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Bipolar Disorder Across the Spectrum: *Novel Screening Tools and Treatment Options*

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Faculty Disclosure

- **Dr. Jenkins**: Major Stockholder (not including mutual funds)—Alkermes, Inc., Trevena, Inc.; Stockholder/Ownership Interest (excluding diversified mutual funds)—Sage Therapeutics.

- **Dr. Whelan**: Advisory Board—AbbVie, Neurocrine Biosciences, Sunovion, Teva Pharmaceuticals; Consultant—AbbVie, ANCC, Cambridge Brain Sciences, Genomind; Employee—Maryville University; Royalties—FullScripts; Speakers Bureau—AbbVie, Avanir Pharmaceuticals, Genomind, Neurocrine Biosciences, Otsuka Pharmaceutical, Takeda Pharmaceutical.

Disclosure

- 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).
  - Dr. Jenkins and Dr. Whelan will be discussing off-label and investigational use of drugs in the presentation and will identify those issues.

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

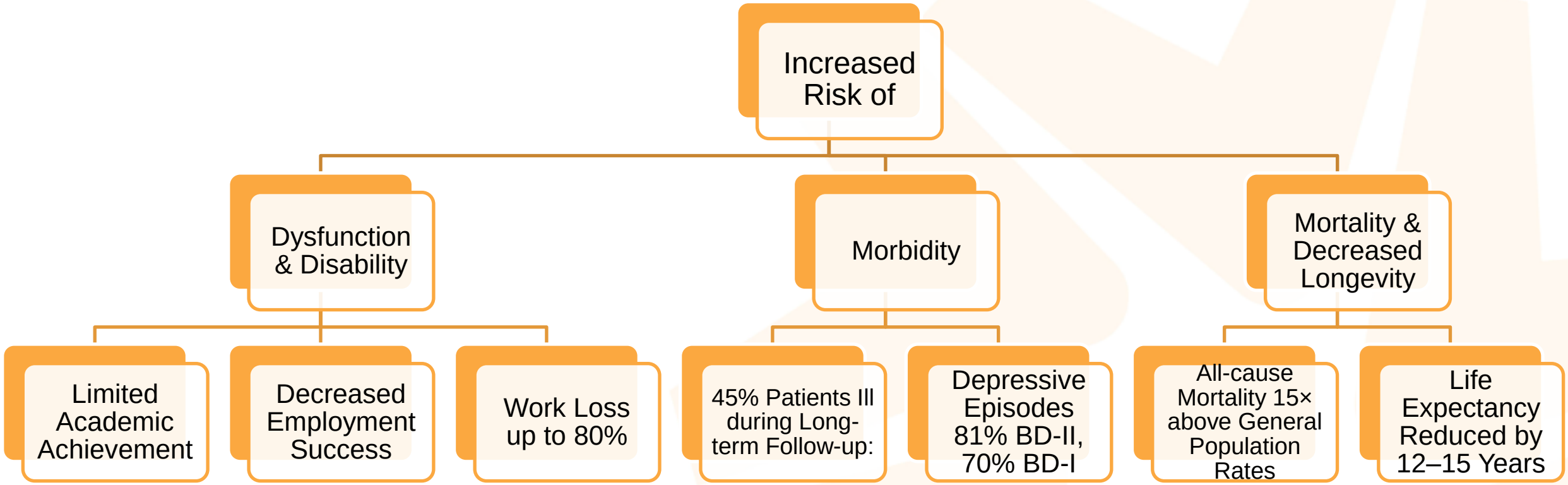
- This activity has been independently reviewed for balance.

Learning Objectives

- Describe tactics to differentiate and identify various symptom domains in bipolar disorder
- Analyze treatment targets for current and emerging bipolar medications and their implications for personalized and comprehensive patient care
- Incorporate agents into personalized and comprehensive bipolar treatment plans for patients with a wide range of symptoms

Burden of Bipolar Disorder Across the Spectrum

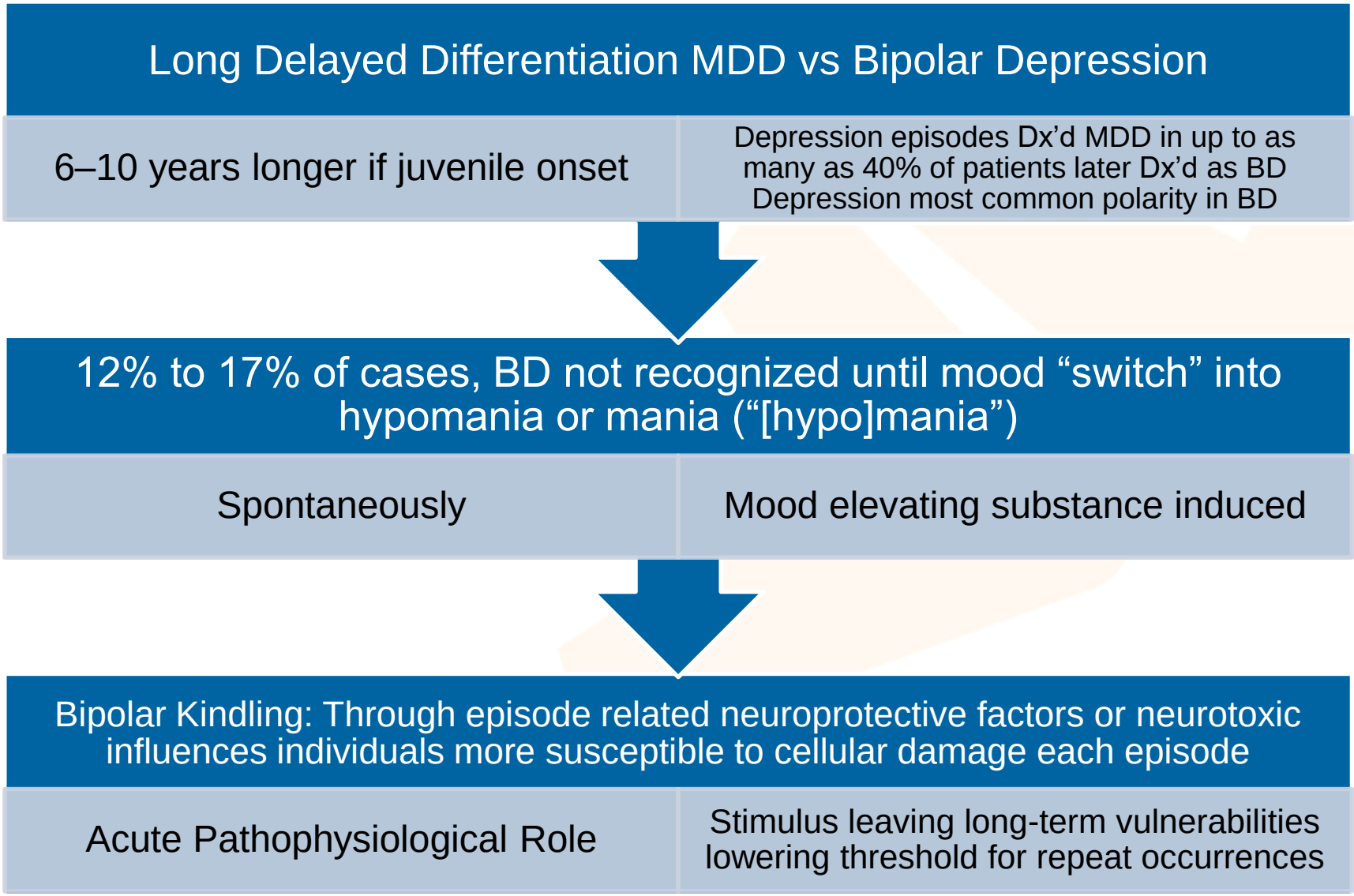
Prognosis in Bipolar Disorder



BD-I = bipolar I disorder; BD-II = bipolar II disorder.

Baldessarini RJ, et al. *Int J Bipolar Disord*. 2020;8(1):1.

Clinical Progression for Bipolar Diagnosis



MDD = major depressive disorder.

Bender RE, et al. *Clin Psychol Rev*. 2011;31(3):383-398.

Vanessa

- 30-year-old single white female graphic designer
- Telemedicine consultation with a new psychiatrist
- History of depression since childhood
- Alcohol and cannabis use disorder in college, now sober
- Treated with SSRIs and other antidepressants off and on since college, no clear benefits
- Identifies “spurts” of high energy in between periods of depression
- Use of a screening tool to facilitate and clarify possible past periods of mania or hypomania

SSRI = selective serotonin reuptake inhibitor.

Obstacles to Bipolar Identification

Diagnosis is often difficult as presentation can overlap with multiple other *DSM-5* diagnoses/criteria

Diagnosis is often delayed, or *unipolar depression* is treated for up to 10 years prior to correct identification of *bipolar depression*

Need increased awareness of social impacts as well as increased suicide rates

Nomenclature (use of an SGA) is noted to have an impact on the choices providers make when making treatment choices

There is avoidance of “stigma” associated with being diagnosed with bipolar disorder when they have previously been told they have *unipolar depression*

SGA = second-generation antipsychotic.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. American Psychiatric Association Publishing; 2013. Scrandis DA. *Nurse Pract*. 2014;39(10):30-37. Cha B, et al. *Psychiatry Investig*. 2009;6(2):96-101. Fritz K, et al. *Bipolar Disord*. 2017;19(5):396-400.

Diagnostic Screening Tools in Bipolar Disorder

Mood Disorder Questionnaire

Mood Disorder Questionnaire (MDQ): 13-item self-report measure; scores ≥7 = casehood

Meta-analysis of 23 studies with 6730 participants:

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

Better sensitivity for BD-I (66.3%) than BD-II (38.6%)

Operating Characteristics of the Mood Disorder Questionnaire Scored According to Hirschfeld and Colleagues' Algorithm in Studies of the General Population, General Psychiatric Outpatients, and Patients with Mood Disorders

Sample	Number of Studies	n	Prevalence of BD (%)	Sensitivity[a] (%)	Specificity (%)	PPV (%)	NPV (%)
General population	3	1875	5.8	25.9	97.9	43.1	95.6
Psychiatric outpatients	3	943	14.7	64.7	82.3	38.8	93.1
Mood disorder patients	10	2052	39.1	64.7	81.1	68.7	78.2

[a]Sensitivity for all bipolar disorders.
NPV = negative predictive value; PPV = positive predictive value.
Hirschfeld RM, et al. *Am J Psychiatry*. 2000;157(11):1873-1875. Zimmerman M, et al. *Harv Rev Psychiatry*. 2011;19(5):219-228.

Mood Disorder Questionnaire

Lower MDQ predictive value in mood disorder patients with comorbid substance use disorders

Precision of Self-Rated MDQ(+) Scores for *DSM-IV-TR* Bipolar Diagnoses
Stratified by Any Substances of Abuse or Dependence (N=113)

Substance	n	Sensitivity	Specificity	PPV	NPV
Alcohol	52	0.71	0.47	0.33	0.82
Sedatives	21	0.67	0.28	0.13	0.83
Opiates	25	0.80	0.30	0.22	0.86
Cocaine	24	0.75	0.50	0.23	0.91
Cannabis	34	0.78	0.48	0.35	0.86
Use of > 2 substances	52	0.78	0.42	0.22	0.90
Use of > 3 substances	24	0.60	0.37	0.20	0.78

+ = positive.

Goldberg JF, et al. *J Clin Psychiatry*. 2012;73(12):1525-1530.

Rapid Mood Screener

Rapid Mood Screener Final 6-Item Set (Table View)

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

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

McIntyre RS, et al. *Curr Med Res Opin*. 2021;37(1):135-144.

Bipolarity Index:
Corroborators of a Suspected Bipolar Diagnosis

	Points	Most points for
Episode characteristics	Up to 20	*DSM-5* mania, fewer for hypomania
Family history	Up to 20	First-degree relatives
Age at onset of depression	Up to 20	Ages 15–19; fewer for earlier or later
Course of illness	Up to 20	Highly recurrent episodes
Response to treatment	Up to 20	Recovery with a mood stabilizer or manic switch with an antidepressant; possible loss of antidepressant response; very rapid antidepressant response

Cut-off score = **50**; sensitivity = 0.91, specificity = 0.90

Aiken CB, et al. *J Affect Disord*. 2015;177:59-64.

Key Learning Point

BD-I is often misdiagnosed as MDD. The reliability of the MDQ self-assessment screening tool may be confounded by current or past substance abuse. The Rapid Mood Screener is a novel, pragmatic, 6-item screening tool designed to help differentiate the two conditions and determine whether the patient should undergo a more comprehensive assessment for BD-I.

Treatment of Bipolar Disorder:
Critical Updates

Traditional Treatments and Their Limitations

- **Mood Stabilizers**: Useful as maintenance treatment, no predictable class effects, polarity specific, response is typically slow
- **Antidepressants**: No demonstrated efficacy in bipolar depression, can worsen cycling or precipitate affective switches
- **Antipsychotics**: Useful in acute mania, only some have antidepressant value, not uniformly effective for maintenance treatment, high side-effect burden

Pharmacologic Treatment Approaches for Bipolar Disorder: *Basic Concepts*

In manic/mixed episodes:

- ✓ Eliminate antidepressants
- ✓ Optimized dosing of antimanic mood stabilizers (lithium levels ~1.0–1.02 mEq/L; valproate levels 70–120 µg/L)
- ✓ Restore normal sleep-wake cycle

In depressive episodes:

- ✓ Favor FDA-approved medications (lurasidone, cariprazine, quetiapine, olanzapine-fluoxetine combination)
- ✓ Other evidence-based pharmacotherapies: lumateperone*, modafinil*, pramipexole*, ketamine*, NAC*, omega-3 fatty acids*; ECT

In maintenance phase:

- ✓ Favor evidence-based interventions (eg, lithium, lithium + divalproex > divalproex, some SGAs)
- ✓ Assure adherence
- ✓ Balance tolerability with efficacy

***Not FDA-approved in bipolar depression.**
ECT = electroconvulsive therapy; NAC = N-acetylcysteine.

Approaches to Maintenance Therapy
Mood Stabilizers

Mood Stabilizers	Efficacy
Lithium	Prevents mania > depression
Divalproex	Failed maintenance trial; but post hoc analysis found preventive efficacy if enriched for divalproex acute antimanic response
Lithium + Divalproex	BALANCE Trial: Lithium + divalproex > divalproex monotherapy (but not superior to lithium monotherapy)
Carbamazepine	No data
Lamotrigine	Prevention of depression > mania in BD-I; lamotrigine + divalproex no better than lamotrigine monotherapy

Geddes JR, et al. *Am J Psychiatry*. 2004;161(2):217-222. Bowden CL, et al. *Arch Gen Psychiatry*. 2000;57(5):481-489. McElroy SL, et al. *J Affect Disord*. 2008;107(1-3):127-133. BALANCE investigators and collaborators, Geddes JR, et al. *Lancet*. 2010;375(9712):385-395. Goodwin GM, et al. *J Clin Psychiatry*. 2004;65(3):432-441. Bowden CL, et al. *Acta Psychiatr Scand*. 2012;126(5):342-350.

Clinical Profiling

When to Use Antidepressants

Favors Antidepressant Use	Discourages Antidepressant Use
BD-II	BD-I
Pure depressed episodes	Mixed features
Absence of rapid cycling	Past year rapid cycling
Absence of recent mania/hypomania	Mania/hypomania in past 2–3 months
Absence of comorbid alcohol/substance use disorders	Alcohol or substance use comorbidity
Prior favorable antidepressant response	Suboptimal responses to prior antidepressants
No history of antidepressant-induced mania	History of antidepressant-induced mania/hypomania
SLC6A4 “l/l” genotype	*SLC6A4* “s/s” genotype

Goldberg JF. Determining Patient Candidacy for Antidepressant Use in Bipolar Disorder. *Psychiatric Annals*. 2019;49(9):386-391.

Approaches to Maintenance Therapy
Second-Generation Antipsychotics

SGAs	Efficacy
Aripiprazole	Oral or LAI prevention of mania but not depression
Asenapine	1 (+) 26-week maintenance trial; prevented mania or depression
Lurasidone	1 (-) 28-week maintenance trial
Olanzapine	3 (+) RCTs (vs placebo, lithium, or divalproex)
Quetiapine	2 (+) adjunctive trials, comparable prevention of mania or depression
Risperidone	LAI (prevention of mania but not depression)
Ziprasidone	1 (+) adjunctive trial

LAI = long-acting injectable; RCT = randomized controlled trial.

Keck PE Jr, et al. *J Clin Psychiatry*. 2007;68(10):1480-1491. Keck PE, et al. *J Affect Disord*. 2009;112(1-3):36-49. Calabrese JR, et al. *J Clin Psychiatry*. 2017;78(3):324-331. Szegedi A, et al. *Am J Psychiatry*. 2018;175(1):71-79. Calabrese JR, et al. *Eur Neuropsychopharmacol*. 2017;27(9):865-876. Tohen M, et al. *Am J Psychiatry*. 2006;163(2):247-256. Tohen M, et al. *Am J Psychiatry*. 2005;162(7):1281-1290. Suppes T, et al. *Depress Anxiety*. 2013;30(11):1089-1098. Quiroz JA, et al. *Biol Psychiatry*. 2010;68(2):156-162. Bowden CL, et al. *J Clin Psychiatry*. 2010;71(2):130-137.

Differences between Atypical Antipsychotics

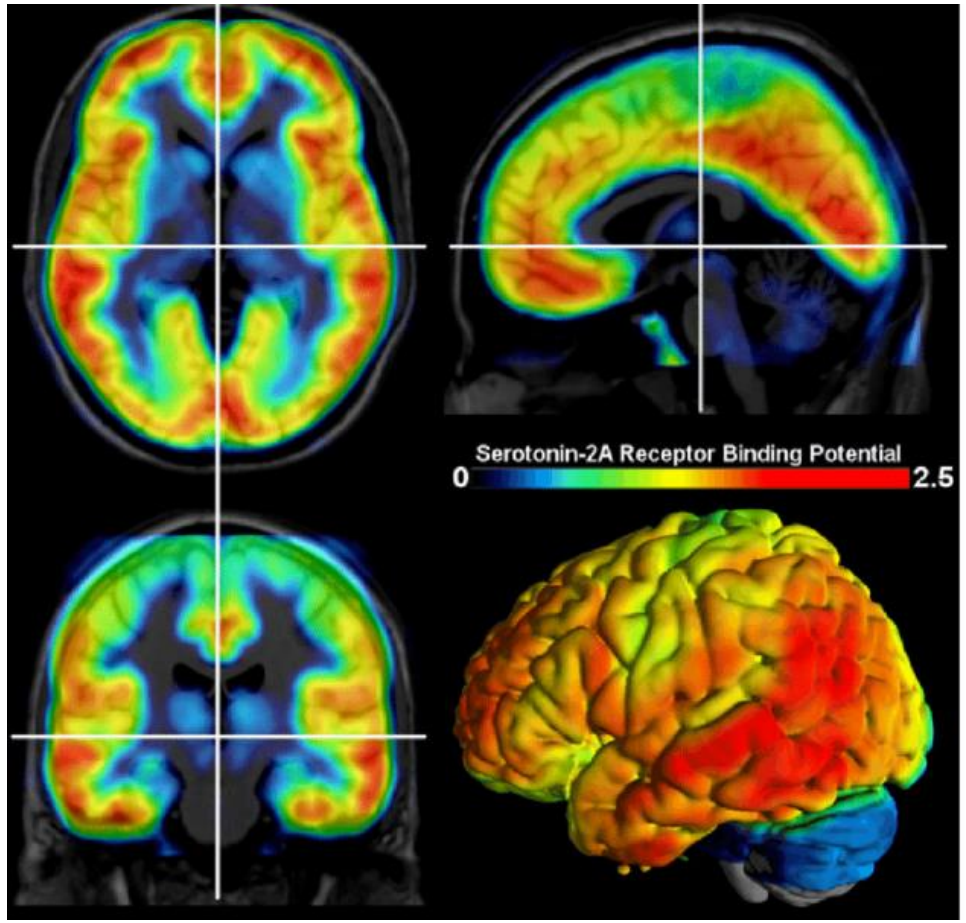
5-HT_{1A} (agonism)	Regulated serotonin release; antidepressant and anxiolytic effects
5-HT_{1B} (antagonism)	Antidepressant effects
5-HT_{2A} (antagonism)	Increases prefrontal dopamine; enhanced attention, memory; mitigates movement disorder
5-HT_{2A} (agonism)	Psychedelic effects; enhanced learning, oxytocin release
5-HT_{3} (agonism)	Enhance release of dopamine, GABA; improves cognition and anxiety
5-HT_{7} (agonism)	Helps regulate glutamate:GABA balance; may influence mood, memory, learning, pain

D_1 (agonism)	Pre-frontal cortex enhances working memory and social cognition; striatum anti-parkinsonian effects
D_2 (agonism)	Enhance attention, reward, and anti-parkinsonian effects
D_2 (antagonism)	Antipsychotic, parkinsonian effects
D_3 (agonist)	Enhance motivation, exacerbate psychosis, compulsive behaviors
D_3 (partial agonist)	Antipsychotic, antidepressant, anti-craving

Goldberg JF, et al. *Practical Psychopharmacology: Translating Findings From Evidence-Based Trials into Real-World Clinical Practice*. Cambridge University Press; 2021:17-19.

Mechanisms of Action of Atypical Antipsychotics: Beyond D_2 Blockade

5-HT_{2A} antagonism



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

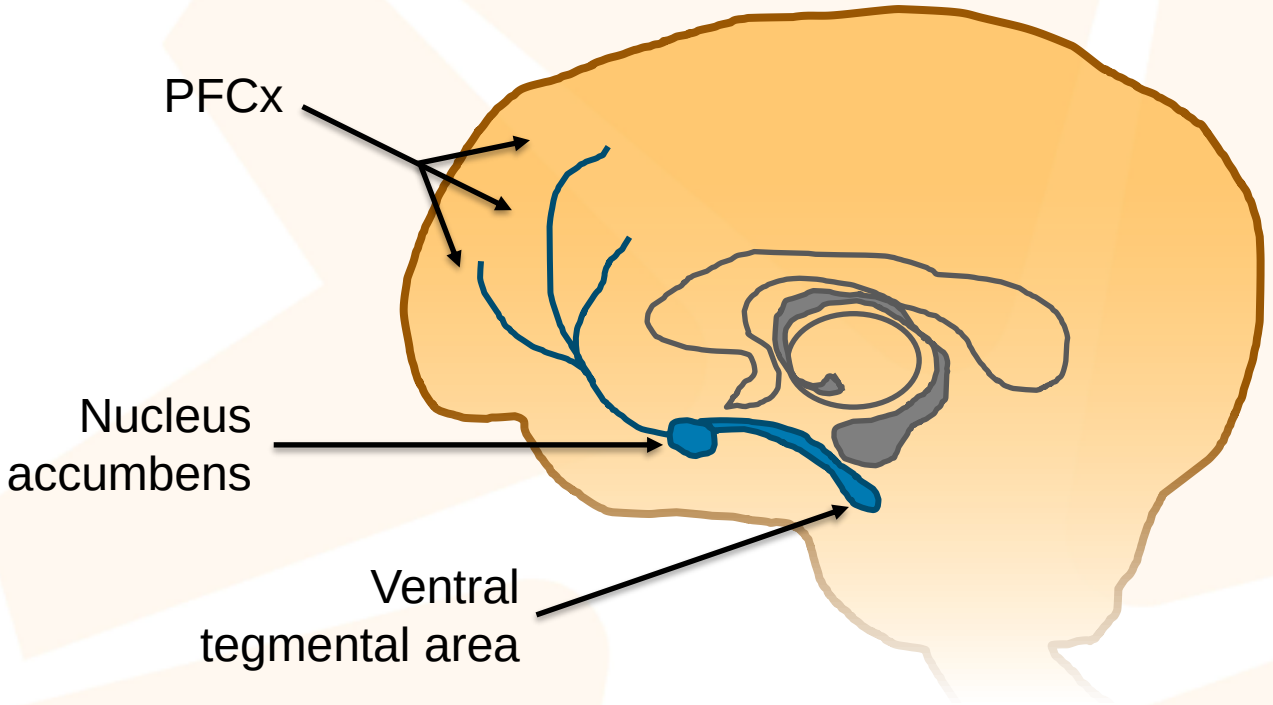
***Not FDA-approved in bipolar depression.**

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; 2018:85-134. Goldberg JF, et al. *Practical Psychopharmacology: Translating Findings From Evidence-Based Trials into Real-World Clinical Practice*. Cambridge University Press; 2021. Schotte A, et al. *Psychopharmacology*. 1996;124(1-2):57-73.

Mechanisms of Action of Atypical Antipsychotics

D_2 / D_3 Partial Agonists

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

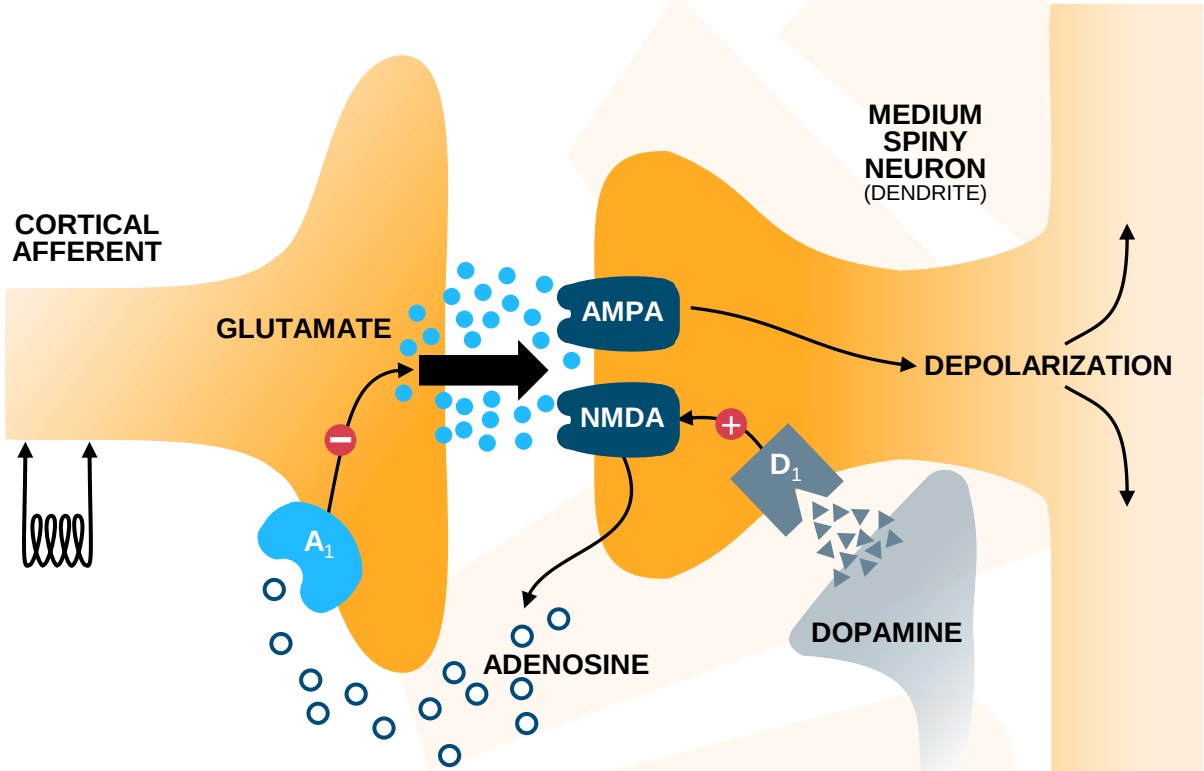


***Not FDA-approved in bipolar depression.**

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

D_1 Indirect Modulation of Glutamate Function

Agent	Ki (nM)
Asenapine*	8.9
Ziprasidone*	30–130
Olanzapine*	35–118
Lumateperone*	41
Brexpiprazole*	160
Aripiprazole*	265–1170
Clozapine*	266
Quetiapine	712



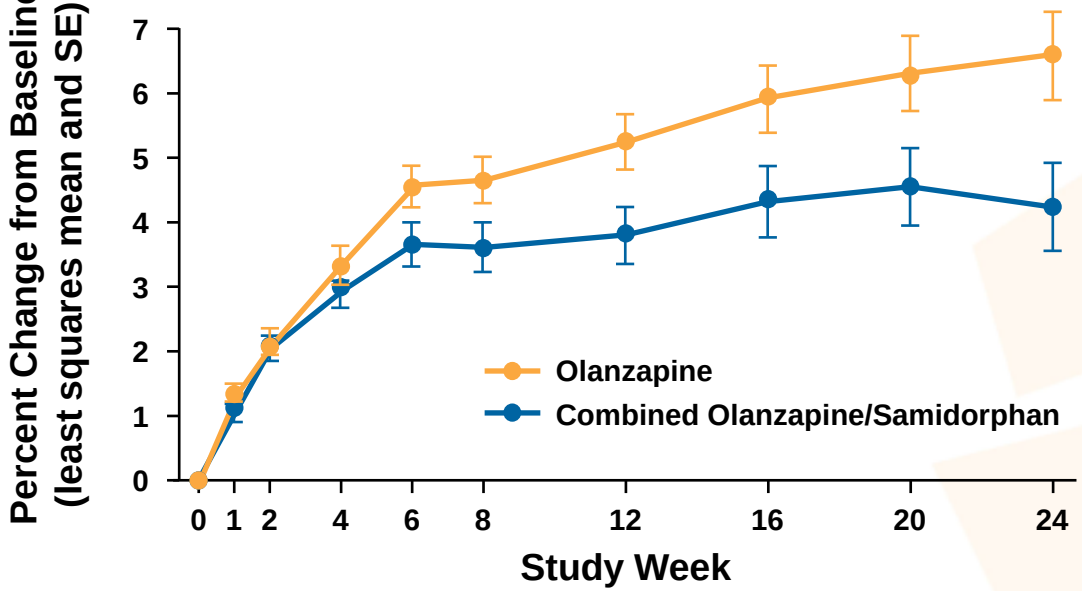
D_1 postsynaptic receptors modulate presynaptic glutamate release and amplify current caused by activation of NMDA receptors

***Not FDA-approved in bipolar depression.**
AMPA = α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.
Harvey J, et al. *J Neurosci*. 1997;17(14):5271-5280.

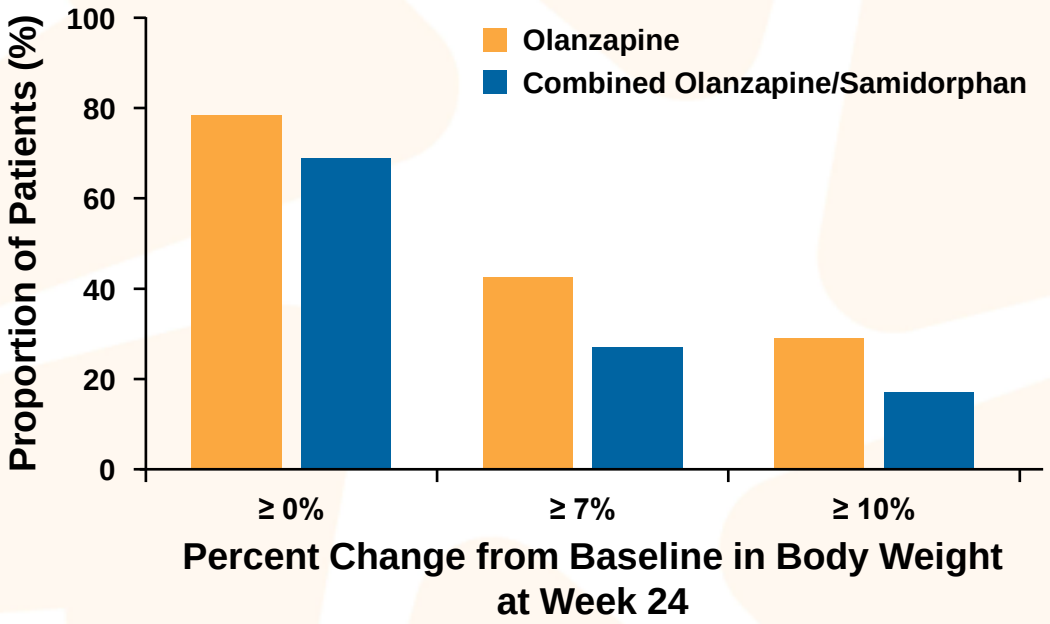
Olanzapine + Samidorphan in Bipolar I Manic/Mixed Episodes

- Samidorphan (10 mg) = μ opiate receptor (MOR) antagonist structurally related to naltrexone + olanzapine 5 mg, 10 mg, 15 mg, or 20 mg
- Current data demonstrate attenuated weight gain in schizophrenia

Least Squares Mean of Percent Change from Baseline in Body Weight by Visit



Proportion of Patients with Weight Changes at Week 24

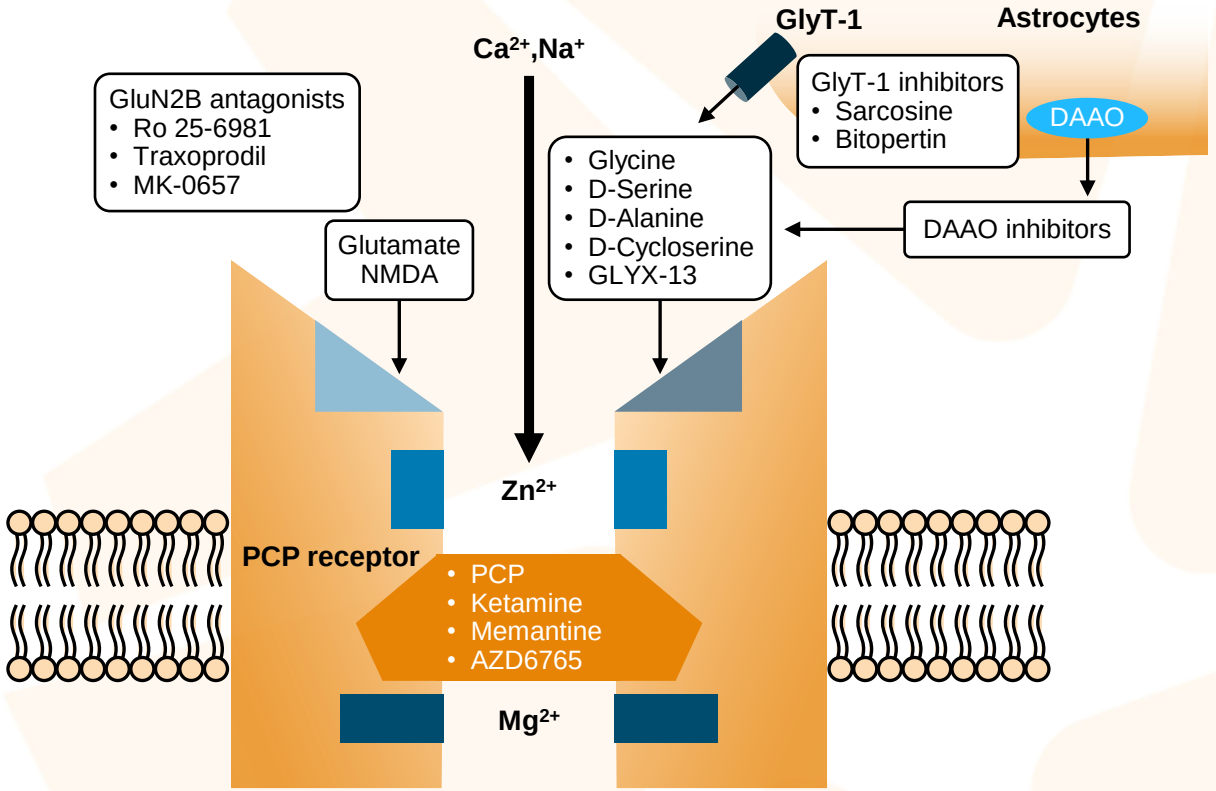


Correll CU, et al. *Am J Psychiatry*. 2020;177(12):1168-1178.

NRX-101

- Fixed-dose combination of lurasidone plus d-cycloserine (putative NMDA antagonist believed to increase glutamate/glutamine (Glx) at the glycine site, with activity in the anterior cingulate cortex)

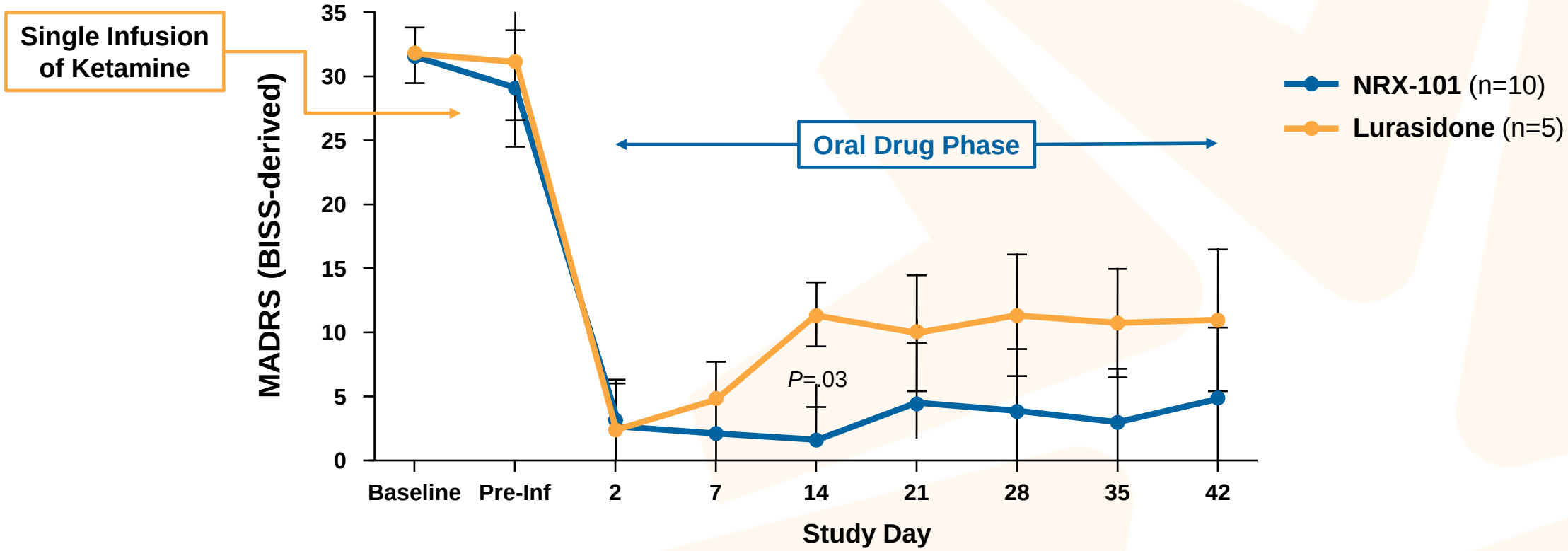
Under Phase 2b/3 investigation as a maintenance therapy after acute response to IV ketamine in bipolar depression as compared to lurasidone monotherapy



Hashimoto K, et al. *Eur Arch Psychiatry Clin Neurosci*. 2013;263(5):367-377. ClinicalTrials.gov Identifier: NCT03396068.

NRX-101
Proof-of-Concept Clinical Data

Depression Score NRX-101 vs Lurasidone

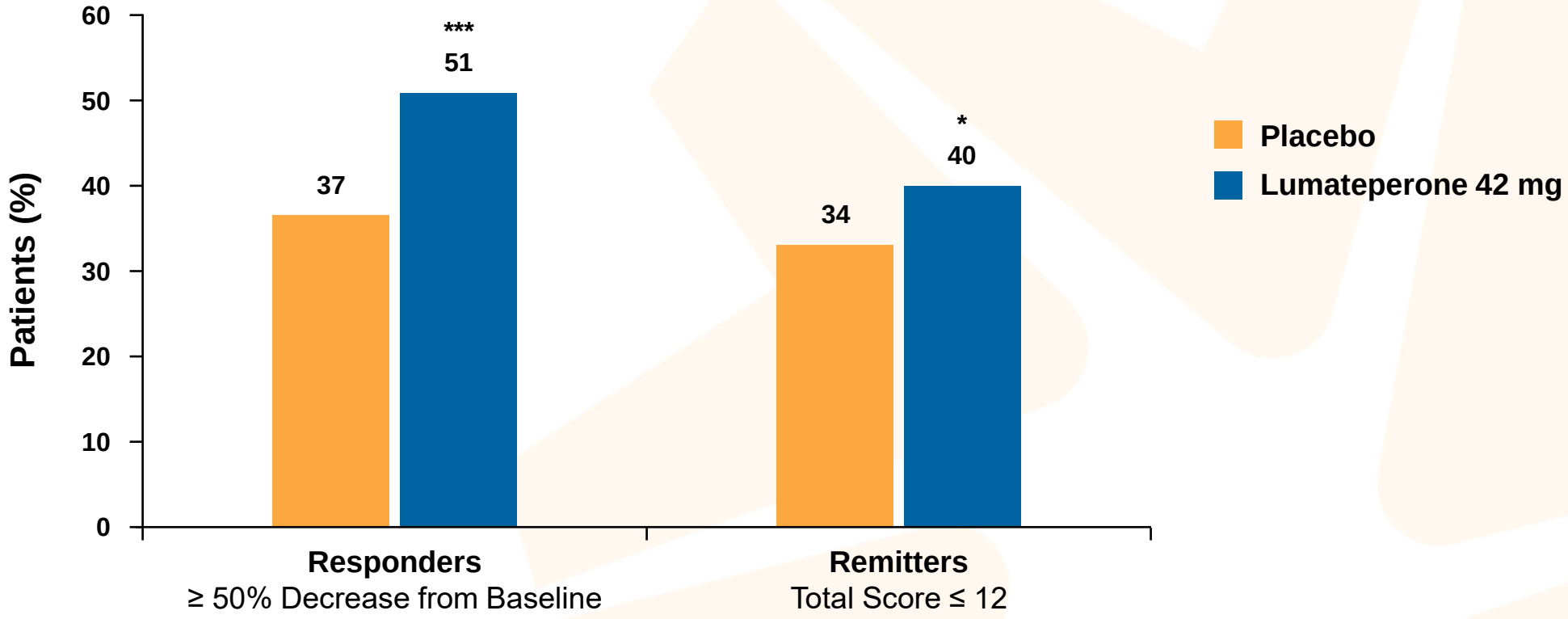


Mixed model to day 42: *P*=.059

BISS = Bipolar Inventory of Symptoms Scale.
ClinicalTrials.gov Identifier: NCT02974010.

Lumateperone in Bipolar I and II Depression

MADRS Response and Remission at Day 43 in the ITT



***P*<.05, ****P*<.001 vs placebo in the ITT population. Responder and remitter analyses based on logistic regression analysis with terms for site, treatment, and the bipolar disorder stratification at screening.

D'Souza I, et al. Efficacy and Safety of Lumateperone (ITI-007) in the Treatment of Depressive Episodes Associated with Bipolar I and II Disorders. Presented at: 2020 Psych Congress Virtual Experience; September 10–13, 2020.

Other Novel Pharmacotherapies for Bipolar Depression

- **(Ar)modafinil***: pooled analysis of 2 randomized trials, ES=-0.30
- **Pramipexole***: pooled analysis of 2 studies; ES=4.12 (response)
- Anti-inflammatory agents:
  - **NAC***: 1–2 g/day, ES=-0.75
  - **Omega-3 fatty acids***: 1–6 g/day, ES=-0.36
- **Ketamine***: 3 randomized trials in bipolar depression:

Authors	N	Day 3–4 Response (OR, 95% CI)
Murrough et al.	24	**4.67 (1.57–13.84)**
Diazgranados et al.	18	15.55 (0.70–346.72)
Zarate et al.	15	3.92 (0.14–112.90)

***Not FDA-approved in bipolar depression.**

Goss AJ, et al. *J Clin Psychiatry*. 2013;74(11):1101-1107. Tundo A, et al. *Acta Psychiatr Scand*. 2019;140(2):116-125. Rosenblat JD, et al. *Bipolar Disord*. 2016;18(2):89-101. Murrough JW, et al. *Psychol Med*. 2015;45(16):3571-3580. Diazgranados N, et al. *Arch Gen Psychiatry*. 2010;67(8):793-802. Zarate CA Jr, et al. *Biol Psychiatry*. 2012;71(11):939-946.

Key Learning Point

Several emerging and novel agents are in different phases of clinical development for bipolar depression, including NRX-101 and lumateperone. A recent Phase 3 randomized, double-blind, placebo-controlled trial of lumateperone found improvement in MADRS scores in patients with depressive episodes associated with bipolar I and II disorders.

Vanessa

- Clinical history suggests past high periods and poor efficacy with antidepressants
- Comprehensive care plan involves
  - psychoeducation about bipolar disorder,
  - lifestyle factors including risk for mood worsening with alcohol and substance use,
  - introduction of an evidence-based treatment for bipolar depression,
  - symptom reassessment, and
  - role for ongoing comprehensive care including pharmacology and psychotherapy

Take-Home Messages

- Use rating scales as initial screens for bipolar disorder; not proxies for diagnosis
- Recognize corroborative features for ruling in or out diagnoses of bipolar disorder
- Consider within-class differences among “mood stabilizers” and SGAs in demonstrated antimanic vs antidepressant efficacy
- Recognize potential breadth of mechanisms of action among SGAs (involving serotonergic and dopaminergic effects, among others) that may contribute to efficacy in bipolar depression for at least some agents
- Emerging role for novel pharmacotherapies and forms of neuromodulation targeting bipolar depression

psychcongress.com/newsroom/bipolar-360

Access the latest clinical updates on bipolar disorder.