# BRINGING BIPOLAR TOLIGHT

CONNECTING ON DIAGNOSIS AND TREATMENT CHALLENGES



### FACULTY PRESENTERS



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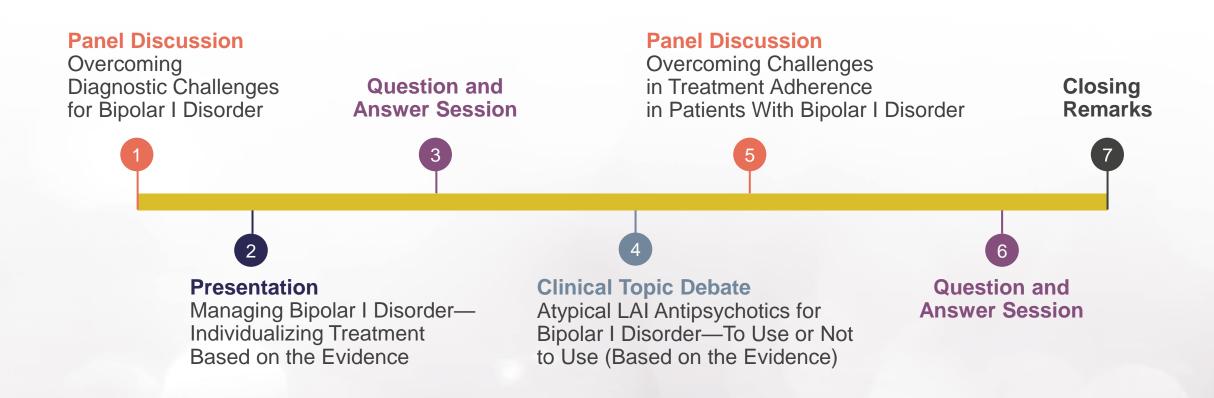
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## ACTIVITY OVERVIEW



### TO SUBMIT QUESTIONS TO THE FACULTY

# Submit your questions in the chat control panel on the left-hand side throughout the program

OR

In your comment box through Facebook Live

# TO RESPOND TO POLLING QUESTIONS



Via your phone
Text ReachMD to 22333

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Respond to activity!

### OVERCOMING DIAGNOSTIC CHALLENGES FOR BIPOLAR I DISORDER

Moderated by

Roger S. McIntyre, MD, FRCPC

#### **Panelists**

Amy Becher-Smith, DNP, MSW, PMHNP, FNP Joseph F. Goldberg, MD, MS

# POLLING QUESTION

How confident do you feel utilizing the DSM-5 criteria to diagnose patients with bipolar I disorder?

A. Very confident

- B. Confident
- C. Somewhat confident
- D. Not confident at all

# **DSM-5 DIAGNOSTIC CRITERIA FOR BIPOLAR I DISORDER**



The occurrence of at least 1 manic episode is essential for a diagnosis of bipolar I disorder



Manic episodes may be preceded by or followed by hypomanic or major depressive episodes



A manic episode is defined as at least 1 continuous week of daily, abnormal, and persistent elevated, expansive, or irritable mood and increased goal-directed activity or energy

- Includes at least **3 of 7 symptoms** (4 if the mood is only irritable)
  - · Inflated self-esteem or grandiosity
  - Less need for sleep
  - Increased talkativeness
  - Racing thoughts
  - Easy distractibility
  - Increase in goal-directed activity
  - Excessive engagement in reckless activities

- Episode must be severe, causing impaired social or occupational functioning
- May include elements of psychosis and can require hospitalization
- Symptoms cannot be explained by substance abuse or any other medical condition

# POLLING QUESTION

What do you think is the average time from disease onset to diagnosis for a patient with bipolar I disorder?

A. 1-2 years
B. 2-5 years
C. 5-10 years
D. 10-15 years
E. <u>15-20 years</u>

# THE DIAGNOSIS OF BIPOLAR I DISORDER REMAINS A CHALLENGE

### Delays in diagnosis are common

Mean delay between the onset of illness and diagnosis is **5 to 10 years** 

### Misdiagnoses are common



reported that they were initially misdiagnosed by psychiatrists\*



of patients were misdiagnosed with MDD\* MEAN OF **3.5** other diagnoses received\*

Delays in accurate diagnosis lead to delays in appropriate treatment, inappropriate treatment, and worse patient outcomes.

\*In a survey of patients with bipolar disorder involved with NDMDA support groups. NDMDA=National Depressive and Manic-Depressive Association. McIntyre RS, Calabrese JR. *Curr Med Res Opin.* 2019;35(11):1993-2005.

# WHAT IS CONTRIBUTING TO THIS DIAGNOSTIC CHALLENGE?

Manic episodes



Depressive episodes

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Differential diagnosis

Comorbidities

Mixed features



Misdiagnosis

Delays in diagnosis

# DISCUSSION



How can we overcome these challenges and improve the diagnosis of bipolar I disorder?

# **CLINICAL CLUES FOR BIPOLAR DEPRESSION**

Early onset of depression	Multiple prior	Positive family history	Hypersomnia/increased
(<25 years)	episodes (≥5)	of bipolar disorder	daytime napping
Hyperphagia/	Atypical	Psychomotor	Psychotic features/
increased weight	depression signs	retardation	pathological guilt
Mood lability/ irritability/psychomotor agitation/racing thoughts	Postpartum affective symptoms	Substance abuse	Anxiety disorders

# **POLLING QUESTION**

### Which screening tool do you most commonly use in practice?

- A. Mood Disorders Questionnaire (MDQ)
- **B.** Rapid Mood Screener
- C. Bipolar Spectrum Diagnostic Scale (BSDS)
- **D.** Bipolar Disorder Screening Scale
- E. Other
- F. I do not use screening tools

# DISCUSSION



How have you adapted to some of the new diagnostic challenges arising due to COVID-19?

### MANAGING BIPOLAR I DISORDER— INDIVIDUALIZING TREATMENT BASED ON THE EVIDENCE

Joseph F. Goldberg, MD, MS

## MATCHING: BROKERING THE BEST FIT<sup>1,2</sup>

#### Clinical Domains

Mania Depression Mixed features **Psychosis** Rapid cycling Attentional problems Anxietv Alcohol/substance use disorders Impulsive aggression Affective instability Overweight/metabolic dysregulation Insomnia Suicidality Neuropathic pain

#### Moderators and Mediators

Age Sex Race Age at onset Familiality Pharmacogenetics Baseline severity Polarity proneness Episode number Chronicity Past treatment response Psychosocial context Bipolar I vs II

#### **Treatments**

Lithium Divalproex Carbamazepine Lamotrigine Topiramate Gabapentin Antidepressants Lurasidone, quetiapine, OFC Other AAPs Stimulants Hormones (eg, T4) Ca++ channel blockers Psychoeducation

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Therapy (cognitive behavioral, familyfocused, interpersonal and social rhythm) Peer support

AAPs=atypical antipsychotics; Ca++-calcium; OFC=olanzapine and fluoxetine hydrochloride; T4=thyroid hormone. 1. Goldberg JF. *Focus (Am Psychiatr Publ)*. 2019;17(3):206-217. 2. Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170.

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# **CLINICAL PROFILING: WHEN TO USE LITHIUM**



First (few) episode(s)<sup>1</sup>

+ family history of lithium responsivity<sup>2</sup>

Mania-prone > depression prone<sup>3</sup>

Pure euphoric > mixed features<sup>4</sup>

Absence of rapid cycling<sup>5</sup>

Absence of comorbid substance use disorders<sup>6</sup>

History of suicide attempt (though divalproex may be noninferior)<sup>7</sup>

Extra: presence of gout; absence of psoriasis; desired WBC bump during clozapine co-therapy.8

WBC=white blood cell.

Gelenberg AJ, et al. N Engl J Med. 1989;321(22):1489-1493. 2. Grof P, et al. J Clin Psychiatry. 2002;63(10):942-947. 3. Geddes JR, et al. Am J Psychiatry. 2004;161(2):217-222. 4. Swann AC, et al. Arch Gen Psychiatry. 1997;54(1):37-42. 5. Dunner DL, Fieve RR. Arch Gen Psychiatry. 1974;30(2):229-233. 6. Goldberg JF, et al. J Clin Psychiatry. 1999;60(11):733-740. 7. Oquendo MA, et al. Am J Psychiatry. 2011;168(10):1050-1056.
 Goldberg JF, Ernst CL. Managing the Side Effects of Psychotropic Medications. APA Publishing; 2019.

# CLINICAL PROFILING: WHEN TO USE DIVALPROEX OR CARBAMAZEPINE



Multi-episode presentations <sup>1</sup>
Mania-prone > depression prone <sup>2</sup>
Mixed or pure manias <sup>3</sup>
Impulsivity/aggression <sup>4</sup>
Presence or absence of rapid cycling <sup>5</sup>
Presence or absence of comorbid alcohol/substance use disorders <sup>6</sup>
Potential for oral loading/rapid response <sup>7</sup>
Avoid in sexually active women of reproductive potential

#### Extra: migraine

1. Swann AC, et al. Am J Psychiatry. 1999;156(8):1264-1266. 2. Popovic D, et al. Eur Neuropsychopharmacol. 2012;22(5):339-346. 3. Swann AC, et al. Arch Gen Psychiatry. 1997;54(1):37-42. 4. Kavoussi RJ, Coccaro EF. J Clin Psychiatry. 1998;59(12):676-680. 5. Calabrese JR, et al. Am J Psychiatry. 2005;162(11):2152-2161. 6. Goldberg JF, et al. J Clin Psychiatry. 1999;60(11):733-740. 7. Hirschfeld RM, et al. J Clin Psychiatry. 1999;60(12):815-818.

# CLINICAL PROFILING: WHEN TO USE LAMOTRIGINE



Prevention of depression>mania in bipolar I disorder

Adjunctive therapy (with lithium<sup>1</sup> or quetiapine<sup>2</sup>) in bipolar depression

No known value in manic/mixed features episodes

1. van der Loos ML, et al. J Clin Psychiatry. 2009;70(2):223-231. 2. Geddes JR, et al. Lancet Psychiatry. 2016;3(1):31-39.

# CLINICAL PROFILING: WHEN TO USE ANTIDEPRESSANTS

Favors Antidepressant Use	Discourages Antidepressant Use		
Bipolar II disorder	Bipolar I disorder		
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		

## **CLINICAL PROFILING: WHEN TO USE SGAs**

	Mania/Mixed	Depression	Maintenance	LAI	Short-Acting IM	AEs
Aripiprazole <sup>1-3</sup>	(+)	2 (-) trials	Prevention of mania	(+)	(+)	EPS, dizziness, drowsiness, tremor
Asenapine <sup>1,4</sup>	(+)	No data	(+)			Oral hypoesthesia, EPS, fatigue
Brexpiprazole <sup>1,5</sup>	2 (-) trials	No data	No data			Metabolics, EPS, sedation, dizziness
Cariprazine <sup>1,6</sup>	(+)	(+)	No data			GI, EPS, headache
Clozapine <sup>1,7</sup>	(+)	No data	No data			Metabolics, agranulocytosis, sedation
Lurasidone <sup>1,8,9</sup>	No data	2 (+) trials	1 (-) trial			Nausea, somnolence, EPS
Olanzapine <sup>1,10,11</sup>	(+)	(+)	(+)	+ (SZ)	(+)	Somnolence, metabolics, dry mouth
Quetiapine <sup>1,12,13</sup>	(+)	(+)	(+) (adjunctive)			Somnolence, dry mouth, metabolics
Risperidone <sup>1,14,15</sup>	(+)	No data	Prevention of mania	+		EPS, somnolence
Ziprasidone <sup>1,16</sup>	(+)	2 (-) trials	(+)		(+) (Sz)	Headache, nausea, somnolence, EPS

EPS=extrapyramidal symptoms; IM=intramuscular; SGA=second general antipsychotics; SZ=schizophrenia.

1. Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170. 2. Aripiprazole LAI (Abilify Maintena) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 3. Aripiprazole Oral (Abilify) Prescribing Information. FDA website. Last updated February 2020. Accessed August 24, 2020. 4. Asenapine (Saphris) Prescribing Information. FDA website. Last updated February 2017. Accessed August 24, 2020. 5. Brexpiprazole (Rexulti) Prescribing Information. FDA website. Last updated March 2020. Accessed August 27, 2020. 6. Cariprazine (Vraylar) Prescribing Information. FDA website. Last updated May 2019. Accessed August 24, 2020. 7. Clozapine (Clozaril) Prescribing Information. FDA website. Last updated February 2020. Accessed August 27, 2020. 8. Lurasidone (Latuda) Prescribing Information. FDA website. Last updated October 2019. Accessed August 24, 2020. 11. Olanzapine LAI (Zyprexa Relprevy). Prescribing Information. FDA website. Last updated March 2020. Accessed August 24, 2020. Accessed August 24, 2020. 12. Quetiapine (Seroquel) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 12. Quetiapine (Seroquel) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 12. Quetiapine (Seroquel) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 14. Risperidone Oral (Risperdal) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 15. Risperidone LAI (Risperdal Consta) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 16. Ziprasidone (Geodon) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 16. Ziprasidone (Geodon) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 16. Ziprasidone (Geodon) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 16. Ziprasidone (Geodon) Prescribing Information. FDA w

# **POLLING QUESTION**

Which one of the following would be the most appropriate intervention for managing a first-episode euphoric nonpsychotic mania in a 21-year-old female college student who has been taking escitalopram 20 mg/day for the past 8 months?

- A. Lower the escitalopram from 20 to 10 mg/day and observe
- B. Quickly taper off escitalopram and begin lithium carbonate
- C. Quickly taper off escitalopram and begin divalproex
- **D.** Quickly taper off escitalopram and begin brexpiprazole
- E. Obtain pharmacogenetic testing to guide the best treatment

# QUESTIONS?

# BRINGING BIPOLAR TOLIGHT

CONNECTING ON DIAGNOSIS AND TREATMENT CHALLENGES

MIDWAY POINT

CLINICAL TOPIC DEBATE: ATYPICAL LAI ANTIPSYCHOTICS FOR BIPOLAR I DISORDER— TO USE OR NOT TO USE (BASED ON THE EVIDENCE)

**Moderated by** 

Amy Becher-Smith, DNP, MSW, PMHNP, FNP

#### **Debaters**

Joseph F. Goldberg, MD, MS Roger S. McIntyre, MD, FRCPC

## DEBATE TEAMS AND RULES



Team 1 (Dr. McIntyre)

Supports the use of atypical LAI antipsychotics for bipolar I disorder



Team 2 (Dr. Goldberg)

Opposes the use of atypical LAI antipsychotics for bipolar I disorder



### Time Keeper/Moderator (Dr. Becher-Smith)

- 1) Speakers cannot interrupt each other; they must wait their turn to speak
- Each speaker will be given 2.5 minutes to provide his opening argument and then 1.5 minutes to provide a rebuttal and closing statement
- 3) Speakers must use available evidence plus their clinical experience to support their side of the argument

Do you think that atypical LAI antipsychotics can be an appropriate treatment option for patients with bipolar I disorder?

Please select the response that best matches your viewpoint

- A. Yes, for most patients this is a good option
- **B.** Yes, for some of my patients
- C. Yes, but only for a minority of my patients
- **D**. No, I don't think LAIs are an appropriate option for my patients

# DISCUSSION



What is your real opinion about atypical LAI antipsychotics for bipolar I disorder?

Do you think that LAIs can be an appropriate treatment option for patients with bipolar I disorder?

### OVERCOMING THE CHALLENGES OF TREATMENT ADHERENCE

**Moderated by** 

Amy Becher-Smith, DNP, MSW, PMHNP, FNP

### **Panelists**

Joseph F. Goldberg, MD, MS Roger S. McIntyre, MD, FRCPC

## DEFINING TREATMENT NONADHERENCE IN BIPOLAR I DISORDER

Recommended definition of nonadherence in bipolar disorder<sup>1</sup>

Percentage of medication taken

**<80%** 



### 2 Categories of Nonadherence<sup>2</sup>

### **Intentional Nonadherence**

"An active process whereby the patients voluntarily do not take the prescribed medication"

### **Unintentional Nonadherence**

"Refers to unplanned and unconscious behaviors resulting in nonadherence"

# POLLING QUESTION

Approximately what percentage of patients with bipolar disorder are nonadherent to their treatment regimens?

- **A.** 1-20%
- **B.** 20-40%
- **C**. 40-60%
- **D**. 60-80%
- E. 80-100%

# **CONSEQUENCES OF TREATMENT NONADHERENCE**



### Mislabeling patients as nonresponsive to medications, resulting in<sup>1</sup>

- Unnecessary dose increases
- Medication switches
- Adjunctive medications

### Worse clinical outcomes<sup>1,2</sup>

- Disease recurrence
- Increased risk of hospitalization
- Suicide
- Lost productivity

Increased healthcare costs<sup>3</sup>

# DISCUSSION



# How do you monitor for signs of treatment nonadherence?

# **RISK FACTORS FOR POOR ADHERENCE TO TREATMENT**

Category	Risk Factor		
Sociodemographic	Male, younger age, low level of education, single		
Psychological	Poor insight, lack of awareness of disease, negative attitude to treatment, fear of side effects, negative attitude to medication, low overall life satisfaction, low cognitive functioning		
Comorbidity	Alcohol or cannabis use, obsessive compulsive disorder		
Social	No social activities, work impairment		
Chronology	Younger age of onset, current inpatient status, hospitalization or suicide attempt in past 12 months		
Disease characteristics	Mixed episodes, rapid cycling, delusions and hallucinations, greater severity of illness, bipolar I disorder diagnosis, higher number of episodes		
Treatment-related factors	Side effects of medications, inadequate efficacy of medication, use of antidepressants, low treatment doses		

# DISCUSSION



# What techniques do you use to improve treatment nonadherence?

## FACILITATORS OF TREATMENT ADHERENCE

Patient-Focused Modifications	Treatment/Provider Modifications			
Adequate health literacy <sup>1, 2, 3, 4</sup>	Collaborative patient-provider relationship <sup>11</sup>	Long-acting injectables <sup>13,14,15</sup>		
Belief in medication <sup>5</sup>	Shared-decision making <sup>6,12</sup>	Group delivery <sup>8</sup>		
Patient empowerment <sup>6</sup>	Face-to-face intervention delivery <sup>13</sup>	Habit-based and behavioral-focused interventions <sup>16</sup>		
Belief in one's own ability and control <sup>6</sup>	Pharmacist involvement <sup>13</sup>	Psychoeducational techniques <sup>5,8,17</sup>		
Acknowledging the medical expertise and the prescribers influence on one's health <sup>6</sup>	Medication adherence scales <sup>9</sup>	Cognitive behavioral therapy (CBT) <sup>5,8,17</sup>		
Regular routines <sup>7</sup>	Low cost medications <sup>7</sup>	Motivational interviewing <sup>18</sup>		
Early detection of warning signs of relapse <sup>8</sup>	Simplified drug regimens <sup>7</sup>	Family focused therapy <sup>8</sup>		
Value-action consistency9	Brief interventions focused on adherence <sup>5</sup>	Family intervention and involvement <sup>17,18,19</sup>		
Mobile apps? <sup>10</sup>	Prevent progression into full episodes <sup>8</sup>	Decision aids <sup>20,21</sup>		

Brown MT, Bussell JK. Mayo Clin Proc. 2011;86(4):304-314. 2. De Geest S, Sabaté E. Eur J Cardiovasc Nurs. 2003;2(4):323. 3. McHorney CA, et al. Patient Prefer Adherence. 2012;6:789-804. 4. Tibaldi G, et al. Chronic Illn. 2009;5(2):129-133. 5. MacDonald L, et al. J Affect Disord. 2016;194:202-221. 6. Náfrádi L, et al. PLoS One. 2017;12(10):e0186458. 7. Fung VC, et al. J Affect Disord. 2019;257:17-22. 8. Bond K, Anderson IM. Bipolar Disord. 2015;17(4):349-362. 9. Gaudiano BA, et al. J Nerv Ment Dis. 2017;205(3):178-181. 10. Nicholas J, et al. J Med Internet Res. 2015;17(8):e198. 11. Goodyear-Smith F, Buetow S. Health Care Anal. 2001;9(4):449-462. 12. Samalin L, et al. BMC Psychiatry. 2018;18(1):103. 13. Greene M, et al. Neuropsychiatr Dis Treat. 2018;14:1545-1559. 14. Lang K, et al. J Med Econ. 2011;14(2):217-226. 15. Greene M, et al. J Med Econ. 2018;21(2):127-134. 16. Conn VS, Ruppar TM. Prev Med. 2017;99:269-276. 17. Chatterton ML, et al. Br J Psychiatry. 2017;210(5):333-341. 18. Pakpour AH, et al. Psychol Med. 2017;47(14):2528-2539. 19. Hartung D, et al. Psychosomatics. 2017;58(2):101-112. 20. Aoki Y, et al. Psychiatry Res. 2019;281:112531. 21. Chakrabarti S. World J Psychiatry. 2018;8(5):114-124.

## **DECISION AIDS**

Can be used during the shared decision making process to assist in the discussion of treatment options

Convey the **potential risks and benefits** of treatment options Therapy Decision Tool for Patients With Bipolar I Disorder. Mood Stabilizers

Year of FDA Approval	1			
in Bipolar Disorder				
Mania	1970	1995	2004	
Depression	(222)	3111 	222	7
Maintenance	1978			2003
Dosing	Acuta: 600 mg PO TID titrated to serum level; maintenanca: 300 mg PO TID or GID titrated to serum level	Initial: (delayed release): 750 mg/day titrated rapidly to therapeutic blood level; (extended release): oral loading at 25 mg/kg in divided doses as tolerated	Initial: (axtandad releasa): 400 mg/ day (divided), increase by 200 mg/ day (max 1600 mg/day)	Initial (monotherapy): 25 mg/day for 2 weeks then 50 mg/day for 2 weeks then 100 mg/day for 1 week then target of 200 mg/day dose at half this rate with divalpror cotherapy and twice this rate with carbamazepine cotherapy
Half-Life	18-36 hours	9-16 hours	35 hours	29 hours
Therapeutic Drug Monitoring	In mania, serum levels of 1.0-1.5 mEq/L per manufacturer In maintenance, serum levels of 0.6-1.2 mEq/L per manufacturer	In mania, 50-125 µg/mi	Not established in bipolar disorder	Not established in bipolar disorder
Efficacy in Mania	×	~	1	Unproven
Efficacy in Depression	Less robust than in mania	Less robust than in mania	Poorty studied	Moderate, off-label
Efficacy in Mixed Features	Less robust than in pure mania	1	✓	Unknown
Maintenance Efficacy	*	Unproven (but often used off-label)	Modest data suggesting inferiority to lithium	✓ (more robust prevention of depression than mania)
Impact of Multi-Episode	Better when begun in first few episodes	~	Unknown	Unknown
Impact of Rapid Cycling	Modest efficacy	Possibly more robust than lithium, likely better in combination with lithium	Modest efficacy	Modest relapse prevention data, mainly in bipolar II disorder
Impact of Psychosis	Poorer response when psychosis is present	<ul> <li>✓ (ER indication includes "with or without psychotic features")</li> </ul>	Modest data suggesting possible advantage over lithium	Unknown
Most Common Adverse Effects	Tremor, urinary frequency, thirst, Gl upset	Somnolence, Gl upset, tremor, weight gain, alopecia	Dizziness, drowsiness, blurry vision, nausea	Dizziness, drowsiness, headache, Gl upset, rash

Therapy Decision Tool Courtesy of Joseph Goldberg, MD, MS

# QUESTIONS?

## SUMMARY



**Delays in diagnosis and misdiagnosis are common** and have significant consequences for patients, emphasizing the need for improvement<sup>1</sup>

- All patients presenting with depression should be screened for bipolar disorder
- There are clinical clues that can help you diagnose bipolar I disorder earlier



When selecting treatment, the data can help you determine the types of patients who may benefit most from each treatment



Atypical LAI antipsychotics are an approved but underutilized maintenance treatment option for patients with bipolar I disorder that can provide benefit to appropriate patients<sup>2-6</sup>



As many patients with bipolar I disorder are nonadherent to their treatment regimens, identifying the lack of adherence and promptly intervening with modifications is key to improving patient outcomes<sup>7-11</sup>

1. McIntyre RS, Calabrese JR. *Curr Med Res Opin.* 2019;35(11):1993-2005. 2. National Alliance of State Pharmacy Associations and College of Psychiatric & Neurologic Pharmacists website. https://naspa.us/wpcontent/uploads/2017/04/Medication-Administration-Meeting-Report-FINAL.pdf. Updated March 2017. Accessed September 23, 2020. 3. Sajatovic M, et al. *Neuropsychiatr Dis Treat.* 2018;14:1463-1474. 4. Grover S, et al. *Asian J Psychiatr.* 2019;44:200-208. 5. Aripiprazole LAI (Abilify Maintena) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 6. Risperidone LAI (Risperdal Consta) Prescribing Information. FDA website. Last updated January 2020. Accessed August 24, 2020. 7. Lingam R, Scott J. *Acta Psychiatr Scand.* 2002;105(3):164-172. 8. Levin JB, et al. *CNS Drugs.* 2016;30(9):819-835. 9. Prajapati AR, et al. *BMJ Open.* 2019;9(2):e026980. 10. Thompson K, et al. *Schizophr Res.* 2000;42(3):241-247. 11. Yatham LN, et al. *Bipolar Disord.* 2018;20(2):97-170.