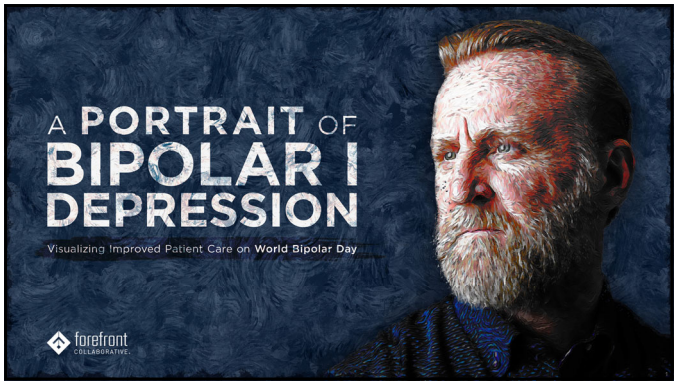

Faculty Presenters

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G

A Call to Action—the Need for Earlier, More Accurate Diagnosis and Improved Treatment of Bipolar I Depression

Joseph F. Goldberg, MD, MS

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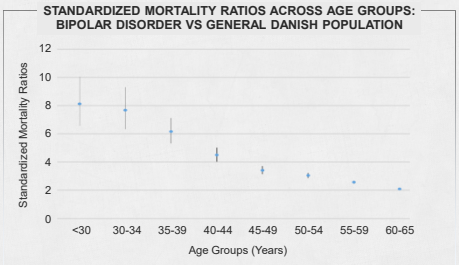
Bipolar Disorder Nearly Triples the Likelihood of Premature Death Due to All Medical Causes

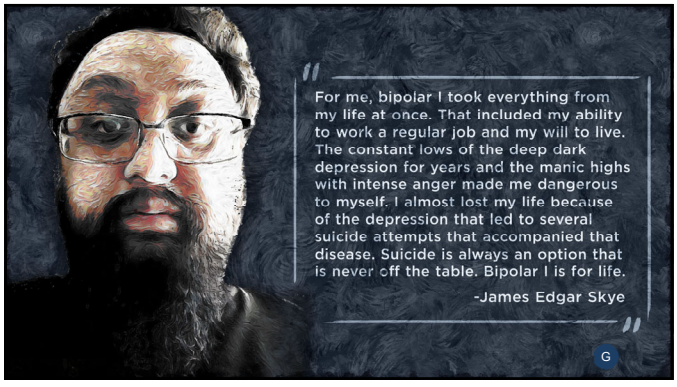


Staudt Hansen P, et al. *Bipolar Disord*. 2019;21(3):270-275.

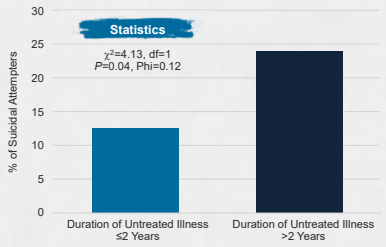
Bipolar Disorder Is the Sixth Leading Cause of Disability Worldwide

All Causes		Total (Millions)	Percent of Total
1	Unipolar major depression	50.8	10.7
2	Iron-deficient anemia	22.0	4.7
3	Falls	22.0	4.6
4	Alcohol use	15.8	3.3
5	Chronic obstructive pulmonary disease	14.7	3.1
6	**Bipolar disorder**	**14.1**	**3.0**
7	Congenital anomalies	13.5	2.9
8	Osteoarthritis	13.3	2.8
9	Schizophrenia	12.1	2.6
10	Obsessive-compulsive disorder	10.2	2.2

Murray CJL, Lopez AD. *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors: 1996*.



Suicide Rates Escalate When the Duration of Untreated Illness for Bipolar Disorder Lasts as Little as 2 Years



Altamura AC, et al. *Eur Arch Psychiatry Clin Neurosci*. 2010;260(5):385-391.

G

Polling Question

Which Patient Case Would You Like to Discuss?

When poll is active, respond at **pollev.com/reachmd**

Text **REACHMD** to **22333** once to join

A. Sam

27 year old referred for psychiatric evaluation after threatening to "knock the lights out" of a colleague

B. Anna

20 year old referred by parents for "failure to thrive" behavior

C. David

50 year old urged by wife to seek help because of mood swings

Hypothetical patient cases.

Note: The 2 patient cases not discussed can be found as an additional resource for this activity.

C

Patient Case 1: **DIAGNOSING SAM**

Larry Culpepper, MD, MPH
Joseph F. Goldberg, MD, MS
Andrew A. Nierenberg, MD

C

Meet Sam

- 27-year-old single aspiring actor, raised with his fraternal twin by their divorced mom
- Low-grade persistent depression since childhood plus social phobia
- Binge drinks before auditions, acting jobs, or first dates; becomes "sloppy drunk" with bad results
- Treated off and on with supportive psychotherapy, adequate trials of SSRIs or SNRIs, and benzodiazepines without benefit
- Instances of dramatic, bossy, loud irritable outbursts attributed by his therapist to "diva" personality traits and/or alcohol after-effects
- Referred by union manager for psychiatric evaluation after threatening to "knock the lights out" of a lighting technician for making too much noise

SNRIs=serotonin and norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors.

C

All of the following would help to corroborate a possible diagnosis of bipolar disorder EXCEPT:

A. A history of either bipolar disorder or panic disorder in his fraternal twin

B. The presence of alcohol use disorder as a freestanding condition

C. A personal history of a suicide attempt

D. A personal history of psychotic depression

C G

Gathering More Information About Sam

The consulting psychiatrist contacted Sam's current psychiatrist to gather more background information.

When the consultant asked about past symptoms of either psychosis or mania/hypomania, Sam's current psychiatrist interjected that Sam did not have bipolar disorder because when he administered a Mood Disorder Questionnaire (MDQ), the score was only 5.

C

Which of the following statements is TRUE about making a diagnosis of bipolar disorder?

A. Sam's Mood Disorder Questionnaire (MDQ) score below 7 means he does not have bipolar disorder

B. Epidemiological studies report prevalence rates for comorbid alcohol use disorder of up to 90% of individuals with bipolar disorder

C. The MDQ may be a less reliable screening instrument in patients with mood disorders with active alcohol or substance use disorders

D. It is not necessary to have a history of mania or hypomania to make a diagnosis of bipolar I or II depression

C G

DISCUSSION

How can screening tools (eg, the Mood Disorder Questionnaire [MDQ], Rapid Mood Screener, Bipolar Spectrum Diagnostic Scale [BSDS], and Bipolar Disorder Screening Scale) be used in the context of a patient's lived experience?

What are their limitations?

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The consultant psychiatrist raised a differential diagnosis of (1) bipolar I disorder, depressed phase with mixed features (based on the presence of irritable mood, diminished need for sleep, grandiose thinking, and psychomotor agitation) vs (2) major depressive disorder with mixed features (MDD-MF).

The key point of differentiation between these 2 DSM-5 diagnoses is which of the following?

A. Agitation and sleep disruption occur in bipolar depression but not MDD-MF

B. Patients with MDD-MF have never met the DSM-5 criteria for a hypomanic episode

C. Irritability is unique to the mood disturbance in bipolar but not MDD-MF

D. In a patient with mixed features, irritability, distractibility, and agitation are symptoms that can "double count" toward simultaneously defining both manic/hypomanic and depressive episodes.

C G

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

Diagnostic Disagreement

Consulting psychiatrist

- Diagnoses Sam with bipolar I depression

Sam's current psychiatrist

- Disagreed with the consultant's opinion
- Felt that Sam has treatment-resistant major depression plus "anger management issues" rather than bipolar depression

DISCUSSION

How would you resolve this diagnostic disagreement?

C N

Overview of Treatments Recommended for Bipolar I Depression

Andrew A. Nierenberg, MD

N

FDA-Approved Treatments for Bipolar I Depression

- Olanzapine/fluoxetine combination (OFC)[1]
- Quetiapine (QTP)[2]
- Lurasidone[3]
- Cariprazine[4]

FDA=US Food and Drug Administration.

1. OFC (Symbyax) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021520s051lbl.pdf. Accessed February 24, 2021.
2. Quetiapine (Seroquel) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020639s070lbl.pdf. Accessed February 24, 2021.
3. Lurasidone (Latuda) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/200603s035lbl.pdf. Accessed February 24, 2021.
4. Cariprazine (Vraylar) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204370s008lbl.pdf. Accessed February 24, 2021.

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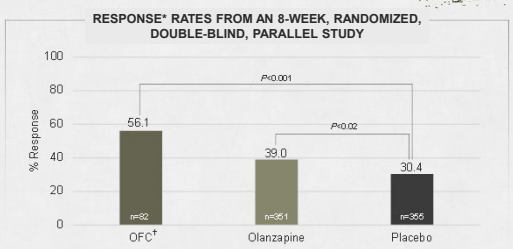
Olanzapine/Fluoxetine Combination (OFC) for Bipolar I Depression



MADRS=Montgomery–Åsberg Depression Rating Scale.
*Response was defined as 50% or greater improvement in the MADRS total score from baseline to an end point and completion of at least 4 weeks of study.
†The OFC arm was included for exploratory purposes.
Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.

Olanzapine/Fluoxetine Combination (OFC) for Bipolar I Depression (cont.)

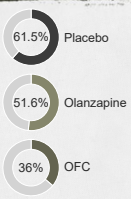
Adjunctive[1]

- With lithium or valproate*

Side effects[2]

- Weight gain, dry mouth, asthenia, diarrhea
- Metabolic syndrome

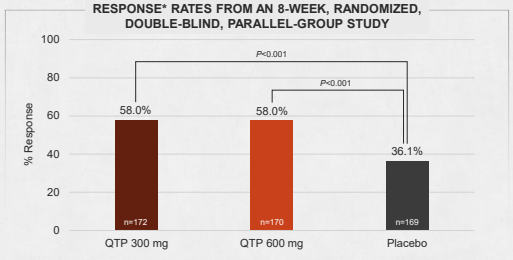
Discontinued treatment due to any reason (8-week study)[3]



***Not an FDA-approved indication.**

1. NICE clinical guideline. https://www.nice.org.uk/guidance/cg185/resources/bipolar-disorder-assessment-and-management-35109814379461. Accessed March 8, 2021.
2. OFC (Symbyax) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021520s051lbl.pdf. Accessed February 24, 2021.

Quetiapine (QTP) for Bipolar I or II Depression



*Responders had at least a 50% improvement in MADRS score.
Calabrese JR, et al. *Am J Psychiatry*. 2005;162(7):1351-1360.

Quetiapine (QTP) for Bipolar I or II Depression (cont.)

Monotherapy[1]

- For acute treatment of depressive episodes

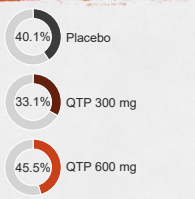
Adjunctive[1]

- For maintenance treatment

Side effects[1]

- Dry mouth, sedation, somnolence, dizziness, fatigue, constipation, headache, nausea
- Metabolic syndrome

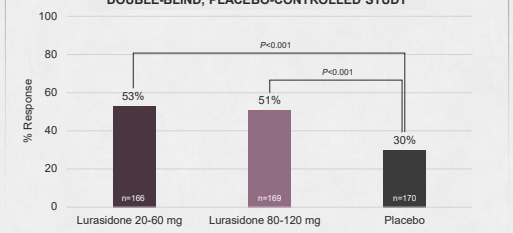
Discontinued treatment due to any reason (8-week study)[2]



1. Quetiapine (Seroquel) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020639s070lbl.pdf. Accessed February 24, 2021.
2. Calabrese JR, et al. *Am J Psychiatry*. 2005;162(7):1351-1360.

Lurasidone for Bipolar I Depression

RESPONSE* RATES FROM A 6-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY



*Responders had at least a 50% reduction from baseline in MADRS total.
Loebel A, et al. *Am J Psychiatry*. 2014;171(2):160-168.

Lurasidone for Bipolar I Depression (cont.)

Monotherapy[1]

- Take with food (350 calories)

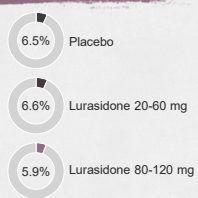
Adjunctive[1]

- With lithium or valproate

Side effects[1]

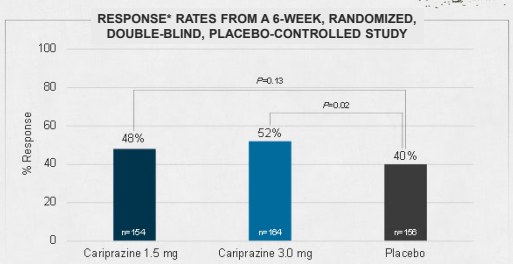
- Akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety

Discontinuation rates due to AEs (6-week study)[2]



AEs=adverse events.
1. Lurasidone (Latuda) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/200603s035lbl.pdf. Accessed February 24, 2021. 2. Loebel A, et al. *Am J Psychiatry*. 2014;171(2):160-168.

Cariprazine for Bipolar I Depression



*Responders had at least a 50% reduction in MADRS score from baseline score.

Earley W, et al. *Am J Psychiatry*. 2019;176(6):439-448.

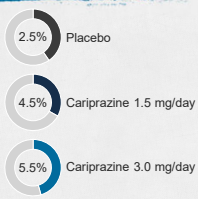
Cariprazine for Bipolar I Depression (cont.)

Monotherapy[1]

Side effects[1]

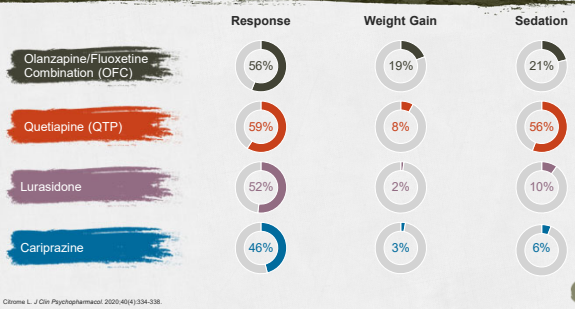
- Restlessness, akathisia, extrapyramidal symptoms, somnolence, vomiting, dyspepsia

Discontinuations due to AEs (6-week study)[2]



1. Cariprazine (Vraylar) PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204370s006lbl.pdf. Accessed February 24, 2021. 2. Earley W, et al. *Am J Psychiatry*. 2019;176(6):439-448.

FDA-Approved Bipolar Depression Treatments



Citrome L. *J Clin Psychopharmacol*. 2020;40(4):334-338.

2018 CANMAT/ISBD Guidelines: Treatments Recommended for Bipolar I Depression

	Level of Evidence by Phase of Treatment		
	Acute Depression	Maintenance	
		Prevention of Any Mood Episode	Prevention of Depression
First-Line Treatments			
Quetiapine (QTP)	**Level 1**	Level 1	Level 1
Lurasidone + lithium/divalproex	**Level 1**	Level 3*	Level 3†
Lithium	**Level 2**	Level 1	Level 1
Lamotrigine	**Level 2**	Level 1	Level 1
Lurasidone	**Level 2**	Level 4	Level 4
Lamotrigine (adjunctive)	**Level 2**	Level 4	Level 4
Second-Line Treatments			
Divalproex	**Level 2**	Level 1	Level 2
SSRIs/bupropion (adjunctive)	**Level 1**	ND	Level 4
Electroconvulsive therapy	**Level 4**	Level 4	Level 4
Cariprazine	**Level 2**	ND	ND
Olanzapine/fluoxetine combination (OFC)	**Level 2**	ND	ND

CANMAT=Canadian Network for Mood and Anxiety Treatments. ISBD=International Society for Bipolar Disorders. ND=no data. SSRI=serotonin reuptake inhibitor.
*Trend for superiority on the primary efficacy measure, hence the lower rating. †Effective in those with an index episode of depression.
Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170.

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2018 CANMAT/ISBD Guidelines: Treatments NOT Recommended for Bipolar I Depression

	Level of Evidence
Aripiprazole monotherapy	Level 1 negative
Ziprasidone monotherapy or adjunctive therapy	Level 1 negative
Lamotrigine + folic acid	Level 2 negative
Adjunctive mifepristone	Level 2 negative
Antidepressant monotherapy	Level 2 negative

Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170.

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What Is One Reason Antidepressant Monotherapy Is Not Recommended for Bipolar I Depression?

A. Antidepressant monotherapy can trigger manic episodes and rapid cycling
B. Antidepressant monotherapy can trigger a depressive episode
C. Antidepressant monotherapy can worsen a depressive episode
D. Antidepressant monotherapy can worsen anxiety

N

Treatments Under Investigation for Bipolar I Depression

- Lumateperone[1]
- Pramipexole[2]
- Modafinil/armodafinil[2]
- Ketamine[2]
- Thyroxine/levothyroxine[2]

1. Intra-Cellular Therapies website [press release]. https://ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-positive-topline-results. Accessed March 8, 2021. 2. Jelen LA, Young AH. *Curr Behav Neurosci Rep*. 2020;7:1-14.

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Patient Case 1 (cont.): **TREATING SAM**

Larry Culpepper, MD, MPH
Joseph F. Goldberg, MD, MS
Andrew A. Nierenberg, MD

C

Deciding on Treatment for Sam

Sam's current psychiatrist

- Disagreed with the consultant's opinion and felt that Sam has treatment-resistant major depression plus "anger management issues" rather than bipolar depression
- Proposed a trial of olanzapine/fluoxetine combination (OFC) saying that it "would cover both diagnoses"

Consulting psychiatrist

- Agreed that OFC would be a reasonable option for treatment-resistant depression
  - However, felt that its metabolic liability outweighed its possible benefit
- Suggested first considering a treatment for bipolar depression with lower risk for metabolic disturbances

C

All of the following evidence-based treatments for bipolar depression are associated with relatively little weight gain during long-term clinical trials EXCEPT:

A. Quetiapine (QTP)
B. Lamotrigine*
C. Lurasidone
D. Cariprazine

*Not FDA-approved.

C G

Sam: Response to Lurasidone

- Sam began treatment with lurasidone 40 mg/day
  - Initially showed improvement in mood
  - Within a few months, began binge drinking again, citing work stresses, and became increasingly depressed
- He reports that he cannot concentrate and thinks that he really has ADD and would like to try taking a stimulant
  - You are skeptical about Sam's self-diagnosed ADD and do not think he needs to take a stimulant
- In reviewing his treatment, he indicates that he has been adherent with the medication, has begun a regular psychotherapy, and has begun attending AA meetings
- You are concerned about both his increased alcohol use as well as the risk for worsening depression
- Previously, Sam's dose of lurasidone was increased to 60 mg/day, but he encountered sedation and akathisia without greater mood benefit

C

AA=alcoholics anonymous. ADD=attention deficit disorder.

Which of the following would be an evidence-based next step in his treatment?

A. Discontinue the lurasidone and try an SSRI that he has not taken previously
B. Switch Sam's lurasidone to topiramate
C. Insist that he retry a higher dose of lurasidone
D. Augment his lurasidone with divalproex

C G

Summary: Improving the Diagnosis and Treatment of Bipolar I Depression

Depression is a **greater burden and source of morbidity and mortality** for patients with bipolar I disorder than manic episodes[1-5]

Early recognition and proper intervention are critical to forestall progression and minimize impact on life functioning; however[3,5]

- Delays in diagnosis and misdiagnosis are common[5,6]
- Many patients are not receiving appropriate interventions[7,8]

1. Viktorin A, et al. *Am J Psychiatry*. 2014;171(10):1067-1073. 2. Kupka RW, et al. *Bipolar Disord*. 2007;9(5):531-535. 3. McIntyre RS, Calabrese JR. *Curr Med Res Opin*. 2019;35(11):1993-2005. 4. Miller S, et al. *J Affect Disord*. 2014;169(suppl 1):S3-S11. 5. Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170. 6. Dagani J, et al. *Can J Psychiatry*. 2017;62(4):247-258. 7. Greene M, et al. *Neuropsychiatr Dis Treat*. 2018;14:1545-1559. 8. Baldessarini RJ, et al. *Int J Bipolar Disord*. 2020;8(1):1.

Summary: Improving the Diagnosis and Treatment of Bipolar I Depression (cont.)

What can we do to improve diagnosis?

Screen all patients with depression for bipolar disorder[1]

Understanding their limitations, **utilize screening tools to detect patients** who require further evaluation for bipolar disorder[2-5]

What can we do to improve treatment?

4 treatments are FDA-approved for bipolar I depression (olanzapine/fluoxetine combination [OFC], quetiapine [QTP], lurasidone, and cariprazine)[6]

- Additional treatments are under investigation[7,8]

The 2018 CANMAT/ISBD guidelines provide evidence-based recommendations for the acute and maintenance treatment of bipolar I depression[2]

- Antidepressant monotherapy is not recommended due to lack of demonstrated efficacy for bipolar I depression and safety concerns[2]

1. APA. Practice Guideline for the Treatment of Patients with Major Depressive Disorder; 2010. 2. Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170. 3. Bobo WV. *Mayo Clin Proc*. 2017;92(10):1532-1551. 4. Miller CJ, et al. *J Affect Disord*. 2011;128(3):199-210. 5. McIntyre RS, et al. *Curr Med Res Opin*. 2021;37(1):135-144. 6. Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 24, 2021. 7. Intra-Cellular Therapies website [press release]. https://ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-positive-topline-results. Accessed March 8, 2021. 8. Jelen LA, Young AH. *Curr Behav Neurosci Rep*. 2020;7:1-14.