REAL PSYCHIATRY

An Educational Experience Designed for and by
APPs on the Frontline of Modern Practice

TURNING THE TIDE IN BIPOLAR DEPRESSION

— JANUARY 13, 2024 —

Program Overview

CHALLENGES

- Depressive episodes make **bipolar disorder (BD) difficult to differentiate** from other psychiatric conditions.
- Historically, few agents have been approved, and **less effective** options such as antidepressant therapy have been commonly used.

OPPORTUNITIES

- **Improved screening approaches** hold promise for improved detection and management.
- **Newer medications** with unique mechanisms of action and favorable side-effect profiles provide improved therapeutic options for patients with bipolar depression.

To address these challenges, this module will examine novel screening and treatment strategies through expert-led clinical case exploration and evidenced-based literature.

1. Goes FS. Diagnosis and management of bipolar disorders. *BMJ*. 2023;381:e073591.

Presenting Faculty

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MODULE 1

DIAGNOSING BIPOLAR DISORDER

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CASE: INITIAL ENCOUNTER

Jada, a 24-year-old female with a history of depression, presents with a persistently depressed mood despite prior treatment.

PAST MEDICAL HISTORY

- Migraines
- Difficulty sleeping (typically 6 hours per night, some days only 3 to 4. No fatigue the next day)

FAMILIY HISTORY

- Both parents – heavy alcohol use
- Maternal grandfather – difficulty maintaining jobs
- Maternal grandmother – two suicide attempts
- Two brothers – ADHD

SOCIAL HISTORY

- “Partied" in high school and college, now lacks the energy
- Consumes four Red Bull drinks per day, regular caffeine prior to sleep

CURRENT MEDICATIONS

- ❑ **Escitalopram 20 mg**
- ❑ **Venlafaxine 75 mg**
- ❑ **Buspirone 30 mg**
- ❑ **Clonazepam 1 mg**
- ❑ **Quetiapine 50 mg**

PAST MEDICATIONS

- ❑ **Fluoxetine 40 mg** (jittery)
- ❑ **Trazodone 50 mg** (no improvement in sleep)

*Fictionalized representation based on a real medical case.

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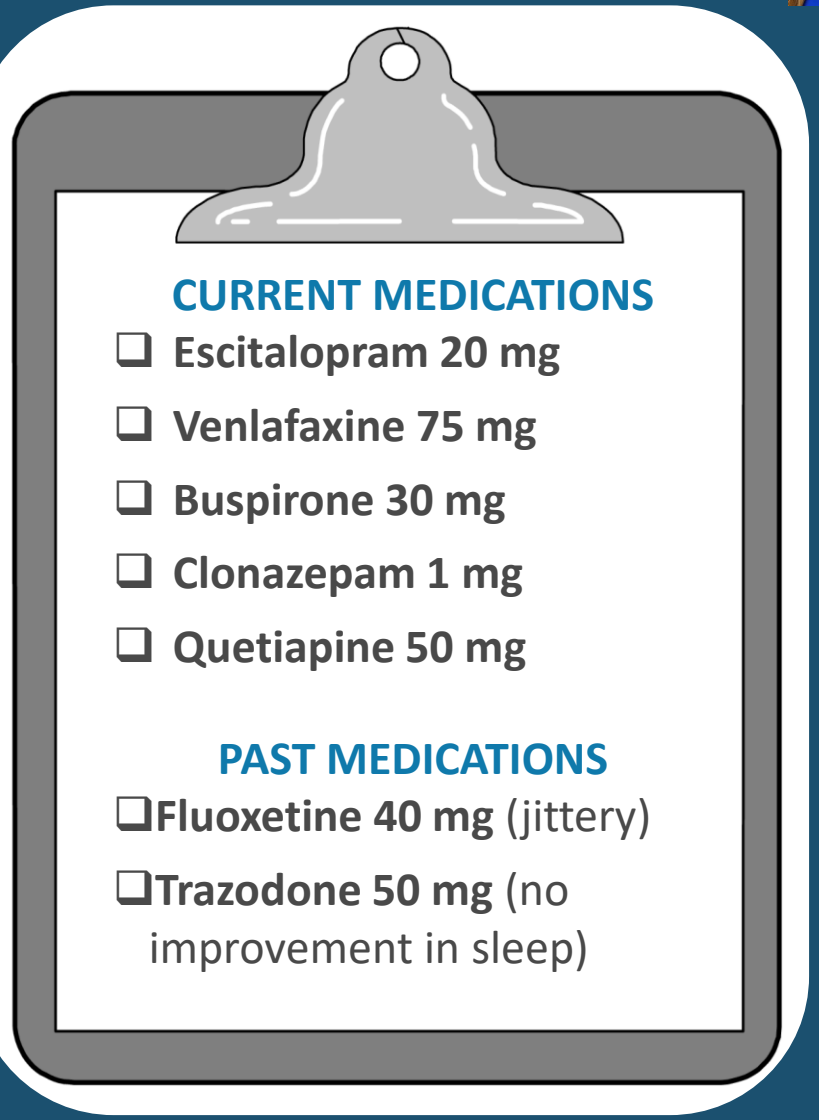
EFFICIENT

CASE: INITIAL ENCOUNTER

Jada, a 24-year-old female with a history of depression, presents with a persistently depressed mood despite prior treatment.

How do we tell if this is unipolar or bipolar depression?



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PAST MEDICATIONS

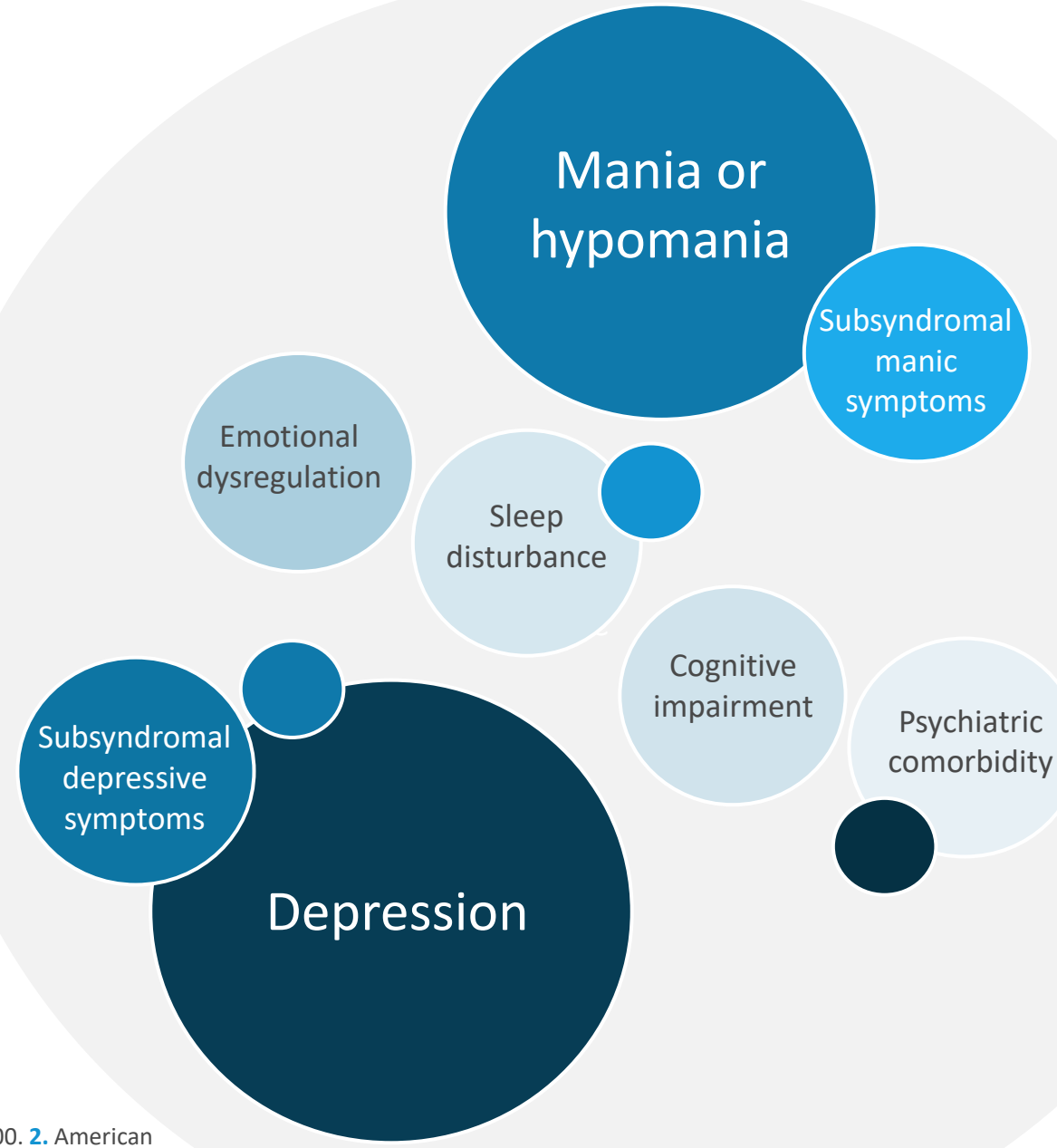
- ❑ **Fluoxetine 40 mg** (jittery)
- ❑ **Trazodone 50 mg** (no improvement in sleep)

*Fictionalized representation based on a real medical case.

DISCLAIMER: This presentation is based on a real case. To protect the identity of individuals, all names and other identifiable information has been changed.

BIPOLAR DISORDER: A COMPLEX PICTURE

- 50% to 80% of patients with bipolar disorder **initially present with depression.**[1]
- Depressive symptoms are the same for major depressive disorder (**MDD**) and bipolar disorder.[2]
- Patients often **lack insight into their (hypo)mania** symptoms.[3,4]
- **Psychiatric comorbidities are common in bipolar disorder,** especially anxiety, substance use disorder, ADHD, personality and eating disorders.[2]



ADHD: attention-deficit/hyperactivity disorder

1. O'Donovan C. Depression preceding diagnosis of bipolar disorder. *Front Psychiatry*. 2020;11:500. **2.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision. 2022. **3.** Goes FS. Diagnosis and management of bipolar disorders. *BMJ*. 2023;381:e073591. **4.** Dell'Osso L et al. Insight into illness in patients with mania, mixed mania, bipolar depression and major depression with psychotic features. *Bipolar Disord.* 2002;4(5):315-322.

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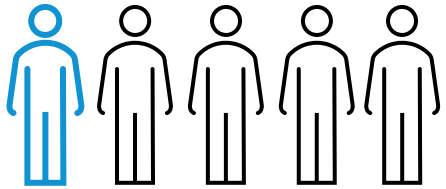
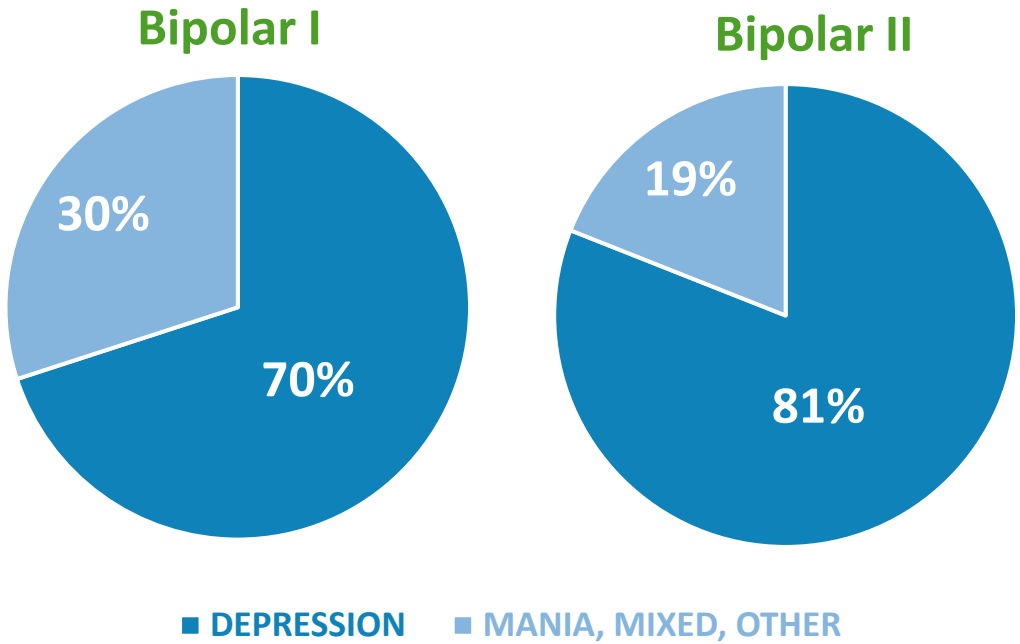
DEPRESSION IS PREDOMINANT IN BD

When you hear DEPRESSION, consider screening for BD.[1]



Nearly one in five patients diagnosed with depression may have bipolar disorder.[2]

PROPORTION OF ILL TIME SPENT DEPRESSED[3]



Adapted from Forte A et al. J Affective Disord. 2015;178(1):71-78.

DSM-5-TR: BD should be ruled out before making an MDD diagnosis.[1]

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision. 2022.
2. Daveney J et al. Unrecognized bipolar disorder in patients with depression managed in primary care: a systematic review and meta-analysis. *Gen Hosp Psychiatry*. 2019;58:71-76. **3.** Forte A et al. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. *J Affective Disord*. 2015;178(1):71-78.

BD: bipolar disorder; ***DSM-5-TR***: *Diagnostic and Statistical Manual of Mental Disorders* 5th ed. Text Revision; **MDD**: major depressive disorder

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PREDICTIVE FACTORS FOR BIPOLAR DEPRESSION

CLINICAL/FAMILY HISTORY	• Family history of bipolar symptoms[1] • Suicide attempts and number of hospitalizations[2] • Younger age of onset[1,2]
TREATMENT HISTORY[3]	• Treatment-resistant depression • Antidepressant-induced mood destabilization or hypomania
SYMPTOMS[4]	• Atypical depressive features • Mixed features • Psychotic features • Comorbid anxiety disorder and/or substance use disorder

1. Stahl SM et al. Guidelines for the recognition and management of mixed depression. *CNS Spectr*. 2017;22(2):203-219. **2.** Xu Z et al. A predictive model of risk factors for conversion from major depressive disorder to bipolar disorder based on clinical characteristics and circadian rhythm gene polymorphisms. *Front Psychiatry.* 2022;13:843400.
3. Perugi G et al. Patterns of response to antidepressants in major depressive disorder: drug resistance or worsening of depression are associated with a bipolar diathesis. *Eur Neuropsychopharmacol.* 2019;29(7):825-834. **4.** Sleem A et al. Advances in the psychopharmacotherapy of bipolar disorder type I. *Expert Opin Pharmacother*. 2021;22(10):1267-1290.

DIFFERENCES BETWEEN BIPOLAR I AND II

	DEPRESSIVE EPISODES*	MANIC EPISODES	HYPOMANIC EPISODES
BIPOLAR I	May have	*MUST have*	May have
BIPOLAR II	*MUST have*	Don't have	*MUST have*

	MANIC EPISODE	HYPOMANIC EPISODE
Length	≥1 week (unless hospitalized)	≥4 days
Marked impairment in social/occupational functioning	Yes	No, **but** change in functioning is observable by others
Psychotic symptoms	Can be present	NOT present
Hospitalization	May be needed	No

Same criteria for depressive episodes as in MDD.

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision. 2022.

Screening and Evaluation Tools

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CASE: SCREENING TOOLS*

CASE NOTES/RECAP

- Jada is a 24-year-old female with depression
- Inadequate therapeutic response with antidepressants
- Family with extensive psychiatric history
- Concerning family history of bipolar disorder

What are your next steps in the assessment of this patient?

*Fictionalized representation based on a real medical case.

AUDIENCE POLL

Which of the following screening assessments would you prioritize to differentiate bipolar disorder from depression?

a) Rapid Mood Screener (RMS)
b) Patient Health Questionairre-9 (PHQ-9)
c) Mood Disorder Questionnaire (MDQ)
d) Bipolarity Index (BI)
e) A combination of the above
f) I do not know/I am unsure.

WHICH TEST IS BEST: RMS OR MDQ?

	RMS[1]	MDQ[2]
VALIDATED IN	Bipolar I	Bipolar I and II**
ITEMS	6	15
TIME TO COMPLETE	<2 min	5 min
POSITIVE PREDICTIVE VALUE	0.80*	0.78
NEGATIVE PREDICTIVE VALUE	0.88*	0.86
SENSITIVITY	0.88*	0.86
SPECIFICITY	0.80*	0.78

Both tests differentiate bipolar disorder from MDD, guiding the need for comprehensive assessment.

**When ≥4 items endorsed.*

***Potentially stronger psychometric validity for bipolar disorder I.*

1. McIntyre RS et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. *Curr Med Res Opin*. 2021;37:135-144. **2.** Hirschfeld RM et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry.* 2000;157(11):1873-1875.

MDD: major depressive disorder; **MDQ**: Mood Disorder Questionnaire; **RMS**: Rapid Mood Screener

ITEMS ASSESSED (ABBREVIATED)

Respond yes or no to having experienced the following:

RMS[1]
1. ≥6 periods of deep depression in 2 weeks
2. Depression before the age of 18
3. Irritability or hyperactivity from antidepressant
4. Period of ≥1 week spent more talkative or with thoughts racing
5. Period of ≥1 week spent unusually happy, outgoing, or energetic
6. Period of ≥1 week needing much less sleep
POSITIVITY: ≥4 *YES* RESPONSES

MDQ[2]	
1. A period of time where you were **not yourself and**:	
• Felt unusually good or hyper (with consequences)	• Had much more energy
• Were unusually irritable (shouting, starting fights)	• Were much more active
• Were much more self-confident	• Were much more social/outgoing
• Required much less sleep	• Were much more interested in sex
• Were much more talkative or had much faster speech	• Had unusual or risky behavior
• Had racing thoughts	• Were excessively spending
• Were easily distractable	
2. **Several of the above** during the same period	
3. **How much of a problem** did any of these cause?	
POSITIVITY: 1. ≥7 *YES* 2. *YES* 3. *MODERATE* TO *SEVERE*	

Adapted from Hirschfield et al. Am J Psychiatry. 2000;157(11):1873-1875.

MDQ: Mood Disorder Questionnaire; **RMS**: Rapid Mood Screener

1. McIntyre RS et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. *Curr Med Res Opin*. 2021;37:135-144. **2.** Hirschfeld RM et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry.* 2000;157(11):1873-1875.

CASE: SCREENING SCORES*

GAD-7 (11/21)	PHQ-9 (19/27)	PSS (35/40)

MDQ (12/13)
12 items were a *yes* in question 1.
Answered *Yes* in question 2 and *Moderate* in question 3

What is Jada's diagnosis?

Jada is a 24-year-old female with depression and an extensive psychiatric family history.

GAD-7: General Anxiety Disorder Screener 7; **MDQ**: Mood Disorder Questionnaire; **PHQ-9**: Patient Health Questionnaire-9; **PSS**; Perceived Stress Scale

*Fictionalized representation based on a real medical case.

RESOURCES/BILLING TOOLS

SCALES

Rapid Mood Screener (RMS)

- **Reference:** McIntyre RS et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. *Curr Med Res Opin*. 2021;37:135-144

Mood Disorder Questionnaire (MDQ)

- **Reference:** Hirschfeld RM et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry.* 2000;157(11):1873-1875.

Patient Health Questionnaire-9 (PHQ-9)

- Scale: https://www.apa.org/depression-guideline/patient-health-questionnaire.pdf
- Scoring: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1495268/

Generalized Anxiety Disorder (GAD-7)

- Anxiety is a prevalent comorbid diagnosis with BD.[1]
- May increase risk of suicidality, quality of life, and functioning[1]

BILLING & *ICD-10* CODES[2]

Generic Mental Health Screening:

CPT: 96127 (1-4 units)[2,3]

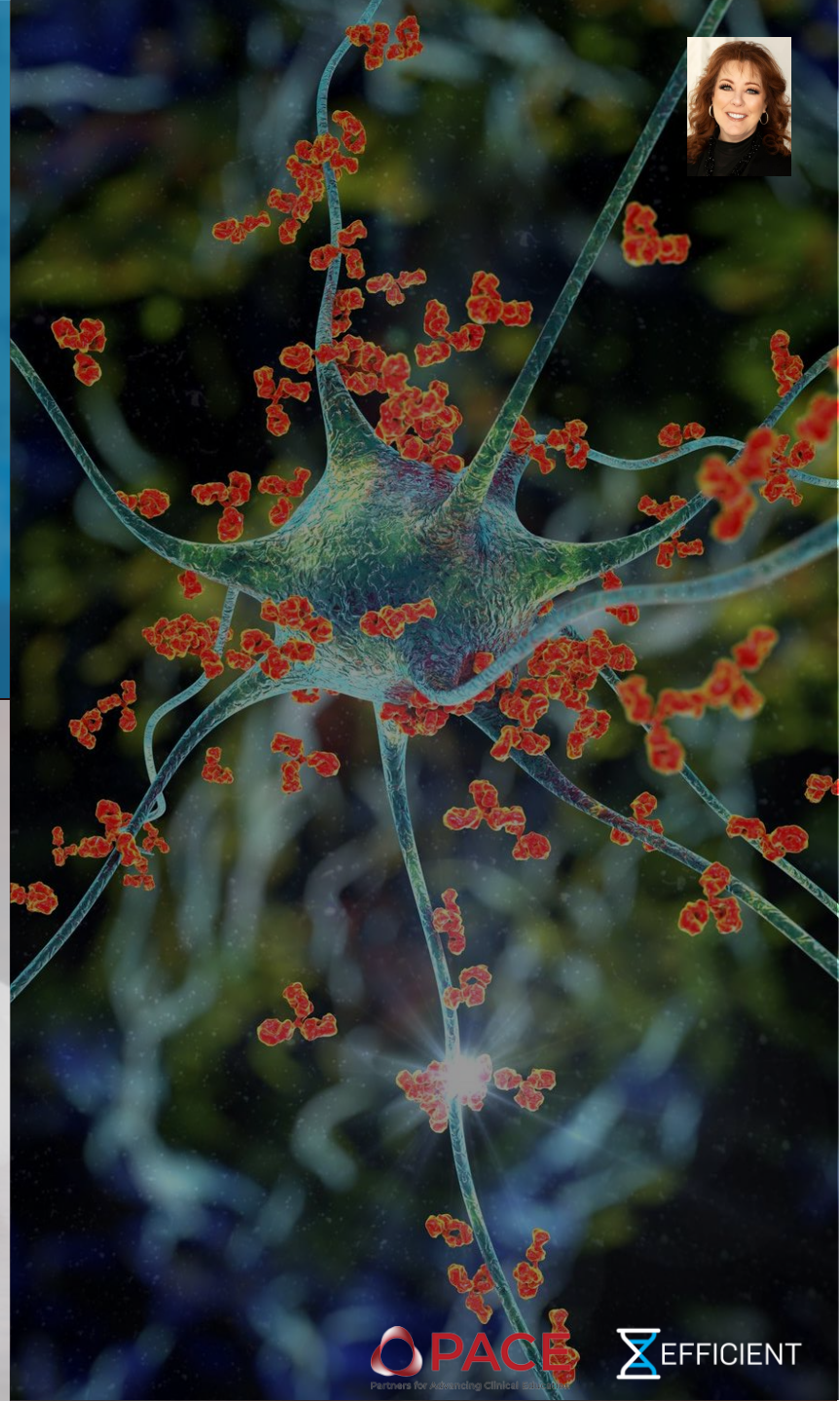
ICD-10: Z13.30,[4] Z13.39,[5] & Z13.89[6]

Adjunct codes (90833 vs 90836) for psychotherapy[7]

1. Ott CA. Treatment of anxiety disorders in patients with comorbid bipolar disorder. *Ment Health Clin*. 2018;8(6):256-263. **2.** Centers for Medicare & Medicaid Services. Billing and coding: psychological and neuropsychological testing. October 31, 2019. **3.** Hughes C. Getting paid for screening and assessment services. *Fam Pract Manag*. 2017;24(6):25-29. **4.** 2024 ICD-10-CM Diagnosis Code Z13.30. ICD10Data. Accessed 12.18.23. **5.** 2024 ICD-10-CM Diagnosis Code Z13.39. ICD10Data. Accessed 12.18.23. **6.** 2024 ICD-10-CM Diagnosis Code Z13.89. ICD10Data. Accessed 12.18.23. **7.** Centers for Medicare & Medicaid Services. Billing and Coding: Psychiatry and Psychology Services (A56937). Accessed 12.14.23. https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=56937

MODULE 2

TREATMENT OF BIPOLAR DEPRESSION



The Role of Antidepressants in Bipolar Disorder

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CASE CONTINUED*

EVALUATION OF CURRENT MEDS

Now that Jada has a diagnosis of BD, how would you approach her current med list?

CURRENT MEDICATIONS

- ❑ Escitalopram 20 mg
- ❑ Venlafaxine 75 mg
- ❑ Buspirone 30 mg
- ❑ Clonazepam 1 mg
- ❑ Quetiapine 50mg

*Fictionalized representation based on a real medical case.

AUDIENCE POLL

Would you use an antidepressant to treat depression in patients with bipolar disorder?

a) Yes, either monotherapy or adjunctive therapy is appropriate for most patients

b) Yes, but only adjunctive therapy is appropriate for most patients

c) Yes, but only as adjunctive in patients with a history of a positive response to antidepressants

d) No, never

e) I do not know/I am unsure.

AUDIENCE POLL

Would you use an antidepressant to treat depression in patients with bipolar disorder?

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c) Yes, but only as adjunctive in patients with a history of a positive response to antidepressants

d) No, never

e) I do not know/I am unsure.

WHY/HOW ANTIDEPRESSANTS ARE USED

PITFALLS

MIMICKING

- Refilling prior medications even if suboptimal
- Prescribing out of familiarity vs. benefit

POLYPHARMACY

- Only **adding** agents → increasing risk of side effects

AVOIDING PAs

- Picking what's easiest to prescribe

SOLUTIONS

- **Prescribe evidence-based medications**
- **Consolidate medications**
- **What would you want in their shoes?**

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ANTIDEPRESSANT USE IN BIPOLAR DEPRESSION

WHAT DO THE DATA SHOW?

- Generally, poor evidence of efficacy[1]
- Can increase risk of suicide in younger patients with any form of depression[2]
- Can induce (hypo)mania, mixed features, and rapid cycling[1]

WHAT DO THE GUIDELINES SAY?

- Avoid monotherapy in bipolar disorder[1]
- May be appropriate in those with a history of positive response[1]
- Discontinue if patient develops associated mania or hypomania[1]

Are the data strong enough to support patient selection?[1]

1. Goes FS. Diagnosis and management of bipolar disorders. *BMJ*. 2023;381:e073591. **2.** Giorgi-Guarnieri D. Clinician liability in prescribing antidepressants. *Focus*. 2019;17(4):372-379.

SHORT-TERM ANTIDEPRESSANTS
STEP-BD

STUDY DESIGN

- 366 patients randomized to receive mood stabilizer with either **antidepressant or placebo for 26 weeks**

RESULTS

- Adjunctive antidepressants were **not associated with increased efficacy or with increased risk** of treatment-emergent affective switch.

ANTIDEPRESSANTS ARE NO MORE EFFECTIVE THAN MOOD STABILIZER ALONE

	MOOD STABILIZER + ANTIDEPRESSANT	MOOD STABILIZER + PLACEBO
TRANSIENT REMISSION	17.9%	21.4%
DURABLE RECOVERY	23.5%	27.3%
TREATMENT EFFECTIVENESS RESPONSES	32.4%	38.0%
TREATMENT-EMERGENT AFFECTIVE SWITCH	10.1%	10.7%

Adapted from Sachs GS et al. N Engl J Med. 2007;356(17):1711-1722.

1. Sachs GS et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356(17):1711-1722.

STEP-BD: Systematic Treatment Enhancement Program for Bipolar Disorder

LONG-TERM ANTIDEPRESSANTS

CAPE-BD

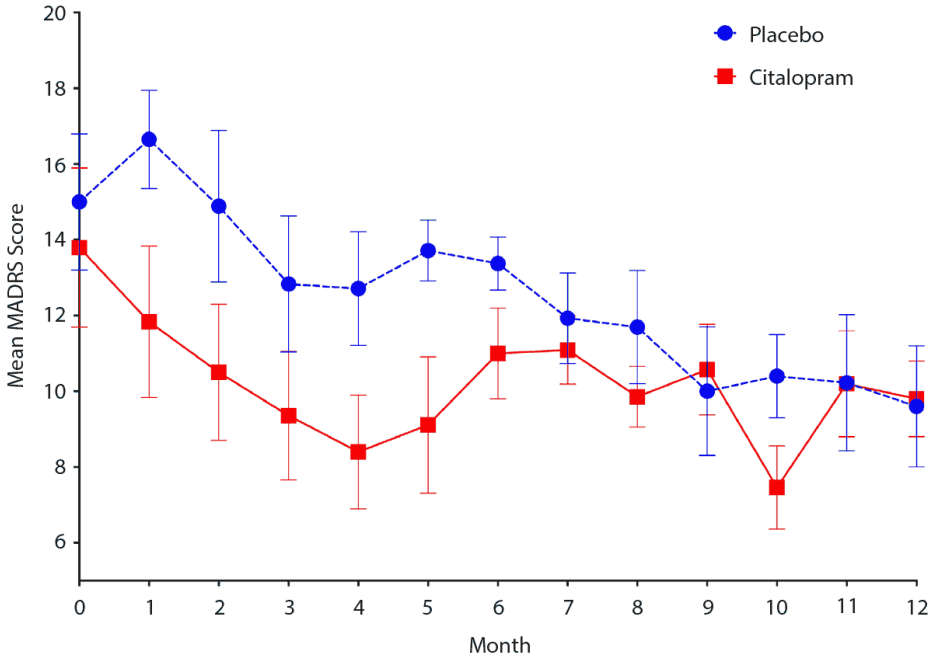
STUDY DESIGN

- 119 patients with bipolar disorder I or II and a major depressive episode
- Randomized to **citalopram or placebo added to mood stabilizers for up to 1 year**

RESULTS

- **Similar improvement with both citalopram and placebo** (acute or maintenance)
- High placebo response rate
- Comparable outcomes in bipolar disorder I and II

COMPARATIVE EFFECTS OF CITALOPRAM VS. PLACEBO ON MADRS SCORE



Modified from Ghaemi SN et al. J Clin Psychiatry. 2021;82(1):19m13136.

1. Ghaemi SN et al. Citalopram for Acute and Preventive Efficacy in Bipolar Depression (CAPE-BD): a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2021;82(1):19m13136.

CAPE-BD: Citalopram for Acute and Preventive Efficacy in Bipolar Depression; **MADRS**: Montgomery–Åsberg Depression Rating Scale

ANTIDEPRESSANTS

CLINICIAN LIABILITY: SIDE EFFECTS

- ***Adjunctive antidepressants*** are used ***off label*** as ***third-line treatment for BD depression.***[1]
- ***Weigh the risks*** for the patient and the clinician when prescribing[2]

- **Violence** (homicide/suicide)
- **Pregnancy considerations**
- **Movement-related disorders**[3]
- **Withdrawal**
- **Arrythmias** (e.g., QTc prolongation) [citalopram]

1. Department of Veterans Affairs and Department of Defense. VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder (Version 2.0). Accessed 12.18.23. https://www.healthquality.va.gov/guidelines/MH/bd/index.asp. **2.** Giorgi-Guarnieri D. Clinician liability in prescribing antidepressants. *Focus*. 2019;17(4):372-379. **3** Revet A et al. Antidepressants and movement disorders: a postmarketing study in the world pharmacovigilance database. *BMC Psychiatry*. 2020;20(1):308.

ANTIDEPRESSANTS

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1. Department of Veterans Affairs and Department of Defense. VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder (Version 2.0). Accessed 12.18.23. https://www.healthquality.va.gov/guidelines/MH/bd/index.asp. **2.** Giorgi-Guarnieri D. Clinician liability in prescribing antidepressants. *Focus*. 2019;17(4):372-379. **3** Revet A et al. Antidepressants and movement disorders: a postmarketing study in the world pharmacovigilance database. *BMC Psychiatry*. 2020;20(1):308.

AUDIENCE POLL

What is the maximum recommended daily dose of citalopram for patients for patients 18-65 years of age?

a) 10 mg/day
b) 20 mg/day
c) 30 mg/day
d) 40 mg/day
e) I do not know/ I am unsure.

AUDIENCE POLL

What is the maximum recommended daily dose of citalopram for patients for patients 18-65 years of age?

a) 10 mg/day
b) 20 mg/day
c) 30 mg/day
d) 40 mg/day
e) I do not know/ I am unsure.

AUDIENCE POLL

What is the maximum recommended daily dose of escitalopram for patients 18-65 years of age?

a) 10 mg/day
b) 20 mg/day
c) 30 mg/day
d) 40 mg/day
e) I do not know/ I am unsure.

AUDIENCE POLL

What is the maximum recommended daily dose of escitalopram for patients 18-65 years of age?

a) 10 mg/day
b) 20 mg/day
c) 30 mg/day
d) 40 mg/day
e) I do not know/ I am unsure.

ANTIDEPRESSANTS

CLINICIAN LIABILITY: DOSING

Dear Doctor Letter (DDL)

In 2011, a DDL recommended a reduction in maximum dosing with escitalopram/citalopram to avoid QTc prolongation

Changes prescription patterns:

- Significant reductions in providers exceeding dose from 2012-2017 compared with 2001-2019

Caveats

- Less impactful change in older patient populations
- For many, patterns have not changed

2011 DDL RECOMMENDATION

	Age ≤65 years	Age >65 years
Citalopram	Not to exceed >40 mg/day	Not to exceed >20 mg/day
Escitalopram	Not to exceed >20 mg/day	Not to exceed >10 mg day

REDUCTION IN OVER-DOSING AFTER DDL RELEASED

	Age ≤65 years	Age >65 years
Citalopram	**53% reduction** (RR=0.47 [0.28-0.80]; *P*<0.05)	**26% reduction** (RR=0.74 [0.57-0.97]; *P*<0.05)
Escitalopram	**38% reduction** (RR=0.62 [0.48-0.79]; *P*<0.05)	17% reduction (RR=0.83 [0.69-1.01]; *P*>0.05)

Between ~50% and 80% of clinicians still exceeding dosing limits 5 years after DDL released

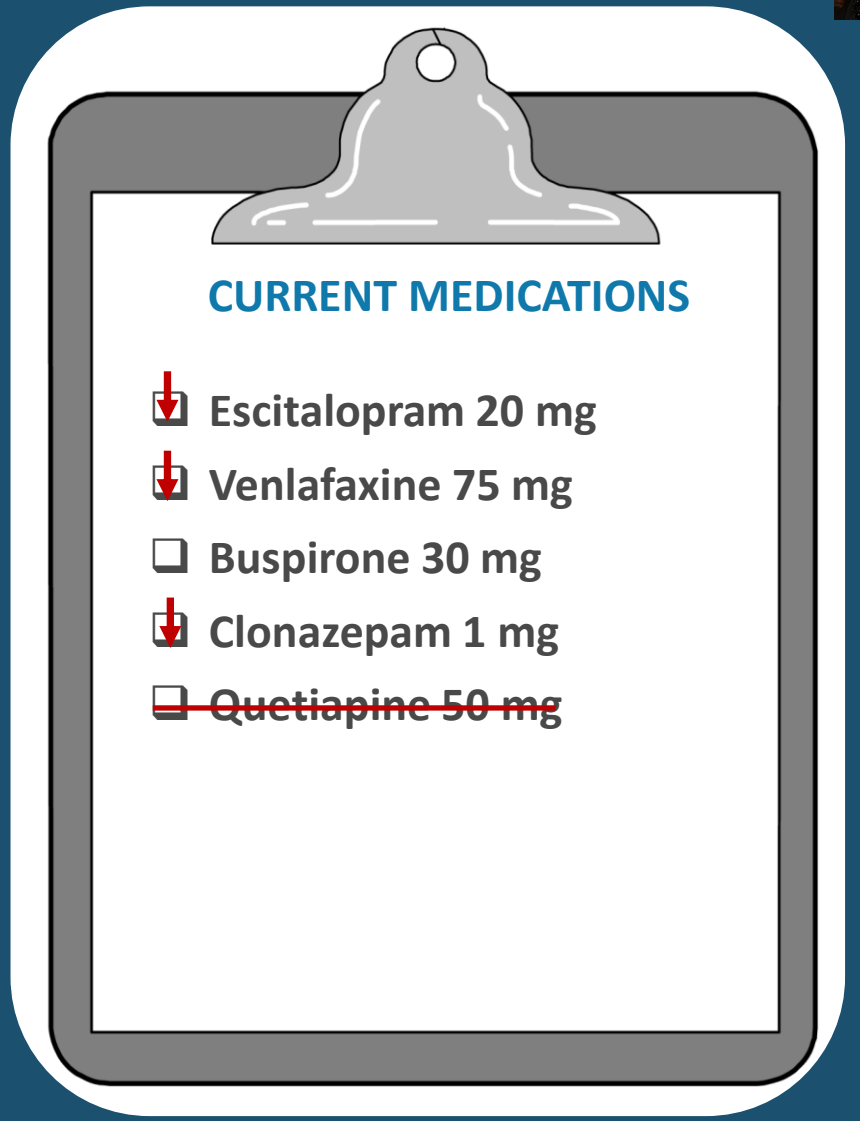
1. de Bardeci M et al. Dear doctor letters regarding citalopram and escitalopram: guidelines vs real-world data. *Eur Arch Psychiatry Clin Neurosci*. 2023;273(1):65-74.

CASE CONTINUED*

EVALUATION OF CURRENT MEDS

Now that the patient has a diagnosis of BD, how would you approach her current med list?

MODIFY	DISCONTINUE
Escitalopram • Lower to 10 mg • Plan to discontinue next visit	**Quetiapine** • Perform AIMS
Venlafaxine • Primarily SSRI effect at ≤150 mg[1] • Lower to 37.5 mg for 7 days, then d/c	
Clonazepam • Lower to 0.5 mg • Plan to ultimately discontinue	



*Fictionalized representation based on a real medical case.

1. Aldosary F et al. Differential potency of venlafaxine, paroxetine, and atomoxetine to inhibit serotonin and norepinephrine reuptake in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2022;25(4):283-292.

AIMS: Abnormal Involuntary Movement Scale

WHAT'S RELEVANT AND WHAT'S NOT WHEN CHOOSING BETWEEN BD MEDICATIONS?

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CASE CONTINUED*

MANAGEMENT OF BIPOLAR DEPRESSION

CASE NOTES

24-year-old woman with a history of depression; venlafaxine/escitalopram/clonazepam doses lowered

What medication, if any, would you consider adding to Jada's therapeutic regimen?

MEDICATION OPTIONS

- Lithium/lamotrigine
- Quetiapine
- Olanzapine/fluoxetine
- Lurasidone
- Cariprazine
- Lumateperone
- Carbamazepine
- Aripiprazole

*Fictionalized representation based on a real medical case.

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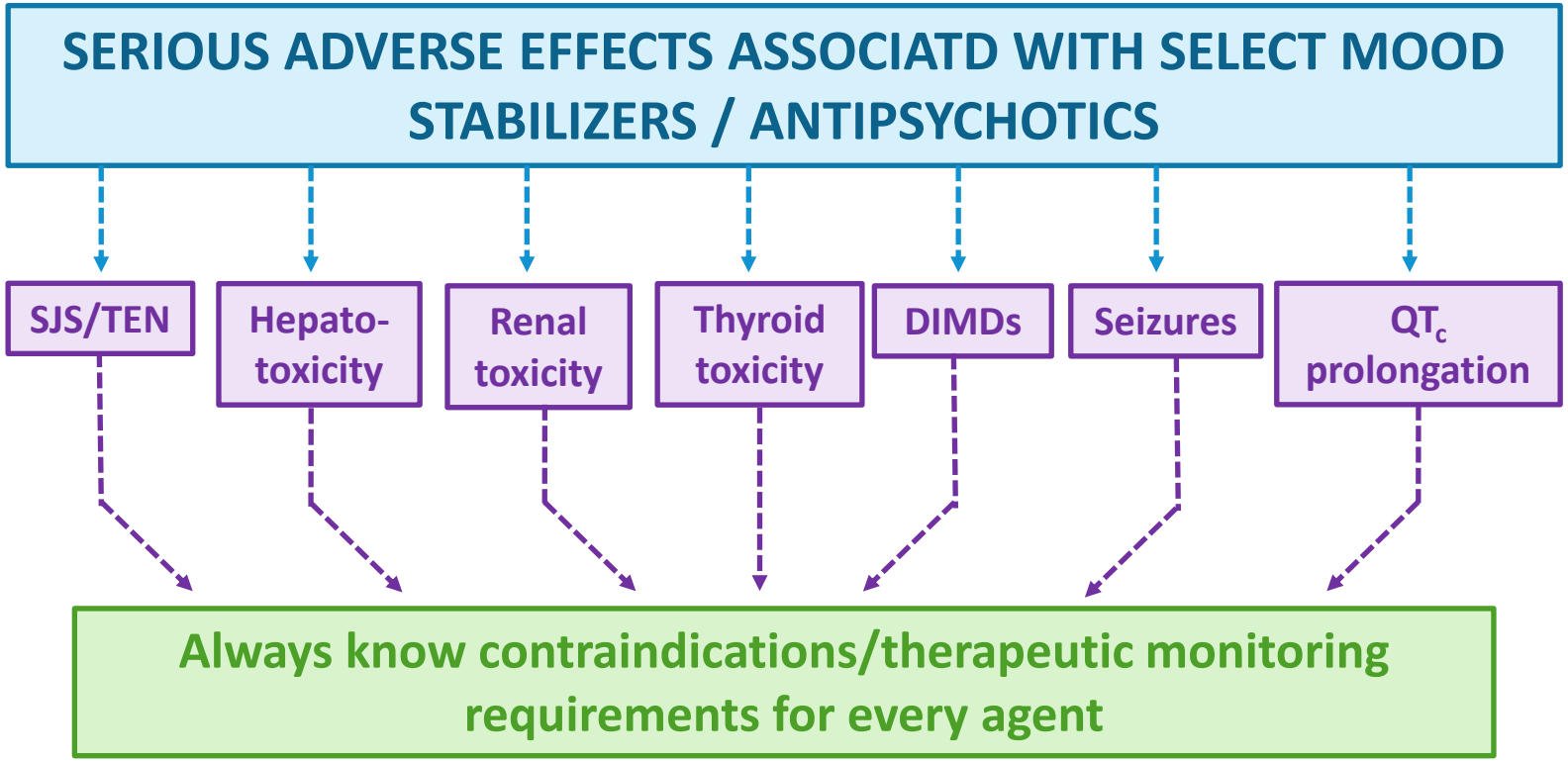
AUDIENCE POLL

Which of the following agents would you choose as **first-line therapy** for this patient?

a) Aripiprazole
b) Cariprazine
c) Carbamazepine
d) Lithium/lamotrigine
e) Lurasidone
f) Lumateperone
g) Olanzapine/fluoxetine
h) Quetiapine
i) Other

CONSIDERATIONS WITH OFF-LABEL TREATMENTS

- Although less common, many off-label treatments are associated with **serious side effects**,[1,2] which may impact individual drug monitoring.
- In addition to common side effects, **know serious adverse effects of each medication you are prescribing**.



DIMDs: drug-induced movement disorders; **SJS:** Stevens-Johnson syndrome**; TEN:** toxic epidermal necrolysis

1. Levenberg K et al. Bipolar depression: a review of treatment options. *Gen Psychiatr*. 2022;35(4):e100760. **2.** Goes FS. Diagnosis and management of bipolar disorders. *BMJ*. 2023;381:e073591.

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APPROVED MEDICATIONS FOR BIPOLAR DEPRESSION

	Olanzapine/ fluoxetine[1,2]	Quetiapine (IR or XR)[1-3]	Lurasidone[1,2]	Cariprazine[1,2]	Lumateperone[1,2,4]
BIPOLAR I DEPRESSION	2003	2006 (IR), 2008 (XR)	2013	2019	2021
BIPOLAR II DEPRESSION	2008				2021
ADJUNCTIVE USE WITH LITHIUM OR VALPROATE*	✗	✗	✓	✗	✓

What needs are met by newer agents approved for bipolar depression?

**Lithium and valproate are approved for mania but not depression in BD.*

IR: immediate release; **XR**: extended release

1. Levenberg K et al. Bipolar depression: a review of treatment options. *Gen Psychiatr*. 2022;35(4):e100760. **2.** Ostacher MJ. Slowly working toward more treatments for depression in bipolar II disorder. *Am J Psychiatry*. 2021;178(12):1075-1076. **3.** Srinivas S et al. Efficacy and safety of quetiapine for pediatric bipolar depression: a systematic review of randomized clinical trials. *Cureus.* 2020;12(6):e8407. **4.** Intra-Cellular Therapies. Intra-Cellular Therapies announces U.S. FDA approval of CAPLYTA (lumateperone) for the treatment of bipolar depression in adults. News Release. December 20, 2021. Accessed 12.14.23. https://ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-us-fda-approval-caplytar

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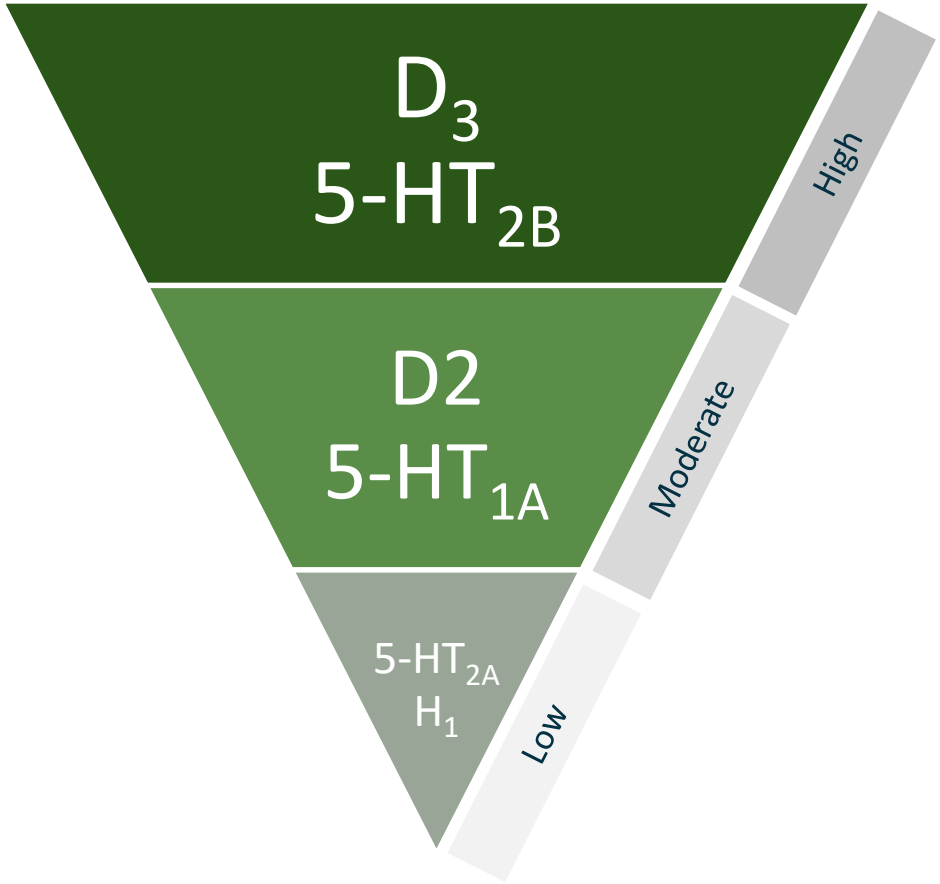
CARIPRAZINE

POTENTIAL MECHANISM OF ACTION[1]

- **Tenfold higher affinity for D_3 receptors** than for D_2
- Nigrostriatal D_3 blockade (may disinhibit prefrontal cortex DA release)
  - Improved reward processing
  - Procognitive/antidepressant effects
- **5-HT_{2B}** antagonism/**5-HT_{1A}** agonism
  - Antidepressant effects

RECEPTOR BINDING AFFINITIES[2]



DA: dopamine

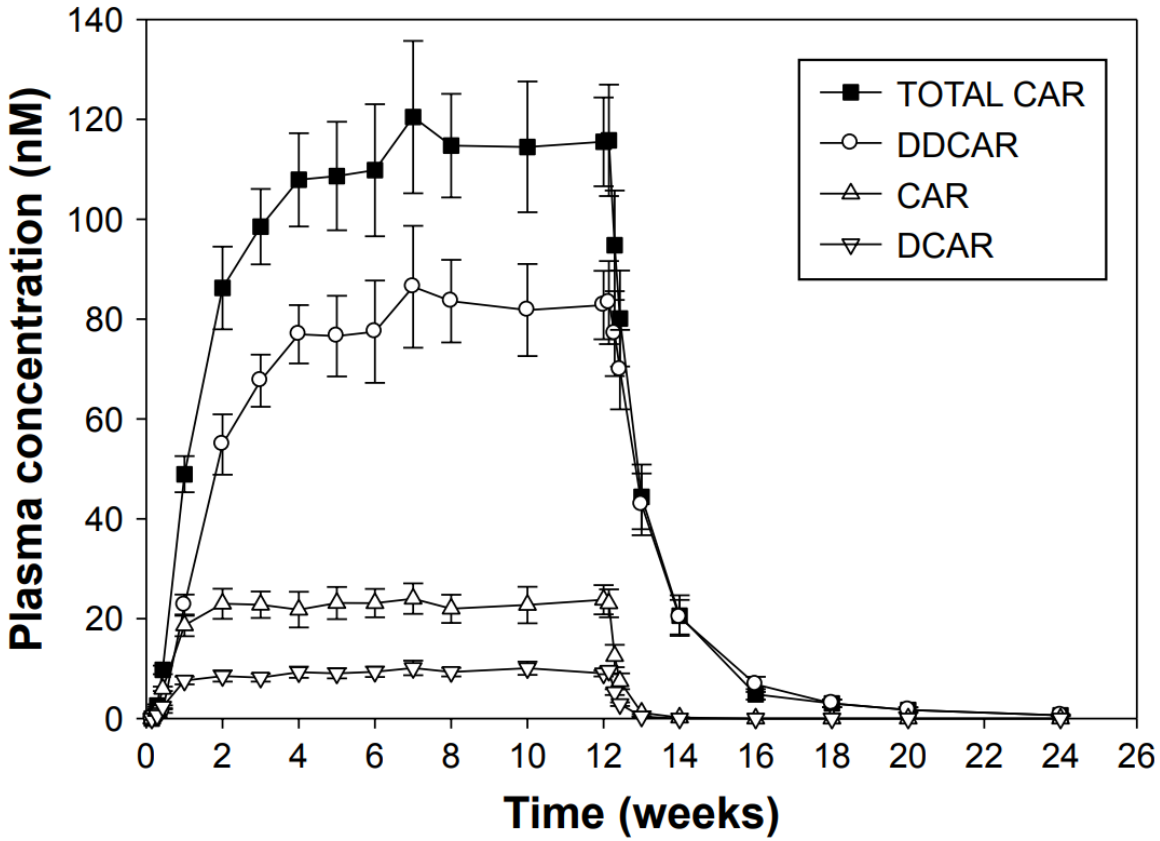
1. Stahl SM et al. Cariprazine as a treatment across the bipolar I spectrum from depression to mania: mechanism of action and review of clinical data. *Ther Adv Psychopharmacol*. 2020;10:1-11. **2.** Stahl SM. Antipsychotic agents. In: *Stahl's Essential Pharmacology. Neuroscientific Basis and Practical Applications*. 4th ed. Cambridge University Press; 2013:129-235.

CARIPRAZINE

UNIQUE PHARMACOKINETICS

- Time to peak concentration = **3 to 6 hours**
- Predominant metabolite (DDCAR) has a long **half-life of 1 to 3 weeks**

CONCENTRATIONS OVER TIME



From Cariprazine. Prescribing information. AbbVie; 2022.

CAR: cariprazine; **DCAR**: desmethyl-cariprazine (intermediate metabolite); **DDCAR**, didesmethyl-cariprazine; **nM**: nanomolar

1. Cariprazine. Prescribing information. AbbVie; 2022. Accessed 12.18.23.

CARIPRAZINE

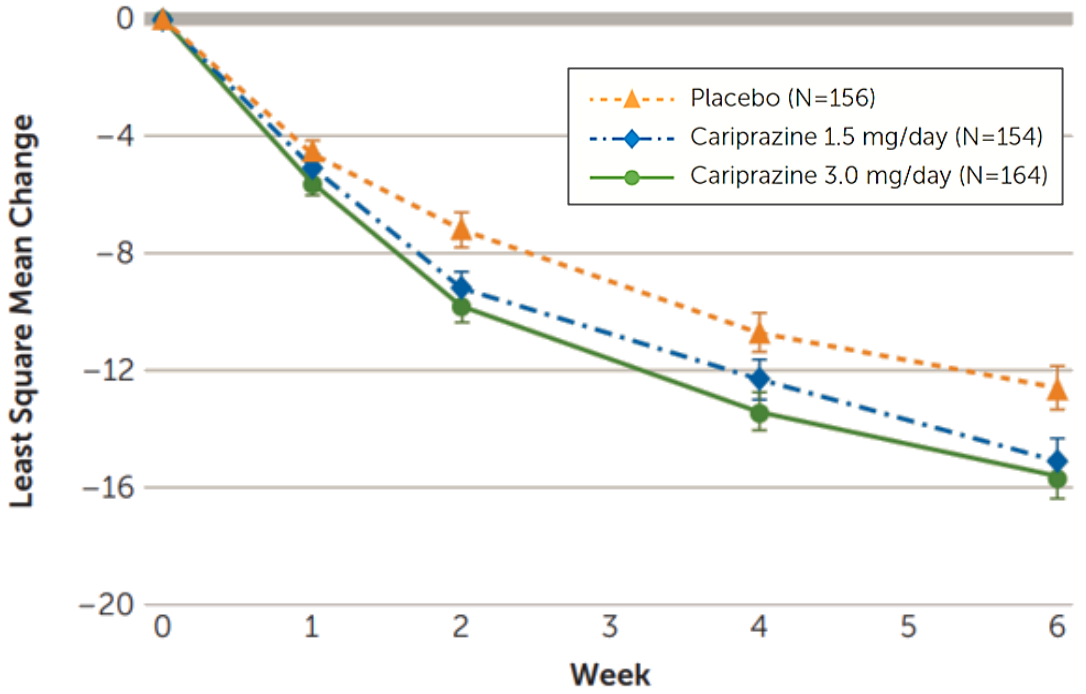
STUDY DESIGN

- 480 patients with bipolar I disorder and current major depressive episode
- Randomized to placebo, cariprazine 1.5 mg/day or 3 mg/day over 6 weeks

RESULTS

- **Cariprazine significantly reduced MADRS total score.**
- **Treatment-emergent adverse effects**: nausea, akathisia, dizziness, sedation

CHANGE FROM BASELINE IN MADRS AT EACH STUDY VISIT



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

MADRS: Montgomery-Åsberg Depression Rating Scale

1. Earley W et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. *Am J Psychiatry.* 2019;176(6): 439-448.

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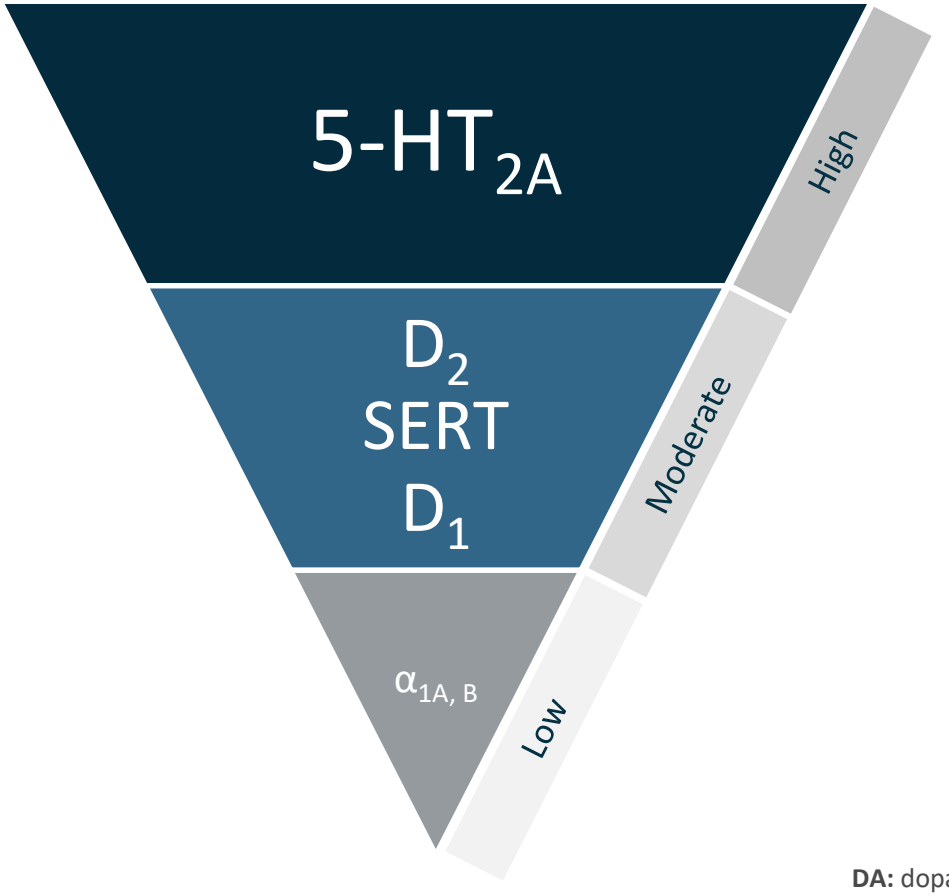
LUMATEPERONE

PROPOSED MECHANISM OF ACTION[1]

- **Reduced postsynaptic D_2 occupancy:** 39% vs. >60% of most other antipsychotics
- **Reduced compensatory DA release:** presynaptic D_2 partial agonism
  - Reduced adverse effects from excess DA
- **D_1 activation** may increase glutamate in the hypoactive prefrontal cortex.
- **Serotonin transporter (SERT) inhibition**
  - Antidepressant effects
- 80% to 90% occupancy of **cortical $5HT_{2A}$**[2]

RECEPTOR BINDING AFFINITIES[3]



DA: dopamine

1. Vanover KE et al. Dopamine D2 receptor occupancy of lumateperone (ITI-007): a PET study in patients with schizophrenia. *Neuropsychopharmacology*. 2019;44(3):598-605. **2.** Davis RE et al. ITI-007 demonstrates brain occupancy at serotonin 5-HT_2A and dopamine D_2 receptors and serotonin transporters using positron emission tomography in healthy volunteers. *Psychopharmacology (Berl)*. 2015;232(15):2863-2872. **3.** Stahl SM. Antipsychotic agents. In: *Stahl's Essential Pharmacology. Neuroscientific Basis and Practical Applications*. 4th d. Cambridge University Press; 2013:129-235.

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LUMATEPERONE

PARTICIPANTS

- 333 patients with bipolar I or II disorder and current major depressive episode

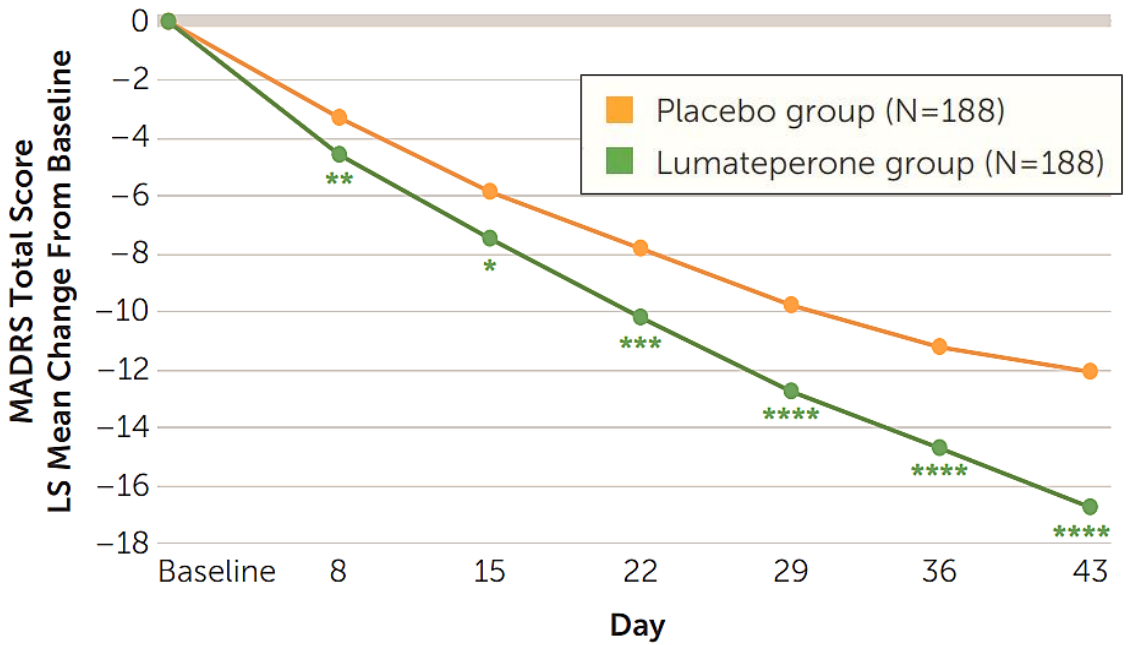
STUDY DESIGN

- Randomized lumateperone 42 mg/day or placebo for 6 weeks

RESULTS

- **Greater MADRS response and remission rates**
- Greater improvement on MADRS and CGI-BP-S
- Treatment-emergent adverse effects: somnolence, sedation, **minimal extrapyramidal /metabolic/endocrine symptoms**

CHANGE FROM BASELINE IN MADRS OVER TIME



From Calabrese JR et al. Am J Psychiatry. 2021;178(12):1098-1106.

CGI-BP-S: Clinical Global Impressions of Bipolar Disorder-Severity scale; **LS**: least-squares; **MADRS**: Montgomery-Åsberg Depression Rating Scale

1. Calabrese JR et al. Efficacy and safety of lumateperone for major depressive episodes associated with bipolar I or bipolar II disorder: a phase 3 randomized placebo-controlled trial. *Am J Psychiatry*. 2021;178(12):1098-1106.

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CLINICAL RESOURCE
SUBMISSION GUIDES

- **Ensure proper documentation**[1]
  - Associated diagnosis
  - All previous schizophrenia or bipolar depression products prescribed within the last year

- **Utilize available support and resources** for each agent[2]
  - Certain systems may be easier to navigate.

(lumateperone) capsules

PA Submission Information

The guidance outlined below may be helpful as you fill out and submit PAs for your patients.

The following information may be needed for the PA:

CLINICAL DIAGNOSIS	PREVIOUS THERAPY WITHIN THE LAST 12 MONTHS
Please see ICD-10 codes *(available on page 2)* **Adult patients (aged ≥18 years):** List all of the patient's diagnoses for the product being requested	List all previous schizophrenia or bipolar depression products prescribed for the patient over the last 12 months

Resources for patients & HCPs - CAPLYTA® (lumateperone). https://www.caplytahcp.com/bipolar/resources

(cariprazine) capsules
1.5mg•3mg•4.5mg•6mg

Support and Resources

Typical time to **complete** and **submit a PA** request using PARx is **3-5 minutes**.	The PARx 'PASS' system and our **rigorous quality assurance process** ensure that PA submissions are **accurate** and **complete.**	Our universal format makes the PA process **simple to use** and **easy to understand.**

Solutions for prescribers | PARX Solutions. PARx Solutions. http://www.parxsolutions.com/solutions/prescribers

1. Intra-Cellular Therapies. CAPLYTA (lumateperone). Resources for healthcare providers. Accessed 12.15.23. https://www.caplytahcp.com/bipolar/resources
2. PARX Solutions. Solutions for prescribers. Accessed 12.15.23. http://www.parxsolutions.com/solutions/prescribers

Clinical considerations when choosing specific therapies/shared decision-making

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CASE CONTINUED*

SHARED DECISION-MAKING

CASE NOTES

24-year-old female with a history of depression; venlafaxine/escitalopram/clonazepam doses lowered

SHARED DECISION-MAKING:

- Patient willing to take medication daily (**no concerns of nonadherence**)
- Looking for **fast onset of action, limited side effects**
- Need medication that is **covered by patient's insurance plan**

Based on shared-decision making, started **lumateperone**

*Fictionalized representation based on a real medical case.

MONITORING CONSIDERATIONS

***Weight/metabolic** and **movement disorder** risks must be closely monitored.*

RELATIVE RISK RATIOS

	LOW	HIGH
WEIGHT & METABOLIC RISKS	- Lurasidone[1-3] - Cariprazine[1-3] - Lumateperone[4,5]	- Olanzapine/fluoxetine[1-3] - Quetiapine (IR and XR) [1-3]
MOVEMENT DISORDER RISKS	***CLASS EFFECT OF ANTIPSYCHOTICS***	

TOLERABILITY AND TREATMENT SATISFACTION ARE IMPORTANT FOR MEDICATION ADHERENCE

1. Citrome L et al. Presented at ASCP Virtual; 2020. Abstract F30. **2.** Citrome L et al. Assessing the benefit-risk ratio of approved treatments for bipolar depression using likelihood to be helped or harmed (LHH) analyses. *CNS Spectr*. 2021;26(2):146. **3.** Citrome L. Food and Drug Administration–approved treatments for acute bipolar depression: what we have and what we need. *J Clin Psychopharmacol.* 2020;40(4):334-338. **4.** CAPLYTA (lumateperone). Prescribing information. Intra-Cellular Therapies, Inc.; 2023. **5.** US Food and Drug Administration. FDA Drug Approval Package for CAPLYTA. Accessed 12.15.23. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/209500Orig1s006_Redacted.pdf

CLINICAL DECISION-MAKING

MY PRACTICE

MY PREFERRED FIRST-LINE THERAPIES

- **Lumateperone**
- **Cariprazine**
- **Lurasidone**

However

ALWAYS A SHARED DECISION

- Discuss side effects, efficacy, and relative costs of each medication
- Direct patient to available resources for further education

KEY TAKEAWAYS

SCREENING AND DIAGNOSIS	TREATMENT
• *Depressive symptoms are the same for MDD and BD.*[1] • Screening tools and predictive factors can help raise clinical suspicion for BD.[2,3]	• **First-line therapies:** cariprazine, lumateperone, lurasidone[4]
EXPERT TIPS	
• *Before I enter the patient's room, **I already have their PHQ-9, GAD-7, MDQ, PSS*** • *Consider comorbidities (especially ADHD)* • *Ask about hallucinations* • *Obtain an extensive family history; **always** ask about personal/family history of mania/hypomania*[1]	• *Consider fiscal obtainability, half-life, history of compliance* • *Use SDM to understand patient goals, improve adherence, and optimize outcomes*[5]

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision. 2022. **2.** McIntyre RS et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. *Curr Med Res Opin*. 2021;37:135-144. **3.** Stahl SM et al. Guidelines for the recognition and management of mixed depression. *CNS Spectr*. 2017;22(2):203-219. **4.** Department of Veterans Affairs and Department of Defense. VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder (Version 2.0). Accessed 12.18.23. https://www.healthquality.va.gov/guidelines/MH/bd/index.asp. **5.** Goes FS. Diagnosis and management of bipolar disorders. *BMJ*. 2023;381:e073591.

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