SYLLABUS AND COURSE GUIDE
Session I: Thursday, June 29, 2017
Session II: Thursday, July 6, 2017

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Four-Part Case Series: Bipolar Disorder with Residual Symptoms - *Q&A Session I & II*

FACULTY: Roger S. McIntyre, MD, FRCPC

neuroscience CME

A Free, 30 Minute CME/CPE LIVE Q&A Case Based Session
Thursday, June 29, 2017 at 3:00 PM ET (Session I) OR
Thursday, July 6, 2017 at 3:00 PM ET (Session II)

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INFORMATION FOR PARTICIPANTS

Statement of Need

Bipolar disorder is a severe psychiatric disorder that is frequently associated with persistent symptoms and significant dysfunction.

Evidence suggests that the symptoms of bipolar disorder are recurrent and can worsen over repeated relapses. Even patients who follow treatment advice are still at a high relapse risk. Repeated relapses and rehospitalizations are main distresses, indicating a "downward spiral" of declined functioning and greater dependency on support and care by others.[1] The goal is to effectively manage symptoms and prevent relapse. .

In this CME Outfitters patient case and expert consult Q & A session, faculty will go in-depth with the case study answering your questions while offering evidence, guidelines, and quality measures to manage residual symptoms and avoid relapse in patients with bipolar disorder.

1. U. S. Public Health Service Office of the Surgeon General. Mental Health: Culture, Race, and Ethnicity: A Supplement to Mental Health: A Report of the Surgeon General. Rockville, MD: Department of Health and Human Services, U.S. Public Health Service; 2001.

Learning Objectives

At the end of this CE activity, participants should be able to:

- Review the efficacy and safety profile of recent agents approved for the treatment of bipolar disorder.
- Implement a treatment plan than addresses residual symptoms by incorporating the latest advances in bipolar disorder management.

Target Audience

Psychiatrists, pharmacists, and other members of the interprofessional team caring for individuals with bipolar disorder.

Financial Support

Supported by an educational grant from Allergan.

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Universal Activity Number Session I: 0376-0000-17-021-L01-P (live program)
0376-0000-17-021-H01-P (recorded program)

Universal Activity Number Session II: 0376-0000-17-022-L01-P (live program)
0376-0000-17-022-H01-P (recorded program)

Type: knowledge-based

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FACULTY BIOS & DISCLOSURES

Roger S. McIntyre, MD, FRCPC

Dr. McIntyre is currently a Professor of Psychiatry and Pharmacology at the University of Toronto and Head of the Mood Disorders Psychopharmacology Unit at the University Health Network, Toronto, Canada.Dr. McIntyre is also Executive Director of the Brain and Cognition Discovery Foundation in Toronto, Canada.

Dr. McIntyre was named by Thomson Reuters in 2014, as one of "The World's Most Influential Scientific Minds". This distinction is given by publishing the largest number of articles that rank among those most frequently cited by researchers globally in 21 broad fields of science and social science during the previous decade.

Dr. McIntyre is involved in multiple research endeavours which primarily aim to characterize the association between mood disorders, notably cognitive functionand medical comorbidity. His works broadly aims to characterize the underlying causes of cognitive impairment in individuals with mood disorders and their impact on workplace functioning. This body of work has provided a platform for identifying novel molecular targets to treat and prevent mood disorders and accompanying cognitive impairment.

Dr. McIntyre is extensively involved in medical education. He is a highly sought-after speaker at both national and international meetings. He has received several teaching awards from the University of Toronto, Department of Psychiatry and has been a recipient of the joint Canadian Psychiatric Association (CPA) / Council of Psychiatric Continuing Education Award for the Most Outstanding Continuing Education Activity in Psychiatry in Canada.

Dr. McIntyre is the co-chair of the Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force on the Treatment of Comorbidity in Adults with Major Depressive Disorder or Bipolar Disorder and as well a contributor to the CANMAT guidelines for the treatment of Depressive Disorders and Bipolar Disorders. Dr. McIntyre has published hundreds of peer-reviewed articles and hasedited and/or co-edited several textbooks on mood disorders.

Dr. McIntyre completed his medical degree at Dalhousie University. He received his Psychiatry residency training and Fellowship in Psychiatric Pharmacology at the University of Toronto.

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Tony Graham, MD (peer reviewer) has no disclosures to report.

Kashemi D. Rorie, PhD (planning committee) has no disclosures to report.

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Four-Part Case Series: Bipolar Disorder with Residual Symptoms – Q&A Session 1

Supported by an educational grant from Allergan.

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Learning Objective 1

Review the efficacy and safety profile of recent agents approved for the treatment of bipolar disorder.

Learning Objective 2

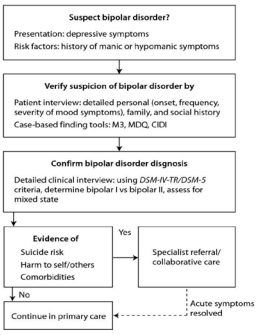
Implement a treatment plan than addresses residual symptoms by incorporating the latest advances in bipolar disorder management.

Revisiting the Case of Mr. RT

- Mr. RT is a 28-year-old male, PhD student in his final year, planning his thesis defense. Mr. RT is living with his partner of 4 years in a stable relationship. Mr. RT has been given a diagnosis of Bipolar I Disorder.

Diagnostic Considerations for Mr. RT

- Confirming his diagnosis
- Differentiating bipolar subtypes
- Course of Illness
- Family history
- Medical and/or psychiatric comorbidities



Culpepper L. *Prim Care Companion CNS Disord.* 2014; 16(3): PCC.13r01609.

Symptom Profile of Mr. RT

- The “polarity predominance” of his illness has been depression, insofar as he rarely has hypo/manic depressive episodes, but he has had greater than 4 depressive episodes prior. He has a past diagnosis of cannabis use disorder in remission. He continues to smoke cigarettes daily. (i.e. 10 pack years).

Features that Distinguish Bipolar from Unipolar

Bipolar Depression (more likely with ≥5 present)	Unipolar Depression (more likely with ≥4 present)
Hypersomnia, more daytime sleeping	Initial insomnia or reduced sleep
Hyperphagia, increased body weight	Appetite or weight loss
Psychotic features during depression, pathologic guilt	Somatic complaints
Psychomotor retardation	Normal or increased activity levels
Atypical symptoms (eg, leaden paralysis)	
Mood lability or manic symptoms	
First depression <25 years of age	First depression >25 years of age
≥5 prior major depressive episodes	Long current episode (>6 months)
Bipolar disorder in family history	No bipolar disorder in family history

Other factors that can help identify bipolar depression include
- **Sudden onset of symptoms**
- **Impulsivity**
- Poor response of depressive symptoms to antidepressants

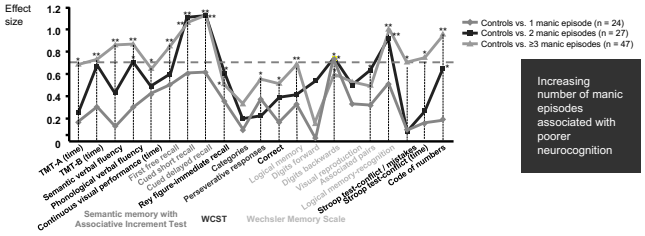
Forty L, et al. *Br J Psychiatry*. 2008;192(5):388-389; Mitchell PB, et al. *Bipolar Disord*. 2008;10(1 Pt 2):144-152; Muzina DJ, et al. *Ann Clin Psychiatry*. 2007;19(4):305-312; Price AL, et al. *Am Fam Physician*. 2012;85(5):483-493.

Differentiating Bipolar I and II Disorder

- **Bipolar I**
  - 1 or more manic or mixed episodes
  - More severe, leading to:
    - Hospitalizations
    - Psychotic features
- **Bipolar II**
  - 1 or more hypomanic episodes and no mania
  - 1 or more major depressive episodes

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.

Cumulative Effect of Previous Bipolar Manic Episodes on Neurocognition



Increasing number of manic episodes associated with poorer neurocognition

TMT-A / B, Trail Making Test A / B; WCST, Wisconsin Card Sorting Test
*p < .01; **p < .001 for effect size vs controls; Effect size >0.70 assumed to be significant
López-Jaramillo C, et al. *Bipolar Disord*. 2010;12(5):557-567.

Best Practices: Factors to Consider

Depressive symptom severity

Presence of mixed features, rapid cycling

Comorbid psychiatric and medical illness

Therapy risk-benefit

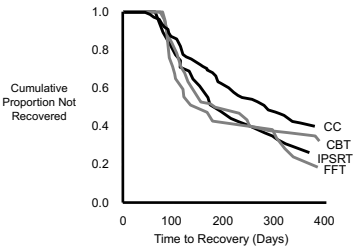
Slide courtesy of Dr Susan McElroy

Comorbid Symptoms in Mr. RT

- Current PHQ-9 score = 15, GAD-7 score = 12. He's complaining of cognitive dysfunction (e.g. inattention), as well as problems with focusing on his thesis.
- His BMI is 28 kg/m^2. He was told that this could be interfering with his cognitive abilities to some extent, and was counselled on appropriate diet, exercise, and sleep hygiene.

PHQ = Patient Health Questionnaire
GAD-7 = Generalized Anxiety Disorder 7-Item

Intensive Psychotherapies Improve Bipolar Depression



- N = 293 bipolar depressed outpatients
- Protocol meds + 9 mos:
  - FFT (family-focused therapy)
  - IPSRT (interpersonal and social rhythm therapy)
  - CBT (cognitive behavior therapy)
  - CC (collaborative care)
- Intensive psychotherapies
  - Higher recovery rate
  - Shorter time to recovery
  - 1.6x more likely to be clinically well during any study month

Miklowitz DJ et al. *Arch Gen Psychiatry*. 2007;64(4):419-426.

FDA-Approved Bipolar Disorder Treatments

Agent	Manic	Mixed	Depression	Maintenance
Aripiprazole	+	+	–	–
Asenapine	+	+	–	+
Cariprazine	+	+	–	–
Lurasidone	–	–	+	–
Olanzapine	+	+	–	–
Olanzapine/Fluoxetine	–	–	+	–
Quetiapine/XR	+	–	+	+
Risperidone (Oral / IM)	+	+	–	+ (IM)
Ziprasidone	+	+	–	+
Chlorpromazine	+	–	–	–
Carbamazepine XR	+	+	–	–
Divalproex DR/ER	+	+	–	–
Lamotrigine	–	–	–	+
Lithium	+	–	–	+

*Aripiprazole, asenapine, olanzapine, quetiapine, risperidone indication as monotherapy and adjunct to Li or DVPX and with / without psychosis

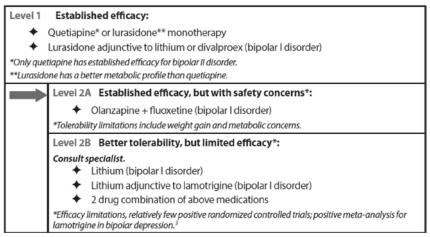
Evidence Base for Treatment of Bipolar Depression

Drug	Evidence Base	Drug	Evidence Base
Quetiapine	++	Modafinil	+/-/-
Lurasidone	++	Aripiprazole	-
Fluoxetine	+	Ziprasidone	-
Lamotrigine	+	High dose thyroxine	+
Lithium	+	Sleep Dep/Pindolol	+
Olanzapine	+	ECT	+
Pramipexole	+	Clozapine	?
Valproate	+	TMS	?
Ketamine	+/+	DBS	?

++ = At least 1 fully powered, randomized, placebo-controlled, double-blind, parallel-group, positive trial with moderate-to-large effect-size; + = At least 1 positive randomized, controlled trial or small placebo-controlled, double-blind, parallel-group trial or small effect size; – = Controlled evidence of lack of efficacy; ? = No data.

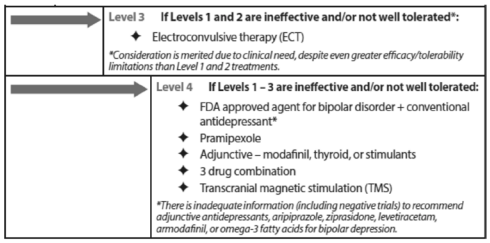
Vieta E., *World J Biol Psychiatry*. 2009;10(2):82-84.; Zarate CA, et al. *Am J Psychiatry* 2004;161(1):169-171.; Diazgranados N, et al. *Arch Gen Psychiatry*. 2010;67(8):793-802.;Goldberg JF, et al. *Am J Psychiatry* 2004;161(3):564-566.; Frye MA, et al. *Am J Psychiatry*. 2007;164(8):1242-1249.; Calabrese JR, et al. *J Clin Psychiatry* 2010;12(4):404-413.

Treatment of Acute Bipolar Disorder – Depression



McIntyre, RS, et al. Available at: http://www.medicaidmentalhealth.org/_assets/file/Guidelines/2015%20Treatment%20of%20Adult%20Bipolar%20Disorder.pdf. Accessed May 16, 2017.

Treatment of Acute Bipolar Disorder – Depression (cont.)



McIntyre, RS, et al. Available at: http://www.medicaidmentalhealth.org/_assets/file/Guidelines/2015%20Treatment%20of%20Adult%20Bipolar%20Disorder.pdf. Accessed May 16, 2017.

Treatment Initiation in Mr. RT

- Mr. RT was given a prescription for an atypical antipsychotic recommended first-line according to the Florida Medicaid Guidelines for depression. Additionally, psychoeducation was offered, and he was referred to mindfulness-based psychotherapy.

The Do's and Don'ts of Managing Mr. RT

- Dosing/titration
- Switching
- Adjunctive therapy
- Initial treatment considerations
- Patient follow-up intervals
- Management of comorbidities

SMART Goals:
Managing Patients Like Mr. RT

- Timely and accurate diagnosis, differentiating Bipolar I, II, and Major Depressive Disorder
- Utilize evidence-based strategies, including treatment guidelines and appropriate clinical tools for appropriate treatment selection and monitoring
- Consider safety and tolerability profiles when developing treatment approaches for Bipolar Disorder
- Treat comorbid medical and psychiatric conditions

Questions & Answers

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Resources

Quality Measure

- The STAndards for BipoLar Excellence (STABLE) project highlights several measures, which provide guidance for performance and quality improvement, particularly in key gap areas. These are also adopted by the AHRQ as quality measures. In the area of metabolic monitoring, STABLE includes: monitoring for weight gain, screening for hyperglycemia, and monitoring for hyperlipidemia when an atypical antipsychotic agent is prescribed.

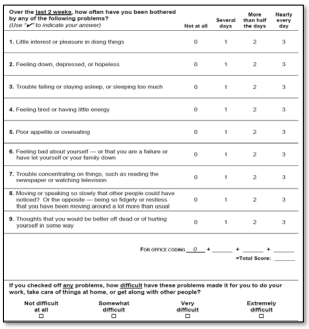
Agency for Healthcare Quality and Research. Available at https://www.qualitymeasures.ahrq.gov/search?f_Developer_String=STABLE%20Project%20National%20Coordinating%20Council&fLockTerm=STABLE%2BProject%2BNational%2BCoordinating%2BCouncil. Accessed June 23, 2017.

Quality Measure

- The percentage of patients diagnosed and treated for bipolar disorder who are monitored for change in their symptom complex within 12 weeks of initiating treatment.

Agency for Healthcare Research and Quality. Available at https://www.qualitymeasures.ahrq.gov/summaries/summary/28262/bipolar-disorder-the-percentage-of-patients-diagnosed-and-treated-for-bipolar-disorder-who-are-monitored-for-change-in-their-symptom-complex-within-12-weeks-of-initiating-treatment. Accessed June 23, 2017.

PHQ-9



Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

For office coding: ___0___ + _____ + _____ + _____ =Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Kroenke K, et al. *J Gen Intern Med*. 2001;16(9): 606–613.

Mood Disorders Questionnaire (MDQ)

1. Has there ever been a period of time when you were not your usual self and…	
…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 much 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 1 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—being unable to work; having family, money, or legal troubles; getting into arguments or fights? Please circle 1 response only	
No problem Minor problem Moderate problem Serious problem	
Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	Yes/No
For a positive screen, 7 of the 13 items in no. 1 must be yes, no. 2 must be yes, and no. 3 must be moderate or serious	

Hirschfeld RM et al. *Am J Psychiatry.* 2000;157(11):1873–1875.

The Composite International Diagnostic Interview (CIDI)

I. Stem Questions

1. Some people have periods lasting several days or longer when they feel much more excited and full of energy than usual. Their minds go too fast. They talk a lot. They are very restless or unable to sit still, and they sometimes do things that are unusual for them, such as driving too fast or spending too much money. Have you ever had a period like this lasting several days or longer?[2]
2. Have you ever had a period lasting several days or longer when most of the time you were so irritable or grouchy that you started arguments, shouted at people, or hit people?

II. Criterion B Screening Questions

1. People who have episodes like this often have changes in their thinking and behavior at the same time, like being more talkative, needing very little sleep, being very restless, going on buying sprees, and behaving in ways they would normally think are inappropriate. Did you ever have any of these changes during your episodes of being excited and full of energy/very irritable or grouchy?

III. Criterion B Symptom Questions

Think of an episode when you had the largest number of changes like these at the same time. During that episode, which of the following changes did you experience?

1. Were you so irritable that you either started arguments, shouted at people, or hit people?[2]
2. Did you become so restless or fidgety that you paced up and down or couldn't stand still?
3. Did you do anything else that wasn't usual for you—like talking about things you would normally keep private or acting in ways that you would usually find embarrassing?
4. Did you try to do things that were impossible to do, like taking on large amounts of work?
5. Did you constantly keep changing your plans or activities?
6. Did you find it hard to keep your mind on what you were doing?
7. Did your thoughts seem to jump from one thing to another or race through your head so fast you couldn't keep track of them?
8. Did you sleep far less than usual and still not get tired or sleepy?
9. Did you spend so much more money than usual that it caused you to have financial trouble?

Kessler RC, et al.
J Affect Disord.
2006;96(3):259–269.

Generalized Anxiety Disorder 7- Item (GAD-7)

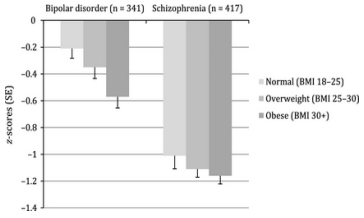
Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Spitzer RL, et al. *Arch Intern Med*. 2006;166:1092-1097.

Association of Obesity with Cognitive Ability in Bipolar Disorder and Schizophrenia



Global cognitive ability by body mass index (BMI) level clustered by diagnosis. Error bars are standard errors (SE).

Group comparisons:
Bipolar Disorder: $F(2,338) = 5.2$, $p = 0.006$ [adjusted for education, Positive and Negative Syndrome Scale *negative* score, atypical antipsychotic use, and residential status: $F(2,320) = 18.2$, p = 0.035]; Tukey post hoc normal > obese

Schizophrenia: $F(2,413) = 0.70$, $p = 0.482$. Effect size from lowest to highest BMI in bipolar disorder is Cohen's $d = 0.43$ compared to $d = 0.16$ for schizophrenia.

Depp CA, et al. *Bipolar Disorders*. 2014;16:422-431.

Mood Stabilizers: Safety and Tolerability Concerns

Lithium	Valproate	Carbamazepine	Lamotrigine
Gastrointestinal	Gastrointestinal	Gastrointestinal	Gastrointestinal
Weight gain	Weight gain	Rash	Rash
Neurotoxicity	Tremor	Neurotoxicity	Headache
Renal toxicity	Hepatotoxicity	Hepatotoxicity	Dizziness
Thyroid toxicity	Thrombocytopenia	Thyroid changes	Pruritis
Hair Loss	Hair Loss	Blood dyscrasias	Dream abnormality
Cardiac toxicity	Pancreatitis	Cardiac toxicity	
Acne, Psoriasis	PCOS	Hyponatremia	
Teratogen	Teratogen	Teratogen	Teratogen
	Suicidality	Suicidality	Suicidality

All mood stabilizers have at least one boxed warning.

= boxed warning in prescribing information.

[Package Insert]. Drugs@FDA Website.; In: Ketter TA (ed). *Advances in the Treatment of Bipolar Disorder*. 2005.

Antipsychotic Safety and Tolerability Concerns

First-Generation	Second-Generation
Depression	Weight gain, Sedation
Akathisia	Hyperglycemia, Diabetes[b]
Acute dystonia	Suicidality in age ≤ 24[c]
Tardive dyskinesia[a]	Akathisia
Weight gain, Sedation	Hyperprolactinemia
Anticholinergic	Cerebrovascular in elderly[d]
Cardiac, Orthostasis	Cardiac, Orthostasis
Hyperprolactinemia	Tardive dyskinesia[a]
Neuroleptic malignant[a]	Neuroleptic malignant[a]
Leukopenia, Neutropenia,	Leukopenia, Neutropenia,
Agranulocytosis[a]	Agranulocytosis[a]
Cardiac/pneumonia in older adults[a]	Cardiac/pneumonia in older adults[a]

All Antipsychotics Have at Least One Boxed Warning

Warnings - boxed; [a] Antipsychotic class warning/precaution; [b] Second generation antipsychotic class warning; [c]Aripiprazole, quetiapine, olanzapine + fluoxetine combination (antidepressant class warning);[d] risperidone, olanzapine.

In: Ketter TA (ed). *Advances in the Treatment of Bipolar Disorder*. 2005.; [Package Insert]. Drugs@FDA Website.

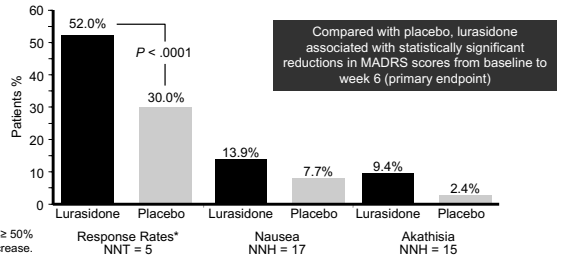
MOA and Safety of Agents Used in Bipolar Depression

Agent	MOA	Dose Range	Comments
Lithium*	Inhibition of dopamine and glutamate; promotes GABA-mediated transmission	300 – 1800 mg/d	Diarrhea; vomiting; diabetes insipidus; ataxia; blurred vision; cardiac arrhythmias; myoclonus
Olanzapine/ Fluoxetine	Increased release of serotonin, norepinephrine, and dopamine	6/25 – 12/50 mg/d	Sedation; cardiometabolic adverse effects; weight increased; appetite increased; edema
Quetiapine XR	Dopamine (D_2), serotonin ($5HT_2$), and histamine (H1) antagonism; adrenergic α_1 receptor antagonist	50 – 300 mg/d	Sedation; cardiometabolic adverse effects; increased appetite; weight gain; fatigue; somnolence
Lurasidone	D_2 and 5-HT_{2A} receptor antagonism	20 – 120 mg/d	Akathisia; extrapyramidal symptoms; somnolence
Lamotrigine**	Na channel block; Ca channel block	25 – 200 mg/d	Low starting dose and slow dose titration required to minimize serious skin reactions; nausea; somnolence; back pain; fatigue
Armodafinil*	Indirect dopamine receptor agonist	50 – 250 mg/ d	Headache, nausea, dizziness, insomnia
Cariprazine*	D_2 and 5-HT_{1A} partial agonist; 5-HT_{2A} partial antagonist	1.5 mg/d – 6 mg/d	Extrapyramidal symptoms, akathisia, dyspepsia, somnolence

*Not FDA-approved for bipolar depression; **Lamotrigine is FDA-approved for maintenance of BD-I

[Package Inserts]. Drugs@FDA Website

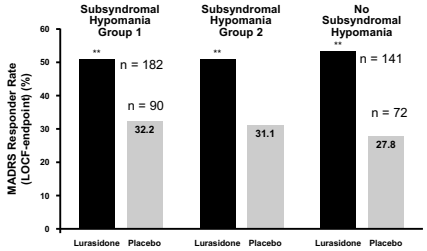
Lurasidone in Bipolar I Depression: PREVAIL 2



*Response: ≥ 50% MADRS decrease.

Loebel A, et al. *Am J Psychiatry*. 2014;171(2):160-168.; Loebel A, et al. *Am J Psychiatry*. 2014;171(2):169-177.

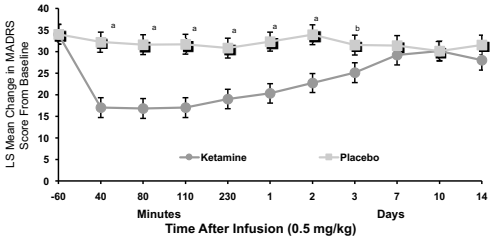
Lurasidone Efficacious in Bipolar Depression with Subsyndromal Hypomania



**$p < .01$

McIntyre RS, et al. *J Clin Psychiatry*. 2015;76(4):398-405.

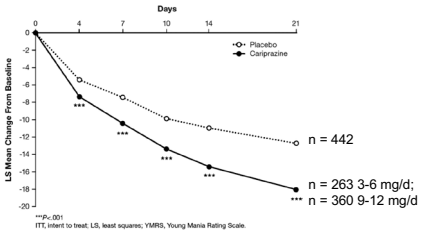
Ketamine in Acute Bipolar Depression



$^{a}P < .001$; $^{b}P < .05$ ketamine vs placebo. Ketamine is not approved by the US FDA for bipolar depression. N = 15 subjects with bipolar I or II depression on therapeutic levels of lithium or valproate received a single intravenous infusion of either ketamine (0.5 mg/kg) or placebo on 2 test days 2 weeks apart.

Zarate CA, et al. *Biol Psychiatry*. 2012;71(11):939-946.

Cariprazine Efficacy in Acute Manic/Mixed BD: Pooled Data

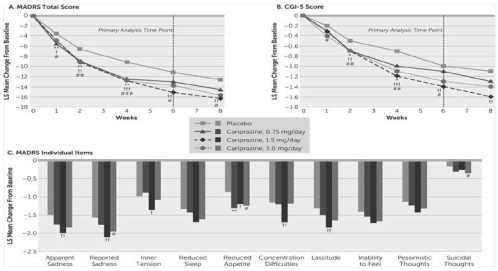


***P<.001
ITT, intent to treat; LS, least squares; YMRS, Young Mania Rating Scale.

Data taken from three 3-week randomized, double-blind, placebo-controlled, flexible dose trials of cariprazine 3 - 12 mg/d.

Earley W, et al. *J Affect Disord*. 2017;215:205-212.

Cariprazine* vs. Placebo in Bipolar I Depression



a Mixed-effects model for repeated measures, intent-to-treat population; p values were not adjusted for multiple comparisons. Cariprazine 0.75 mg/day compared with placebo: *$p < .05$; **$p < .01$; ***$p < .001$. Cariprazine 1.5 mg/day compared with placebo: †$p < .05$; ††$p < .01$; †††$p < .001$. Cariprazine 3.0 mg/day compared with placebo: #$p < .05$; ##$p < .01$; ###$p < .001$.

Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-81.

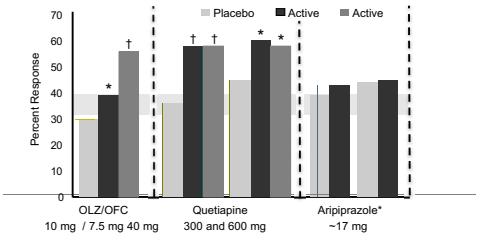
*Not approved by the FDA for treatment of bipolar depression.

ISBD Recommendations for ADs in Bipolar Depression

- International collaboration of 70 experts in BP; 173 studies reviewed
- Adjunctive antidepressants for acute bipolar depression
  - **Permissible** with history of positive antidepressant response
  - **Avoid** in the presence of ≥2 core manic symptoms, psychomotor agitation, or rapid cycling
- Antidepressant monotherapy for acute bipolar depression
  - **Avoid** in bipolar I disorder
  - **Avoid** in bipolar II disorder with ≥2 core manic symptoms
- Antidepressant use in mixed states
  - **Avoid** during mood episodes with mixed features and in patients with predominantly mixed states
  - Discontinue if mixed state emerges

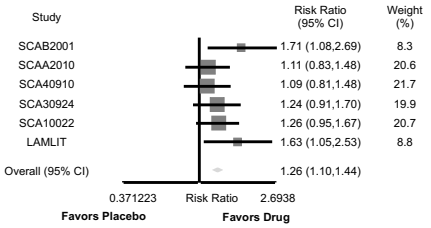
Pacchiarotti I et al. *Am J Psychiatry*. 2013;170(11):1249-1262

Response Rates of Atypical Antipsychotics in BP Depression



Calabrese J, et al. *Am J Psychiatry*. 2005;162(7):1351-1360; Thase ME, et al. *J Clin Psychopharmacol*. 2009;29(1):38; Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.

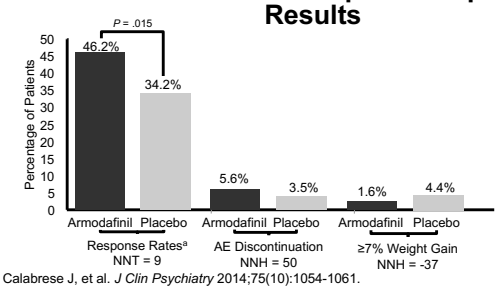
Meta-Analysis of Lamotrigine* in Acute Bipolar Depression



*Not FDA approved for bipolar depression

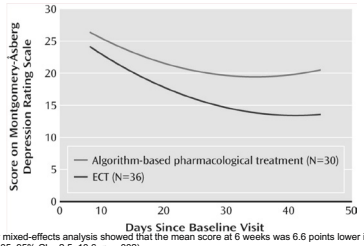
Geddes JR. *Br J Psychiatry*. 2009;194(1):4-9.; Van der Loos ML, et al. *J Clin Psychiatry*. 2009;70(2):223-231.

8-Week Randomized Double-Blind Adjunctive Armodafinil* in Acute Bipolar I Depression: Results



Calabrese J, et al. *J Clin Psychiatry* 2014;75(10):1054-1061.

Treatment-Resistant Bipolar Depression: Electroconvulsive Therapy Versus Algorithm-Based Pharmacological Treatment



a Linear mixed-effects analysis showed that the mean score at 6 weeks was 6.6 points lower in the ECT group (SE = 2.05, 95% CI = 2.5–10.6, p = .002).

Schoeyen HK, et al. *Am J Psychiatry*. 2015;172(1):41-51.

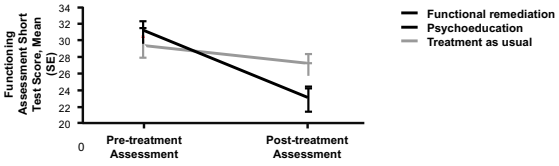
Psychosocial Treatments

- Cognitive behavioral therapy
- Family-focused therapy
- Interpersonal therapy
- Social rhythm therapy
- Psychoeducation
- Healthy lifestyle choices
  - Appropriate food
  - Exercise
  - Sleep hygiene

Bowden CL, et al. *CNS Neurosci Ther*. 2012;18(3):243-249.

Functional Remediation in Bipolar Disorder

Changes in functional impairment scores before and after intervention in patients with bipolar disorder



Higher scores indicate greater impairment. Functional remediation program consisting of 21 weekly sessions lasting 90 minutes. Change for the functional remediation group was significantly different from change for the treatment-as-usual group (Pillai's Trace =.065; F = 6.51, P = .002).

Torrent C, et al. *Am J Psychiatry*. 2013;170(8):852-859.

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