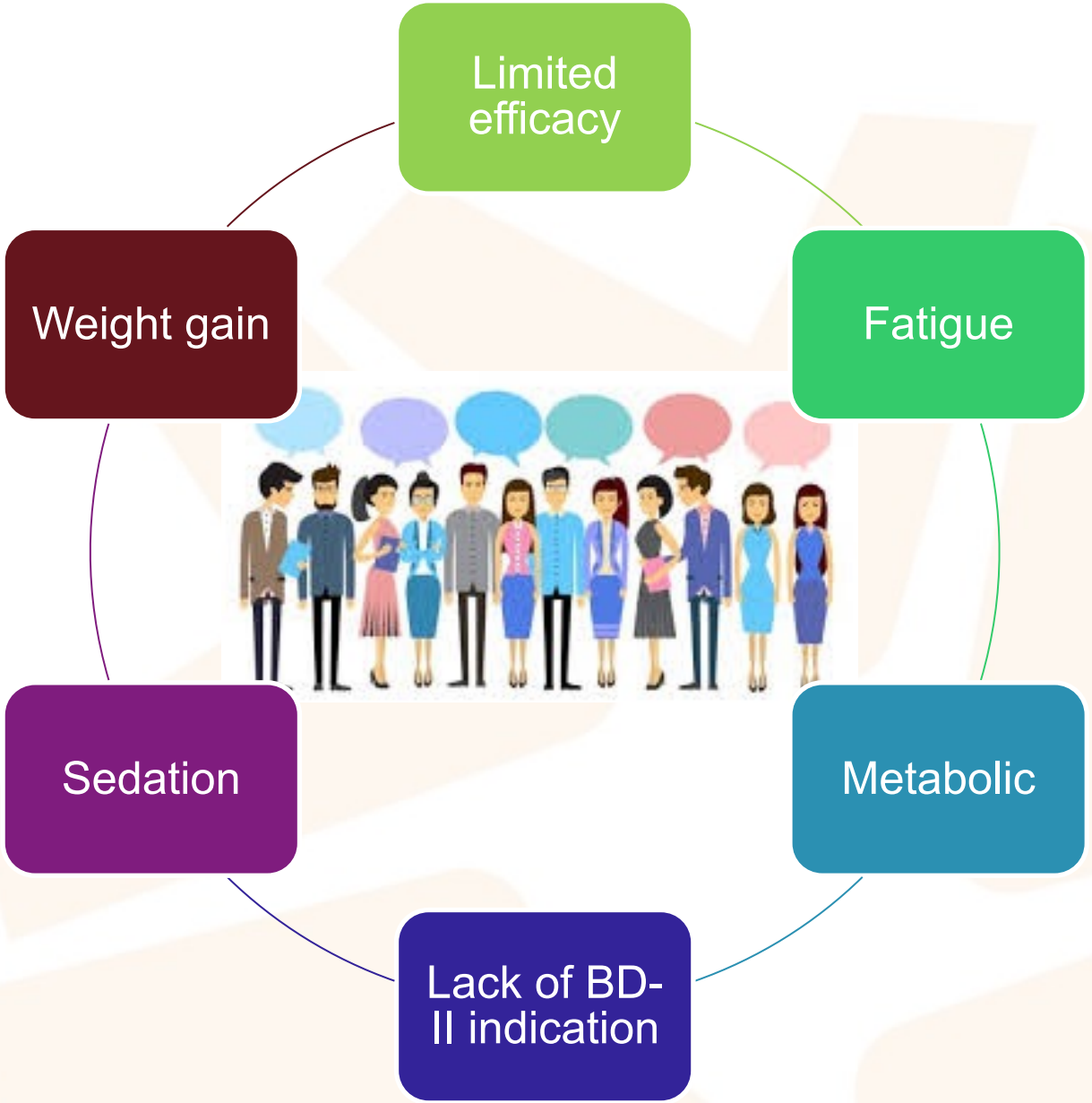
DBSA survey. 896 participants completed the survey; 49.9% unipolar depression and 50.1% bipolar depression



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

In conclusion:

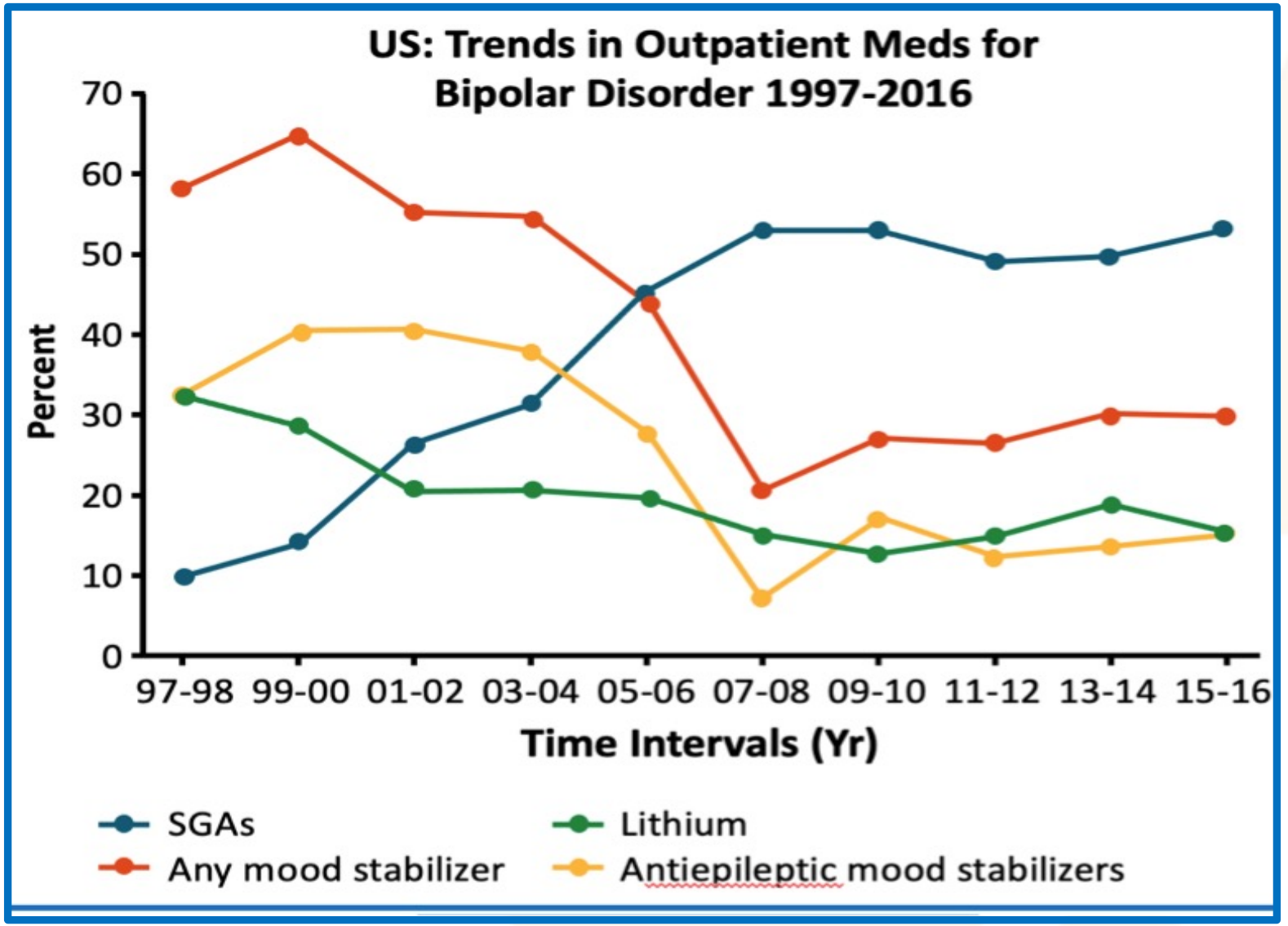
The six major unmet needs with current pharmacotherapy of bipolar disorder



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

New Developments in Bipolar Depression Treatment

Change in Bipolar Treatments?



Gerhard T, et al. *J Clin Psychiatry*. 2014;75(5):490-497.

Clinical Studies Evaluating Adults with a Depressive Episode Associated with Bipolar Disorder (Bipolar Depression)

		Lumateperone	Quetiapine/ Quetiapine XR	Olanzapine/ Fluoxetine	Lurasidone	Cariprazine
Approved for bipolar I	Monotherapy	✓	✓	✓	✓	✓
	Adjunctive*	✓			✓	
Approved for bipolar II	Monotherapy	✓	✓			
	Adjunctive*	✓				

*** With lithium or valproate; ** There are no head-to-head clinical studies comparing the safety and efficacy of these products. This chart is descriptive of the FDA-approved indications.**
FDA = US Food and Drug Administration.
Caplyta. Prescribing information. Intra-Cellular Therapies; 2021. Quetiapine. Prescribing information. BluePoint Laboratories; 2021. Seroquel XR. Prescribing Information. AstraZeneca; 2020. Olanzapine/fluoxetine. Prescribing information. Teva Pharmaceuticals USA, Inc; 2021. Latuda. Prescribing information. Sunovion Pharmaceuticals Inc; 2019. Vraylar. Prescribing information. RemedyRepack Inc; 2019.

In the Clinic

- 5 meds approved for BPD-I
  - Quetiapine, olanzapine/fluoxetine, lurasidone, cariprazine, lumateperone
- 2 meds approved for BPD-II
  - Quetiapine, lumateperone
- 2 meds approved for BPD-I with a mood stabilizer
  - Lurasidone, lumateperone
- 1 med approved for BPD-II with a mood stabilizer
  - Lumateperone

Consider weight gain, sedation, akathisia, sexual side effects, cognition.

Looking Beyond D2

A look at D3, 5HT2a, and D1

D3 vs D2 Receptors

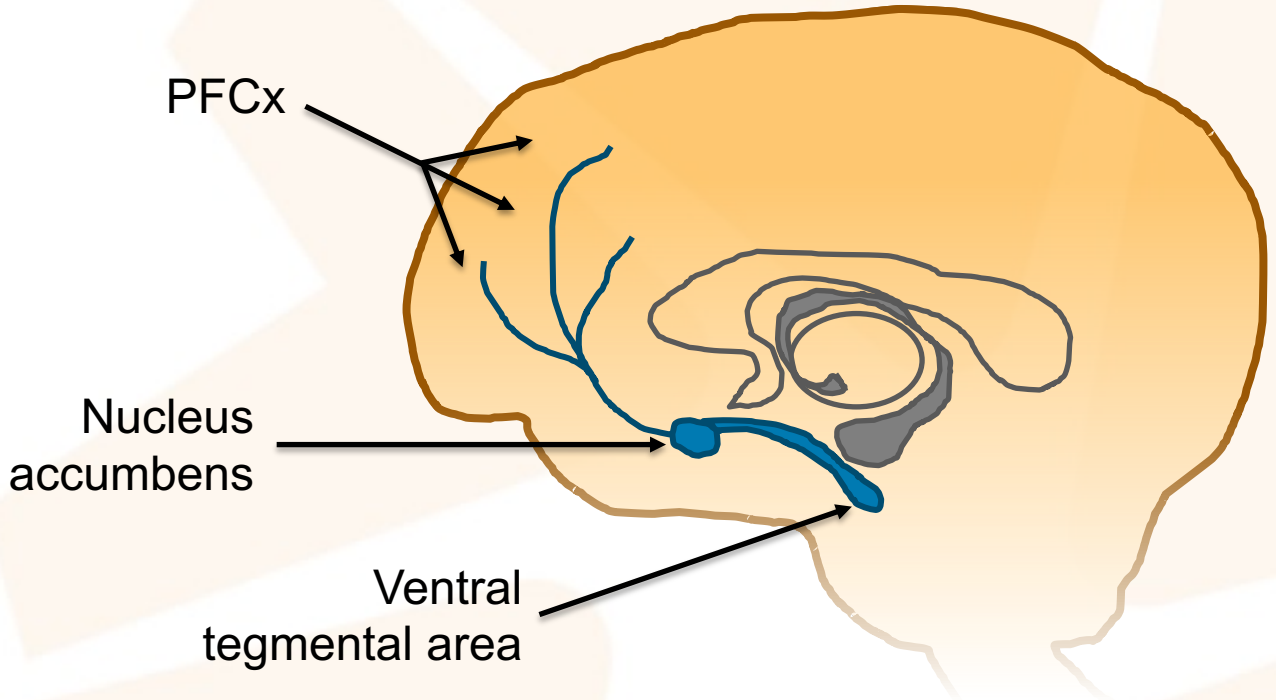
- Considered in the same “family” of dopamine receptors
- Both G protein-coupled receptors
- D2 transcribed by chromosome 11
- D3 transcribed by chromosome 3
- Located in different regions of the brain
- D3 receptor localization has made them targets for
  - Psychosis
  - Mood
  - Addiction
  - And cognition

Grunze H, et al. *Front Psychiatry*. 2021;12:803208. Do A, et al. *Front Psychiatry*. 2021;12:769897.

D3 Receptor Binding

D_3 preferential partial agonist

Agent	D_3 Ki (nM)
Cariprazine	0.085
Aripiprazole*	0.8–9.7
Brexpiprazole*	1.1
Paliperidone*	3.5
Risperidone*	3.6
Iloperidone*	7.1
Ziprasidone*	7.2
Asenapine*	9.4
Lurasidone	15.7



D_3 antagonism increases mesocortical dopamine release

PFCx = prefrontal cortex.

Goldberg JF, et al. *Practical Psychopharmacology: Translating Findings From Evidence-Based Trials into Real-World Clinical Practice*. Cambridge University Press; 2021.

Binding affinities of cariprazine

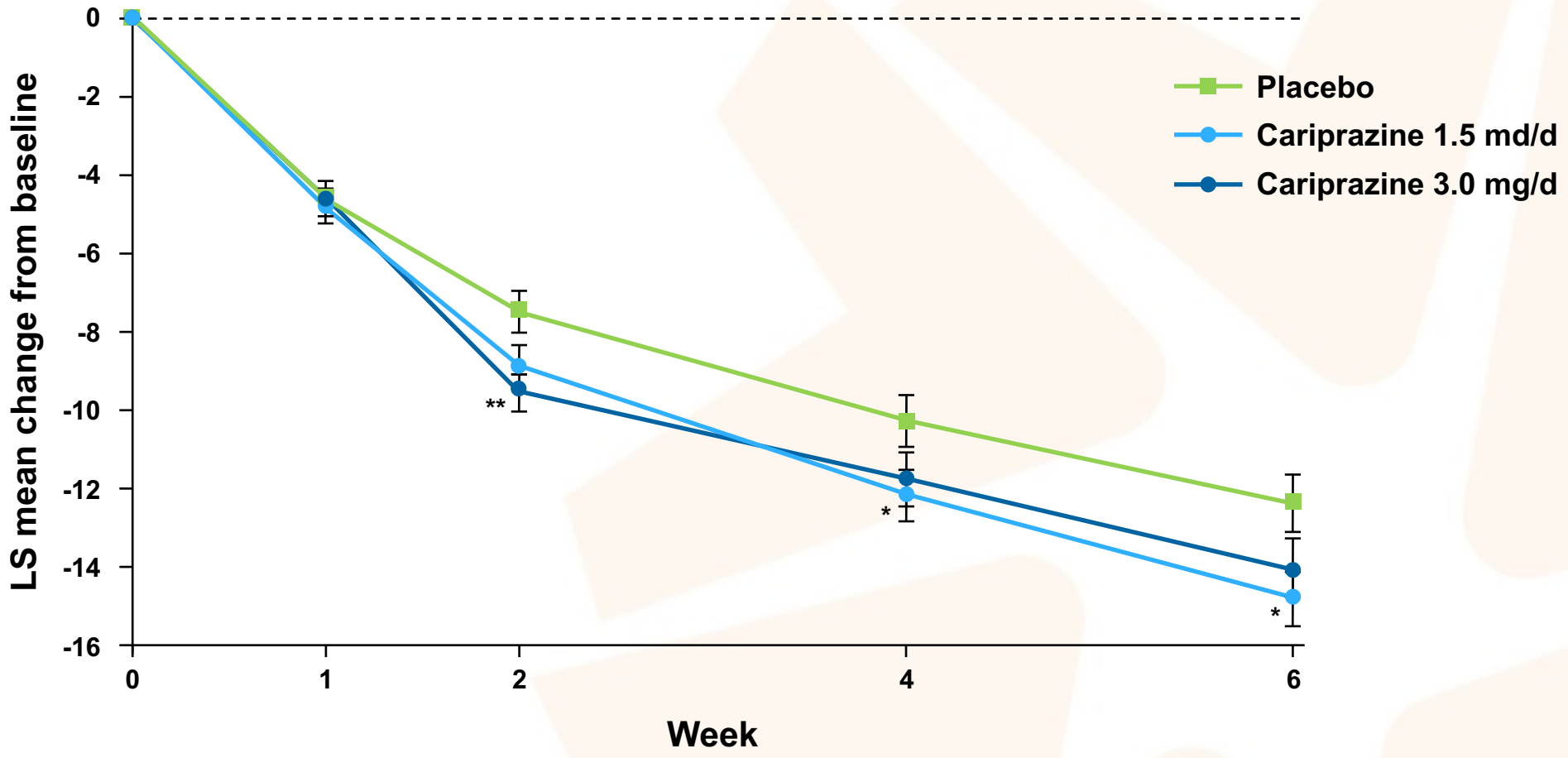
Receptor	Binding affinity (nM Ki)	Binding profile
D3	0.085	Partial agonist
D2L	0.49	Partial agonist
5-HT2B	0.58	Antagonist
D2S	0.69	Partial agonist
5-HT1A	2.6	Partial agonist
5-HT2A	18.8	Antagonist
H1	23.2	Antagonist
5-HT7	111.0	Antagonist
HT2C	134.0	Antagonist
α-1	155.0	Antagonist
Muscarinic	>1,000.0	Antagonist

Mean age: 40 years
12.5 years ill

Vol. 15, No. 4-38.

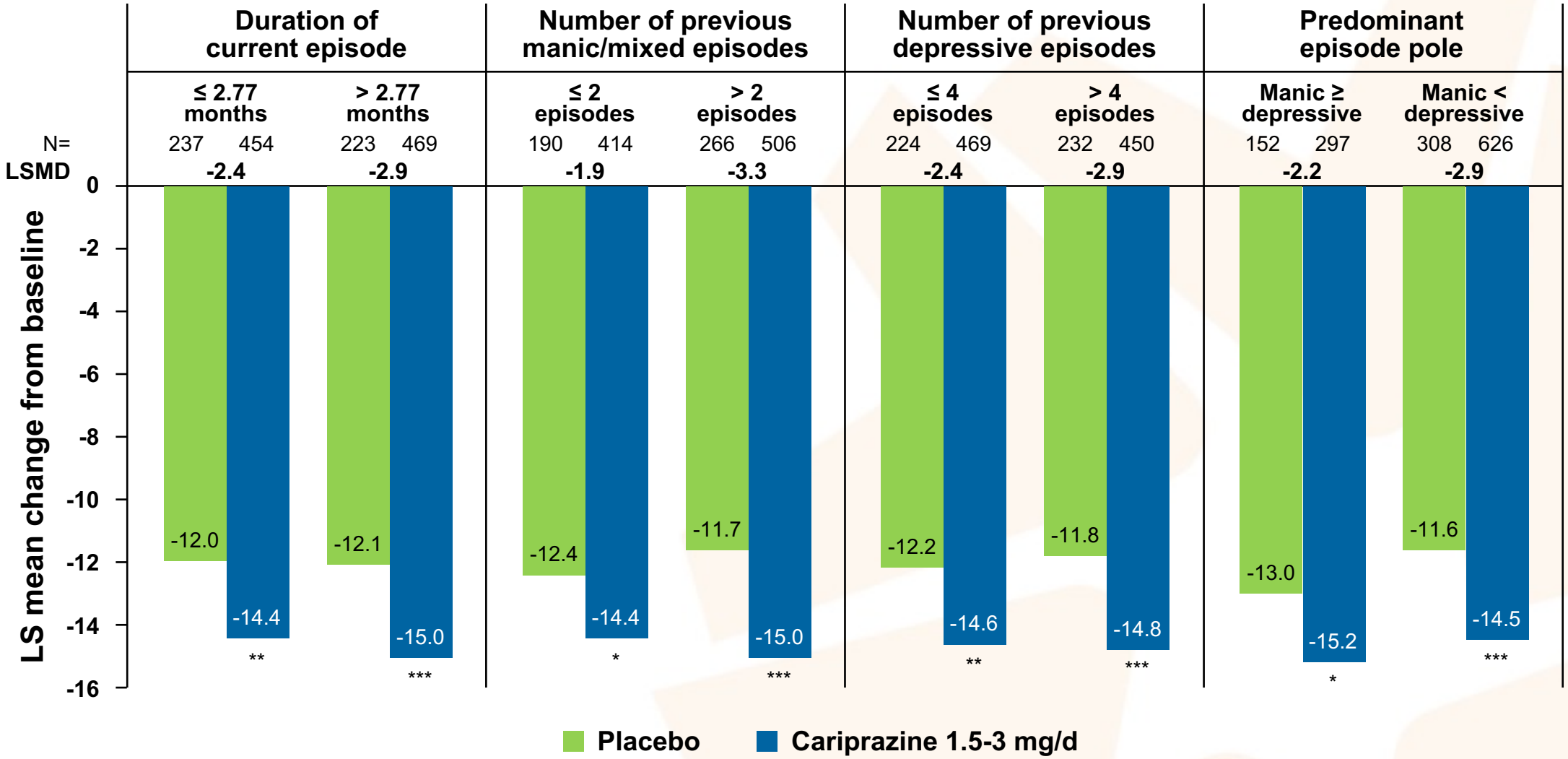
Cariprazine for Bipolar Depression

(A) MADRS Total Score



*P<.05 cariprazine 1.5 mg/d; ** P<.05 cariprazine 3.0 mg/d.
MADRS = Montgomery-Asberg Depression Rating Scale; LS = least squares.

Cariprazine Metanalysis of BPD Trials



*P<.05; **P<.01; ***P<.001 versus placebo.
LSMD = least squares mean difference.

Cariprazine

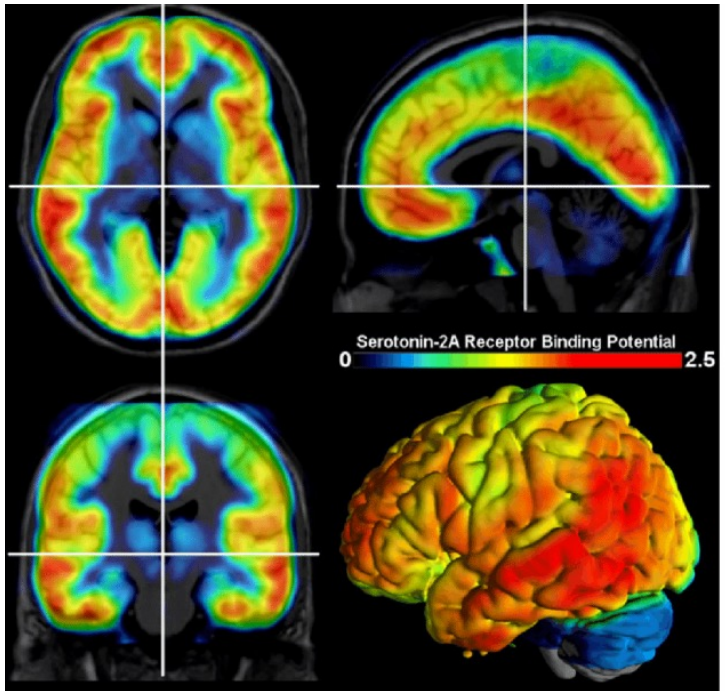
- Approved for bipolar depression, mania, mania with mixed sx
- Partial agonist for D3 > D2
- No change in metabolic parameters or prolactin
- 1 to 1.5 pounds weight gain
- Usually energizing—watch for akathisia
- 7-day half life due to active metabolite
- 1.5 to 3 mg for BPD
- 3 to 6 mg for mania/mixed

Sx = symptoms.

Mattingly G, et al. *Curr Psychiatry Rep*. 2016;15(2):34-39. Earley W, et al. *Am J Psychiatry*. 2019;176(6):439-448.

Mechanisms of Action: Beyond Dopamine

5HT2a antagonism → ↑s cortical DA



Agent	Ki (nM)
Asenapine*	0.06
Ziprasidone*	0.08–1.4
Pimavanserin*	0.087
Risperidone*	0.17
Brexpiprazole*	0.47
Lumateperone*	0.54
Paliperidone*	1.1
Olanzapine*	1.34–24.2
Lurasidone	2.03
Aripiprazole*	3.4–35.0
Clozapine*	9.15
Quetiapine	96–101

Agent	5-HT_{2A}: D_2 ratio
Risperidone*	**11**
Olanzapine*	**12**
Clozapine*	**20**
Lumateperone*	**60**

DA = dopamine; Ki = inhibitory constant.

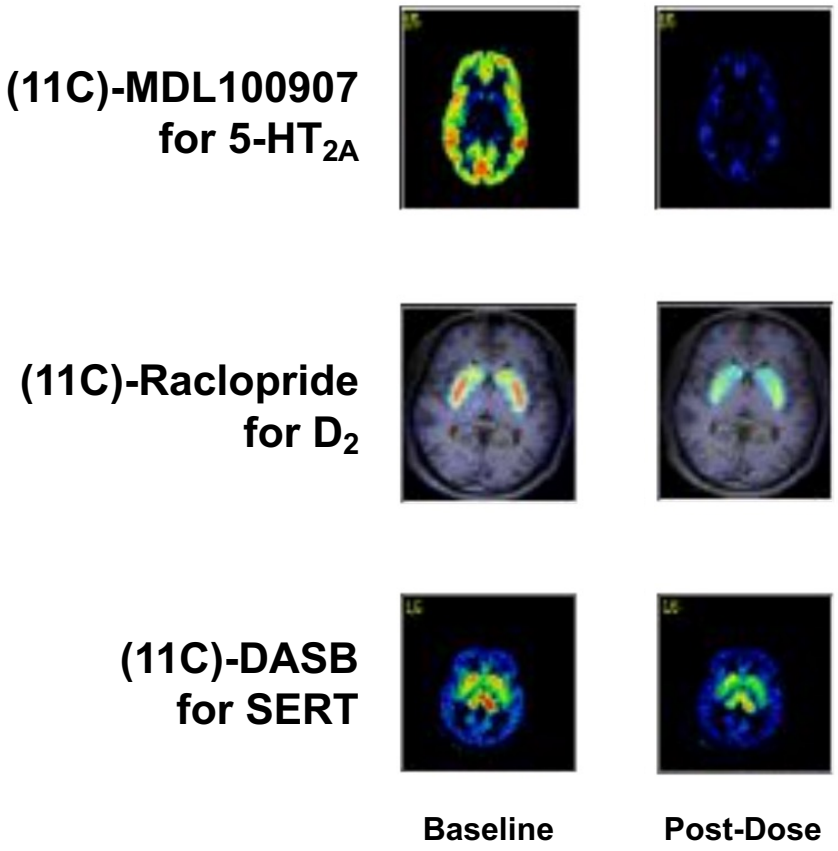
Herth MH, et al. "PET Imaging of the 5-HT_{2A} Receptor System: A Tool to Study the Receptor's In Vivo Brain Function." In: Guiard BP, et al., eds. *5-HT_{2A} Receptors in the Central Nervous System*. Human Press; 2018. Goldberg JF, et al. *Practical Psychopharmacology*. Cambridge University Press; 2021. Schotte A, et al. *Psychopharmacology*. 1996;124(1-2):57-73.

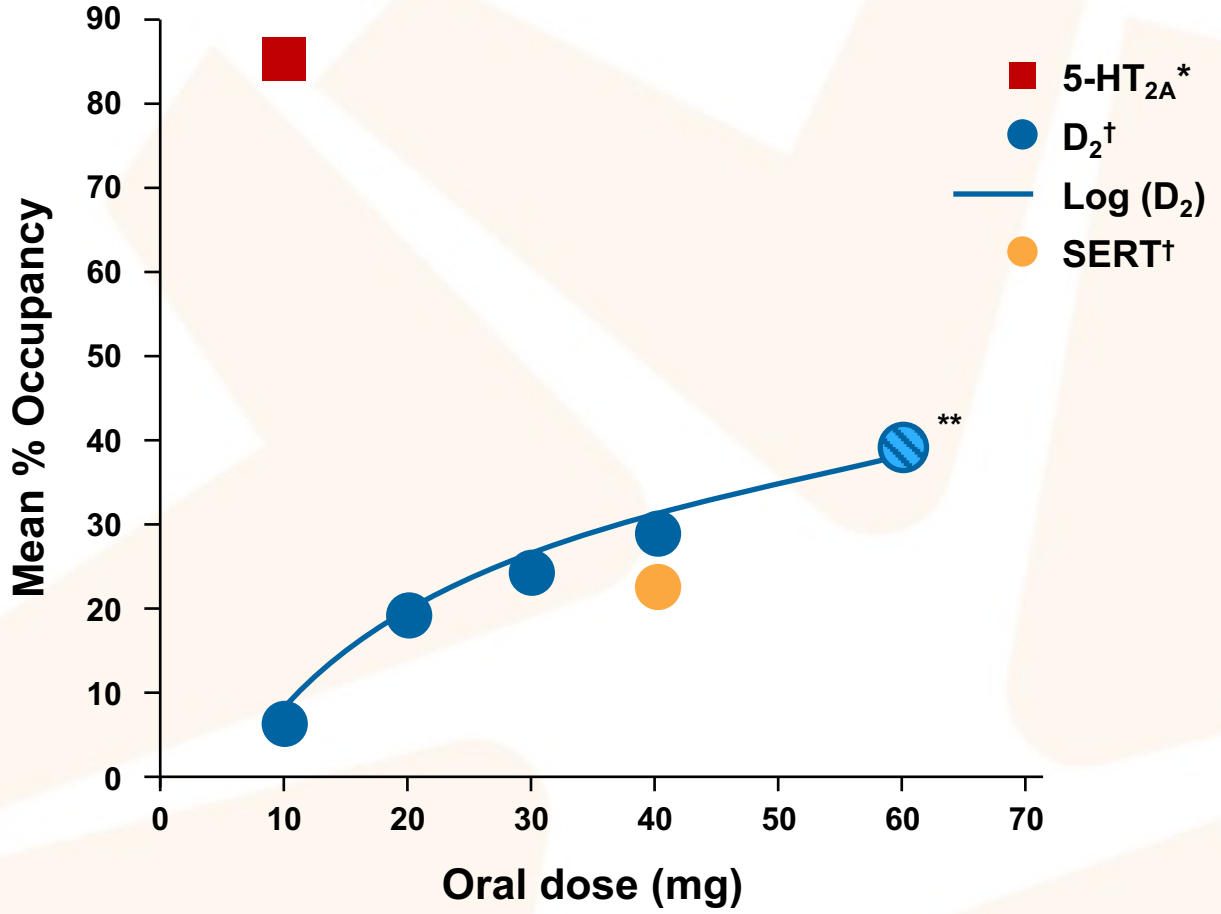
5HT2a Receptors

- Cross talk with dopamine neurons
- Stimulation can cause psychosis—"Psychodelics"
- Blockade can decrease psychosis
  - Pimavanserin for Parkinson's psychosis
- 5HT2a is a target for improving
  - Psychosis
  - Mood
  - PTSD
  - And cognition

PTSD = post-traumatic stress disorder.
Zięba A, et al. *Int J Mol Sci*. 2022;23(1):10.

Lumateperone Receptor Binding





* Cortical occupancy; † Striatal occupancy; ** Patients with schizophrenia.
SERT = serotonin reuptake transporter; DASB = 3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile.
Davis RE, et al. *Psychopharmacology (Berl)*. 2015;232(15):2863-72.

Lumateperone

60X 5HT2a >>> D_2 Receptors

Affinity	Receptor	K_i value[a] (nM)
High	Serotonin 5HT2a	0.54
Moderate	Dopamine D_2	32
	Serotonin reuptake transporter (SERT)	33
	Dopamine D_1	41
	Dopamine D_4	< 100
	α_{1A}-adrenergic	
	α_{1B}-adrenergic	
Low	H_1-histaminergic	< 50% inhibition at 100 nM
	M_1-muscarinic	

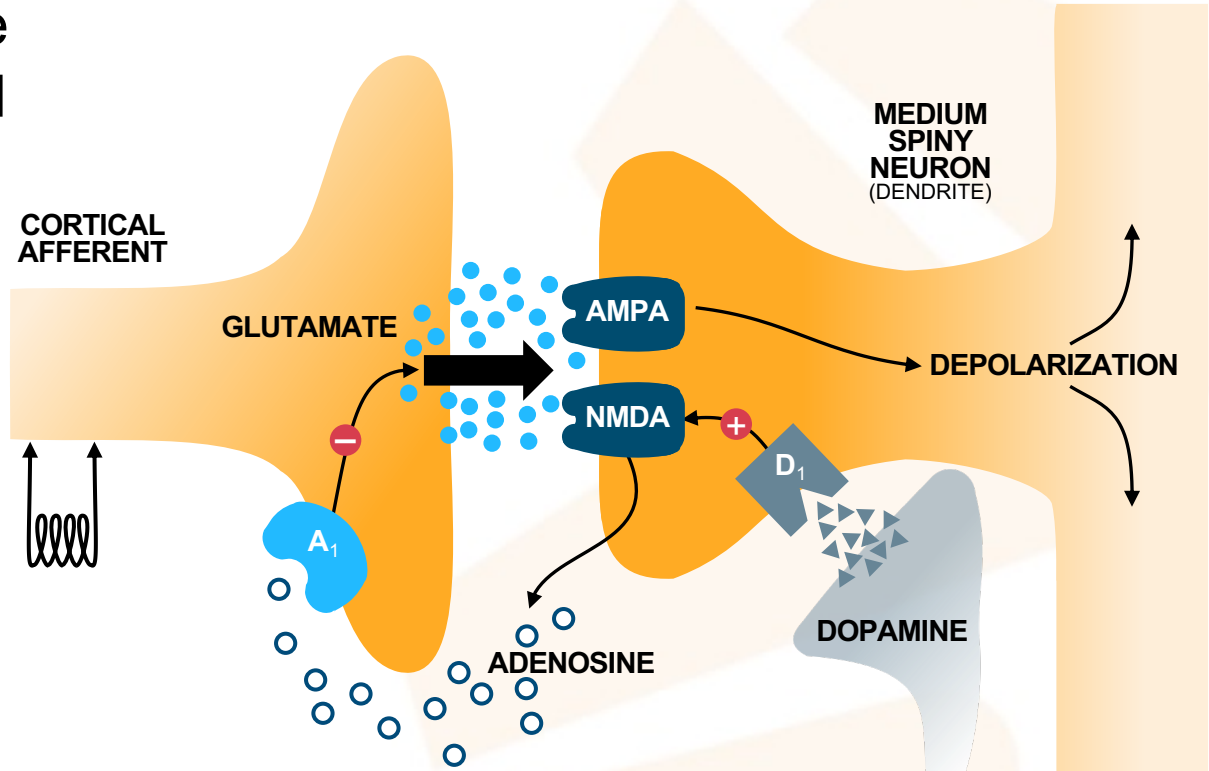
~60x higher affinity for 5HT2a than for D_2 receptors

Low affinity muscarinic and histaminergic receptors

Davis RE, et al. *Expert Rev Neurother*. 2016;16(6):601-614.

D_1 Indirect Modulation of Glutamate Function

D_1 receptors modulate glutamate release and amplify NMDA and AMPA function.



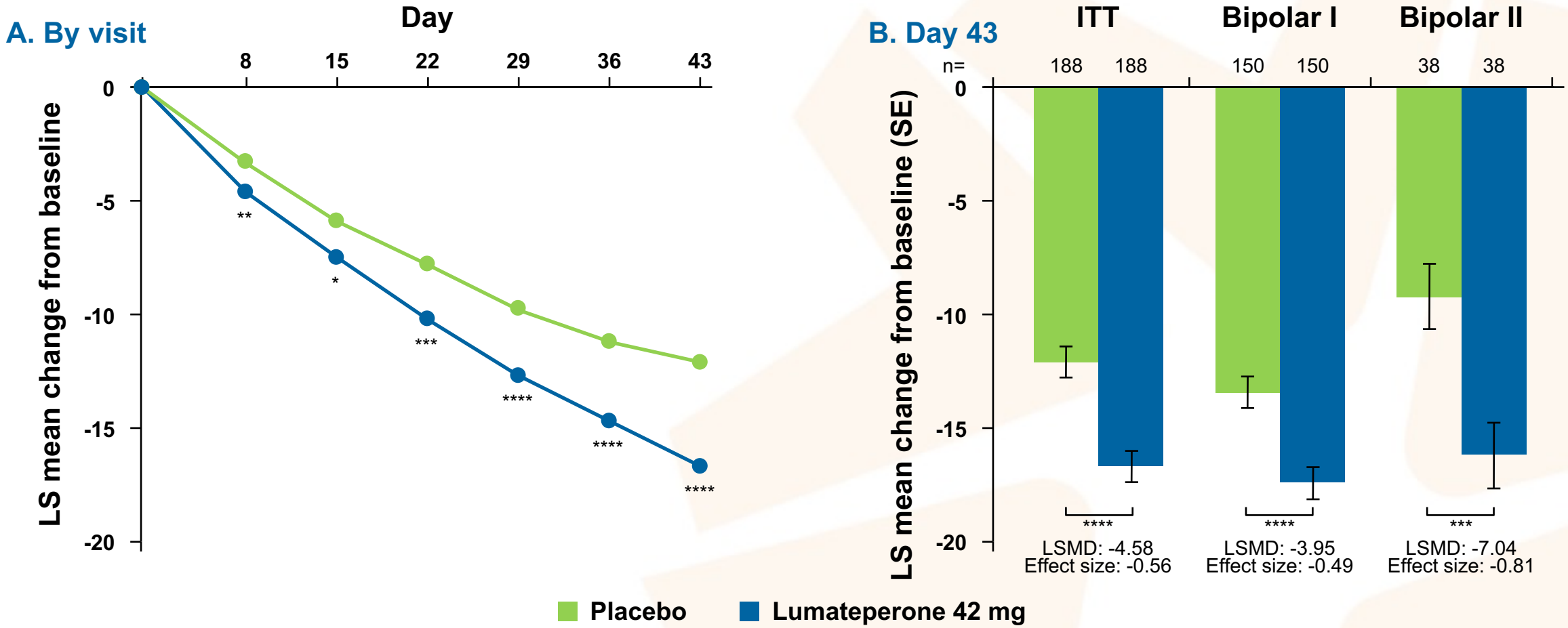
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA = N-methyl-D-aspartate.

Harvey J, et al. *J Neurosci*. 1997;17(14):5271-5280.

Lumateperone 42 mg in Bipolar Depression

Both BP I and BP II

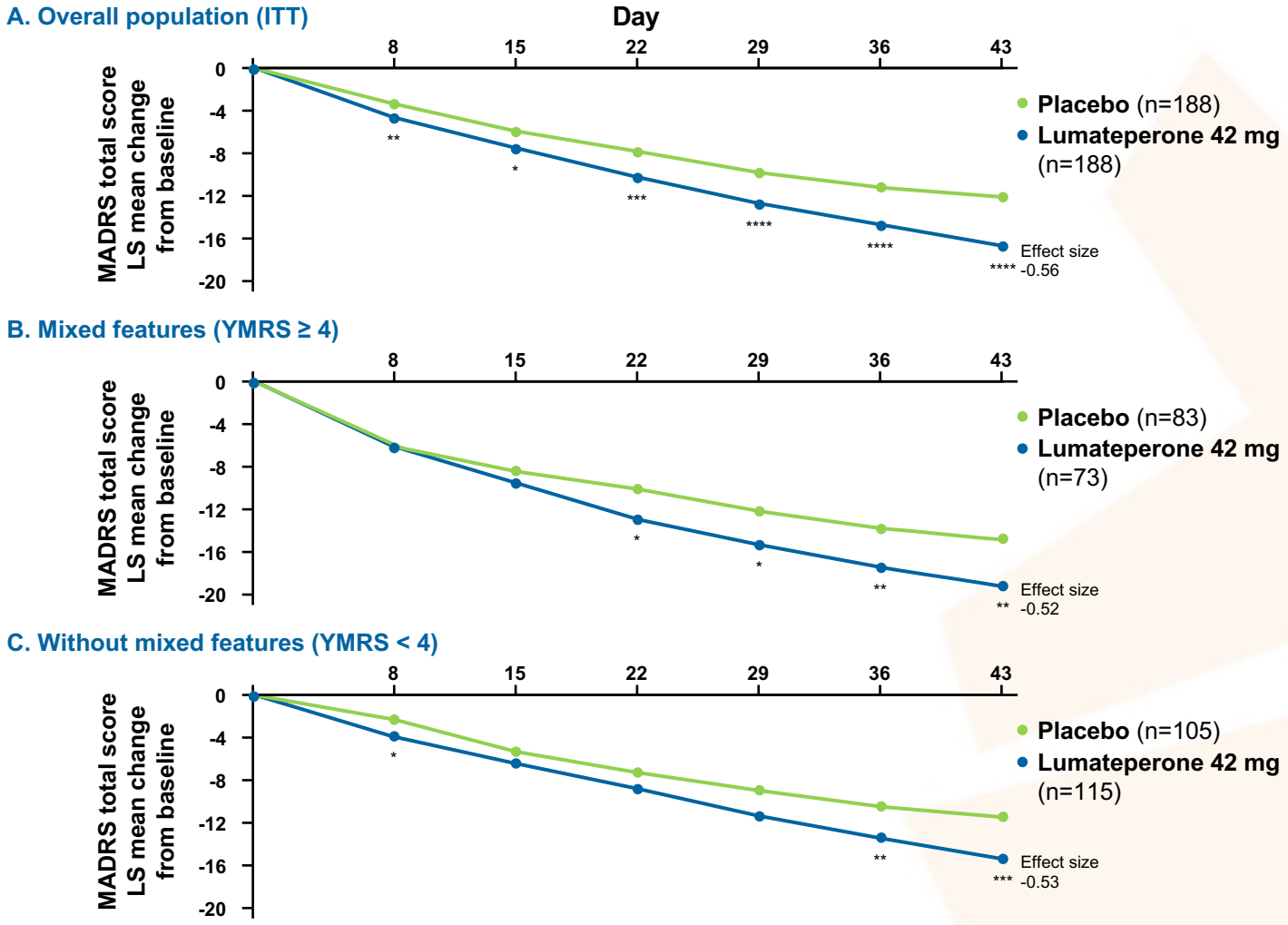
Improvement in Depression (MADRS)



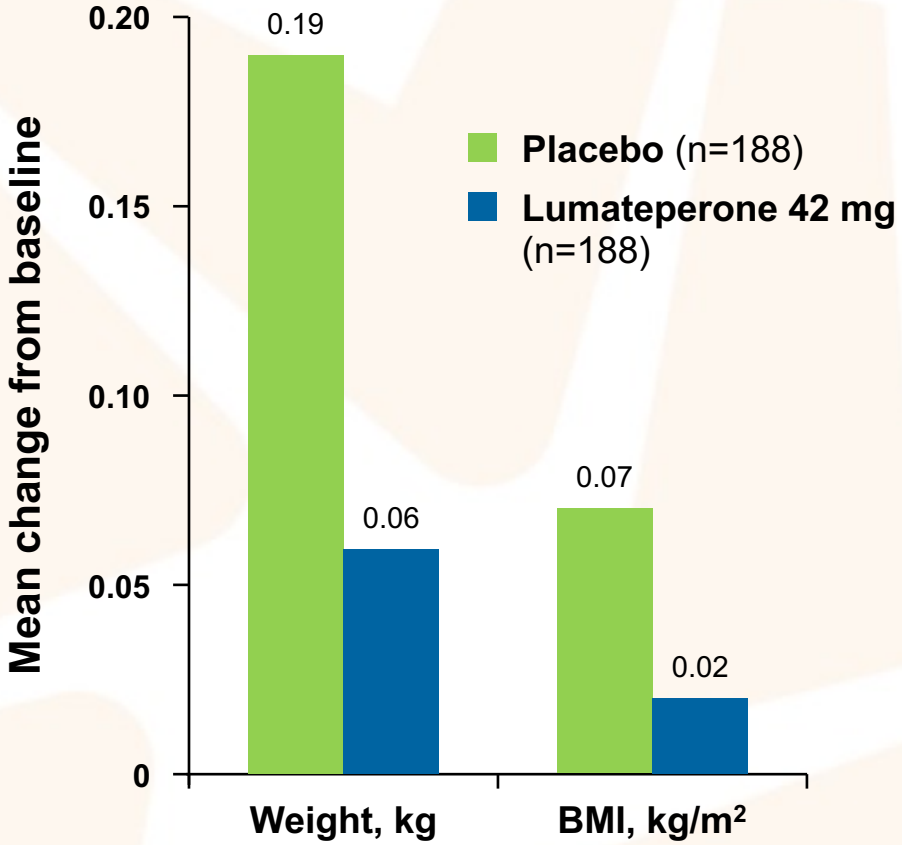
SE = standard error.

American College of Neuropsychopharmacology. Poster presented at: ACNP Annual Meeting; December 6-9, 2020; virtual.

Lumateperone 42 mg: BP Mixed Symptoms and Safety



Weight



- **0 patients with > 7% weight gain**

YMRS = Young Mania Rating Scale.

Posters presented at: American Psychiatric Association (APA) Annual Meeting; May 1-3, 2021; virtual.

Lumateperone Bipolar Depression Side Effects: 42 mg, 6-Week trial

	(N=177)	(N=175)
Somnolence/Sedation	13%	3%
Dizziness[1]	11%	2%
Nausea	9%	4%
Dry mouth	5%	1%
Vomiting	4%	0%
Diarrhea	3%	2%
Upper respiratory tract infection	3%	1%
Blurred vision	3%	1%
Increased blood prolactin	2%	0%

[1] Dizziness, dizziness postural

Caplyta package insert.

Lumateperone Bipolar Depression: Weight and Metabolics

- In 6-week placebo controlled trials
  - Weight
  - Glucose
  - Lipids
  - > 7% weight gain was 0.0% with lumateperone monotherapy or when added to lithium or valproate

*****All similar to placebo**

- In 6-month open-label safety trial
  - Average weight change was -0.01 kg at day 175

Caplyta package insert.

Cariprazine vs Lumateperone for Bipolar Depression

- Cariprazine—D3 > D2 partial agonist
  - Approved monotherapy for BPD 1.5-3mg and mania/mixed 3-6mg
  - Fairly clean for weight and metabolics
  - Watch akathisia—one of the more common side effects

- Lumateperone—5HT2a 60X > D2, also SSRI and D1
  - Approved for BP1 and BP2 depression
  - Approved as monotherapy or with lithium or valproate
  - 42 mg once daily dose
  - No weight gain and 0 patients with 7% weight increase
  - Sedation most common AE—usually mild

SSRI = selective serotonin reuptake inhibitor; AE = adverse event.

Visit the Online Resource Center

STAY UP TO DATE WITH THE LATEST CLINICAL UPDATES, RESOURCES, AND EDUCATION IN THE TREATMENT OF BIPOLAR DISORDER.

BIPOLAR 360