Bipolar Disorder in Older Adults

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LEARNING OBJECTIVES

1. Distinguish between different phases of bipolar disorder, including common presentations in ambulatory older adults.
2. Apply clinical guidelines and pharmacologic information to treat ambulatory older adults experiencing bipolar mania.
3. Apply clinical guidelines and pharmacologic information to treat ambulatory older adults experiencing bipolar depression.
4. Develop a treatment plan for ambulatory older adults currently in the maintenance phase of bipolar disorder, including appropriate monitoring.

ABBREVIATIONS IN THIS CHAPTER

AIMS	Abnormal Involuntary Movement Scale
BAP	British Association for Psychopharmacology
CANMAT	Canadian Network for Mood and Anxiety Treatments
EPS	Extrapyramidal symptoms
MDQ	Mood Disorder Questionnaire
SGA	Second-generation antipsychotic
SJS	Stevens-Johnson syndrome

Table of other common abbreviations.

INTRODUCTION

Bipolar I disorder is characterized by three phases: mania, depression, and euthymia. Although there is a distinction between bipolar I disorder and bipolar II disorder regarding the existence of mania versus hypomania, we will focus on bipolar I disorder because it is the more common and better understood of the two conditions. In addition, most clinical trials and drug approvals have been for bipolar I disorder.

Bipolar disorder is often misdiagnosed for many years because patients tend to present with depressive symptoms initially. Patients with bipolar disorder are estimated to spend 50% their life asymptomatic and 30% of their life with depressive symptoms. This means that a relatively small amount of their lifetime, only about 5%–10%, is spent in the more identifiable manic phase, which can contribute to misdiagnosis and improper treatment (Judd 2002). The 1-year prevalence of bipolar disorder in the United States is around 0.6%, with an equal distribution across men and women (Merikangas 2007). Patients with bipolar disorder are often given the diagnosis in adolescence or early adulthood, with a mean age at onset of 18 years. With respect to male and female sex differences, women tend to have later onset of symptoms than men. However, onset can occur any time in life, including in older adults in their 60s or 70s. Onset of manic symptoms in older adults should prompt clinicians to consider other diagnoses and causes, including medication- or substance-induced mania.

Different Phases of Bipolar Disorder

Mania is characterized by an abnormally elevated, expansive, or irritable mood persisting for at least 1 week. If symptoms are severe enough to require hospitalization, this duration requirement does not have to be met for diagnosis. Another common symptom of a manic episode is a decreased need for sleep. This is important to differentiate from insomnia, in which a person wants to sleep but

cannot. In mania, a person does not feel the need to sleep and may go many days without sleep and not feel physically tired. A decreased need for sleep is one of the more common symptoms of bipolar disorder and is often the first sign of an impending manic episode. Another common and troubling symptom of mania is an increase in risk-taking behaviors. This can include excessive shopping sprees, giving away possessions, reckless driving, bad business investments, and risky sexual behavior. These behaviors often have long-lasting consequences that the patient likely has not considered. Other symptoms of mania include rapid, pressured speech; inflated self-esteem; euphoria; grandiosity; racing thoughts; and distractibility. Psychotic symptoms such as hallucinations and delusions may be present in more severe instances (APA 2013).

The depressive phase of bipolar disorder has the same symptoms as a major depressive episode. Most clinicians are probably familiar with these depressive symptoms: decreased energy, loss of interest in activities, feelings of guilt or worthlessness, sleep disturbances including insomnia or too much sleep, sadness, appetite changes, and a depressed mood. There is no difference in symptoms between a patient having a major depressive episode with or without bipolar disorder. The only difference is the history of mania. Suicidal behavior appears to be more common among individuals with bipolar disorder. It is estimated that 20%–60% of individuals with bipolar disorder will attempt suicide at least once in their lifetime, and up to 4%–19% will end their life by suicide. The risk of suicide death in bipolar disorder is reported to be up to 30 times higher than in the general population (Dome 2019).

Some data analyses suggest that patients with bipolar disorder have prodromal symptoms, such as irritability, anxiety, mood lability, agitation, sleep disturbances, and hyperactivity, before the onset of bipolar symptoms (Skjelstad 2010). However, prodromal symptoms are not a consistent finding and should not be used as a diagnostic tool, given that they can also occur during the manic and depressive phases of bipolar disorder. Clinicians can consider this information when assessing patients.

The maintenance phase is the time between the manic and depressive phases. Patients in this phase are euthymic and asymptomatic. More than 90% of individuals who have a manic episode will have a future manic or depressive episode; therefore, treatment in this phase is crucial because patients with bipolar disorder often require chronic treatment and follow-up to prevent further episodes. Even with adequate medical treatment, 19%–25% of patients will have a recurrence of either mania or depression in a year. However, this is better than the 23%–40% estimate of recurrence in 1 year for untreated patients (Yatham 2018). Risk factors for mania or depression recurrence include younger age at onset, psychotic features, rapid cycling, high frequency of previous episodes, comorbid anxiety, and comorbid substance use disorder. Because patients are expected to adhere to medication for a long time, personalized drug selection to minimize adverse effects and drug-drug interactions is crucial.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic drug knowledge of the mechanism of action for the medications used in bipolar disorder
- General principles on the diagnostic criteria for bipolar disorder from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*)
- Basic knowledge of signs and symptoms of depression and mania

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Price AL, Marzani-Nissen G. Bipolar disorders: a review. Am Fam Physician 2012;85:483-93.
- Singh P, Pandey NM, Tiwari SC. Late-life mania: a brief review. J Geriatr Mental Health 2015; 2:68-73.
- Substance Abuse and Mental Health Services Administration. Mood Disorder Questionnaire (MDQ).

Common Presentations in the Ambulatory Care Setting

In the ambulatory care setting, patients with bipolar disorder most often present with symptoms of depression. Reasons for this can include that patients with manic symptoms most likely do not seek out self-treatment and therefore often seek treatment only when depressive symptoms set in or under urgent circumstances such as a medical emergency. Proper patient assessment, including thorough medical and social histories, is important in developing a treatment plan.

Assessment of Bipolar Disorder

Depressive symptoms can be assessed using the Patient Health Questionnaire-9, which also helps assess for a major depressive episode. Clinicians should be sure to screen patients presenting with depressive symptoms for previous symptoms of mania. Patients can be screened through history-taking or through a standardized screening tool such as the Mood Disorder Questionnaire (MDQ). The MDQ consists of 15 items, which can be self-administered and completed quickly in the ambulatory care setting. Clinicians should also ask about previous psychiatric hospitalizations because this may lead to further insight about the patient's psychiatric

history. Other screening tools that can be used in the ambulatory care setting include the Mini-Mental State Examination, which may help differentiate symptoms of depression from symptoms of a cognitive disorder.

Clinicians should be aware of red flags that may require further referral or evaluation, including suicidal behavior. For a patient presenting with symptoms of depression, medical- and drug-induced causes of depression should be ruled out, particularly if the symptoms are newly present in an older adult. For example, hypothyroidism and dementia are common medical causes of depressive symptoms. Common medications associated with depression include oral corticosteroids, efavirenz, interferon, and certain antiepileptics such as tiagabine and zonisamide. If an older adult patient presents with mania, clinicians should rule out delirium, dementia, hyperthyroidism, neurosyphilis, and a transient psychotic disorder. Conversely, medications that can be associated with mania symptoms include oral corticosteroids, anabolic steroids, and dopamine agonists such as ropinirole and pramipexole (Celano 2011).

Treatment Principles

Table 1, Table 2, and Table 3 contain clinical guideline recommendations, with each table focusing on a different phase of bipolar disorder. The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2018 guidelines specifically address the management and treatment of bipolar disorder in the primary care setting. The American Psychiatric Association guidelines have not been updated since 2002 and are therefore not included.

Guidelines usually do not have specific recommendations in older adult patients; therefore, recommendations for the general adult population should be followed (see Tables 1–3). Clinicians should consider pharmacokinetics and dose adjustments when prescribing in an older adult population because older adult patients are more prone to adverse drug reactions, particularly anticholinergic adverse effects (sedation, constipation, dry mouth, and confusion). The older adult patient's complete medication list should be evaluated thoroughly for drug-drug pharmacodynamic and pharmacokinetic interactions.

TREATMENT OF ACUTE MANIA

Acute mania is not common in the ambulatory care setting because it is usually managed in the inpatient setting. A detailed review is beyond the scope of this chapter; however, we will introduce some basic principles regarding its treatment. The medications commonly used for acute mania can also be used in the other phases of the disorder, and we will introduce them in this section. These agents include the

Table 1. Summary of Guideline Recommendations for Acute Mania in Bipolar Disorder

Acute Mania	Canadian Network for Mood and Anxiety Treatments (2018)[a]	British Association for Psychopharmacology (2017)
First-line/primary recommendation	Monotherapy: Lithium Quetiapine Divalproex Asenapine Aripiprazole Paliperidone (> 6 mg) Risperidone Cariprazine Combination therapy: Lithium or divalproex + one of the following SGAs: quetiapine, aripiprazole, risperidone, or asenapine	Asenapine Haloperidol Lithium Olanzapine Risperidone Quetiapine Divalproex
Second-line/alternative recommendation	Olanzapine Olanzapine + lithium or divalproex Lithium + divalproex Ziprasidone Haloperidol Carbamazepine	Aripiprazole Carbamazepine Haloperidol Lorazepam Loxapine Ziprasidone

[a]The CANMAT guidelines do rank their recommendations; therefore, drugs should be tried in the order listed unless there are patient-specific reasons not to use a particular medication.

SGA = second-generation antipsychotic.

Table 2. Summary of Guideline Recommendations for Acute Bipolar Depression

Acute Bipolar Depression	Canadian Network for Mood and Anxiety Treatments (2018)[a]	British Association for Psychopharmacology (2017)
First-line/primary recommendation	Quetiapine Lurasidone + lithium Lithium Lamotrigine Lurasidone	Lamotrigine Lurasidone Olanzapine Olanzapine/fluoxetine Quetiapine SSRI or bupropion (as adjunct)
Second-line/alternative recommendation	Divalproex SSRI or bupropion (as adjunct) Cariprazine Olanzapine/fluoxetine	Lithium

[a]The CANMAT guidelines do rank their recommendations; therefore, drugs should be tried in the order listed unless there are patient-specific reasons not to use a particular medication.

SSRI = selective serotonin reuptake inhibitor.

Table 3. Summary of Guideline Recommendations for Bipolar Disorder Maintenance

Maintenance Treatment	Canadian Network for Mood and Anxiety Treatments (2018)[a]	British Association for Psychopharmacology (2017)
First-line/primary recommendation	Aripiprazole Asenapine Aripiprazole + lithium or divalproex Divalproex Lamotrigine Lithium Quetiapine Quetiapine + lithium or divalproex	Aripiprazole Carbamazepine Divalproex Lithium Lamotrigine Olanzapine Paliperidone Quetiapine Risperidone
Second-line/alternative recommendation	Carbamazepine Lurasidone + lithium or divalproex Olanzapine Paliperidone Risperidone (long-acting injection) Risperidone (as adjunct) Ziprasidone + lithium or divalproex	

[a]The CANMAT guidelines do rank their recommendations; therefore, drugs should be tried in the order listed unless there are patient-specific reasons not to use a particular medication.

second-generation antipsychotics (SGAs), lithium, and valproic acid and its derivatives (e.g., divalproex).

Review of Guideline Recommendations for Acute Mania

In general, patients experiencing a manic episode should be initiated on one of the first-line medications listed in Table 1. Most recommendations in both the CANMAT and British Association for Psychopharmacology (BAP) guidelines consist of monotherapy with an antipsychotic, predominantly an SGA. Lithium and divalproex sodium are also included as possible single-agent first-line options in both guidelines. Although CANMAT offers some combination therapies as first-line options, monotherapy should be tried initially, when

possible. The CANMAT guidelines do rank their recommendations within each category; therefore, drugs should be tried in the order listed in Tables 1–3 unless there are patient-specific reasons not to use a particular medication. Tolerability, efficacy, and patient-specific factors should be weighed when selecting medications. For example, although lithium is recommended as first line in the CANMAT guidelines, it may not be as palatable for patients because of lesser tolerability and may not be as feasible because of common drug-drug interactions or the need for renal dosing adjustment.

When selecting a medication, clinicians should consider prior treatment response, safety and tolerability concerns, and the ability of the chosen medication to treat other phases of bipolar disorder. Acute mania usually resolves within 3–4 weeks of starting treatment, but patients will continue to require maintenance treatment afterward to prevent further episodes.

SGAs in Acute Mania

Many SGAs have an FDA indication for the treatment of mania. Table 4 lists SGAs and their indications in bipolar disorder. Second-generation antipsychotics have been well documented for their efficacy in treating acute bipolar mania. According to previous clinical trials, the average time to symptom improvement is more rapid with SGAs than with lithium, and SGAs and valproate appear to have a similar time to improvement (Buoli 2017; Keck 2009). In one single-blind study, investigators tried to examine the differences in time to response between various antipsychotics. In this study, asenapine appeared to have a more rapid onset of action than haloperidol and, to a lesser extent, olanzapine (Buoli 2017). In general, almost all antipsychotic agents show clinical response within 1–2 weeks compared with placebo. Therefore, if no response is seen within 2 weeks, a change in therapy should be considered (Yatham 2018).

Table 4. Indications and Uses of Mood Stabilizers in Different Phases of Bipolar Disorder

Medications	Bipolar Mania	Bipolar Depression	Bipolar Maintenance
Lithium	X	Y	X
Divalproex	X		Y
Carbamazepine	X		Y
Lamotrigine		Y	X
Aripiprazole	X		Y (aripiprazole) X (aripiprazole monohydrate IM long-acting injection) X (aripiprazole tablets with sensor)
Asenapine	X		X
Cariprazine	X	X	
Lurasidone		X	
Olanzapine	X	X (only in combination with fluoxetine)	X
Quetiapine/quetiapine XR	X	X	X (in combination with lithium or divalproex sodium) Y (monotherapy)
Risperidone	X		X (risperidone long-acting IM injection as monotherapy or in combination with lithium or divalproex sodium)
Ziprasidone	X		X (in combination with lithium or divalproex sodium) Y (monotherapy)

Blank = insufficient data to support its use; X = FDA approved; Y = off-label use, but recommended by the guidelines.
IM = intramuscular(ly); XR = extended release.

Table 5. Comparison of SGAs and Recommended Monitoring

Risk of Weight Gain and Metabolic Syndrome	Medications	Initial/Max Dose in Bipolar Disorder	Common Adverse Effects/ Clinical Pearls	Monitoring
Lowest	Lurasidone	20 mg/120 mg once daily	Akathisia, minimal weight gain, drowsiness; must be taken with food for adequate absorption (≥ 350 cal)	All patients taking SGAs should have a baseline: -Blood pressure -A1C -Lipid panel -Weight -BMI -Waist circumference -CBC[a] All of these values should be monitored 3 mo after initiation and at least annually thereafter, or as clinically indicated Monitor more often if patient has abnormal laboratory values or additional risk factors at baseline (i.e., diabetes, obesity)
	Cariprazine	1.5 mg/6 mg once daily (max dose for bipolar depression: 3 mg/day)	Akathisia, nausea, pseudoparkinsonism, orthostatic hypotension	
	Aripiprazole	5 mg/30 mg once daily	Akathisia; may cause more weight gain in children, minimal sedation	
	Ziprasidone	40 mg BID/80 mg BID	Fewer EPS than others; possible concern for QT prolongation; must be taken with food for adequate absorption (> 500 cal)	
	Brexpiprazole	0.5/3 mg once daily	Similar to aripiprazole, but with more potential for weight gain	
	Asenapine	5 mg BID/10 mg BID	Must be taken SL; avoid eating or drinking for 10 min after administration; fewer EPS than others	
Highest	Quetiapine/ quetiapine XR	50 mg/800 mg once daily or split BID (target dose = 300 mg in bipolar depression	Sedation; moderate weight gain; very few EPS; may help with anxiety; XR formulation may cause less sedation	
	Risperidone	0.5 mg/6 mg once daily or split BID	More EPS risk than others; moderate weight gain; hyperprolactinemia; orthostatic hypotension	
	Olanzapine	5 mg/20 mg once daily (can be split BID)	Causes the most weight gain and appetite increase; sedation; high risk of anticholinergic adverse effects	

[a]Should be performed in patients with a history of drug-induced leukopenia/neutropenia or with a preexisting low WBC.
BID = twice daily; EPS = extrapyramidal symptoms; SL = sublingual(ly).

Although each SGA has a slightly different adverse effect profile (Table 5), they share some adverse effects as a class. In particular, they all carry a risk of causing, or worsening, metabolic syndrome. Second-generation antipsychotics are usually divided into high, medium, and low metabolic risk. However, even if an SGA has a low risk of causing metabolic syndrome, the risk is still present and requires monitoring. Clinicians should consider the adverse effect profile of each particular SGA before initiating treatment. Second-generation antipsychotics are relatively well tolerated and require less monitoring than other medications available for acute mania. Clinical scenarios in which SGAs, specifically quetiapine and olanzapine, may be preferred include in patients experiencing symptoms of anxiety during a manic episode (Yatham 2018). In addition, SGAs may be preferred if a patient has both manic and depressive symptoms at the same time, also known as a mixed presentation. In a mixed episode, combination therapy of SGA with divalproex may also be required.

Second-generation antipsychotics carry a risk of drug-induced extrapyramidal symptoms (EPS), including akathisia, pseudoparkinsonism, and even tardive dyskinesia. Akathisia is an inner restlessness, which can make a patient very uncomfortable and feel the need to move constantly. The severity of akathisia symptoms can range from mild leg shaking to the inability to sit still without significant movement. The SGAs aripiprazole, lurasidone, and asenapine seem to have a higher incidence of akathisia of around 20%. The adverse effect of akathisia is dose-dependent. Tardive dyskinesia can clinically be assessed using the Abnormal Involuntary Movement Scale (AIMS), while the Barnes Akathisia Rating Scale can be used to screen for akathisia.

Clinicians should remember that all antipsychotics carry a boxed warning regarding their use in dementia-related psychosis because they can lead to an increased risk of death compared with placebo. This warning emphasizes the need for appropriate diagnoses before prescribing antipsychotics in older adults.

Lithium in Acute Mania

Lithium is considered the gold standard in the treatment of acute mania. However, certain factors make lithium less than ideal as a first-line option. Lithium is usually less well tolerated than SGAs, has several significant and common drug-drug and drug-food interactions, and requires therapeutic drug monitoring. Because lithium is eliminated almost entirely through the kidneys and has a narrow therapeutic window, it should be avoided in older adults. Lithium also has certain clinically significant drug-drug interactions with common medications used in the older adult population. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), spironolactone, thiazide diuretics, and NSAIDs can increase lithium concentrations when used concomitantly. Lithium clearance is also susceptible to changes in hydration and salt intake. In addition, lithium concentrations can be reduced by caffeine intake (Finley 2016). Table 6 lists monitoring recommendations and adverse effects.

Clinical scenarios that can skew a clinical decision toward lithium include patients who have classic euphoric grandiose mania, few prior episodes of illness, and a family history of lithium response. Potential drug-drug interactions should thoroughly be assessed before initiating lithium.

Valproic Acid and Derivatives in Acute Mania

Valproic acid, or divalproex sodium, is recommended as a potential first-line agent for acute mania in both the CANMAT and BAP guidelines. Valproic acid seems particularly beneficial in patients presenting with a mixed presentation, as well as in those with several prior episodes, predominant irritable mood, and comorbid substance use (Yatham 2018; Goodwin 2016). Valproic acid is teratogenic and should be prescribed cautiously in women of childbearing age, given that it causes neural tube defects. Valproic acid can be used in combination with an SGA when clinically indicated. Table 7 contains details regarding monitoring and adverse effects of valproic acid.

TREATMENT OF BIPOLAR DEPRESSION

In this chapter, bipolar depression refers to a patient having an acute depressive episode, with a diagnosis of bipolar disorder. Patients with bipolar disorder are most likely to present in the ambulatory care setting during the depressive phase of bipolar disorder, or bipolar depression. It can be difficult to distinguish between a patient with unipolar depression (major depressive disorder with no history of mania) and a patient with bipolar depression, given that the only real difference lies in the history of previous manic episodes. As mentioned earlier, a thorough medical and social history should be taken, especially assessing for previous manic symptoms. However, in some scenarios, establishing the existence of previous manic symptoms may be difficult, given that patients themselves may not realize they have had previous manic symptoms, or they may not have the knowledge to realize their symptoms were indicative of a psychiatric condition. It is also possible that patients' first clinical presentation is in a depressive phase and that they have never had manic symptoms in the past.

Some features may be suggestive of bipolar disorder, which can help a clinician when deciding on treatment. These include an earlier onset of first depression (younger than 25 years), several prior depressive episodes (five or more episodes), positive family history of bipolar disorder, atypical depressive symptoms such as hypersomnia, increased appetite, and psychotic features (Schaffer 2010; Mitchell 2008).

Patients having a bipolar depressive episode must have symptoms for more than 2 weeks to meet the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria. For many patients with bipolar disorder, depressive symptoms are often present more consistently and can be more debilitating than symptoms of mania. Depressive episodes should be treated appropriately with a pharmacologic agent as discussed in the following sections. Once patients achieve remission of symptoms, they will require chronic treatment to prevent further episodes of either depression or mania. We will discuss treatment of this maintenance phase later. If a patient has a depressive episode while receiving maintenance treatment, the dosing and appropriateness of the treatment should be reevaluated.

Review of Guideline Recommendations for Bipolar Depression

See Table 2 for a review of the recommended treatment of bipolar depression in the different guidelines. The CANMAT guidelines recommend quetiapine, lurasidone plus lithium or divalproex, lithium monotherapy, lamotrigine, or lurasidone, in that order, for the treatment of bipolar depression. The

Table 6. Lithium Monitoring and Clinical Pearls

Laboratory Test Results	Monitoring Frequency						Therapeutic Concentration and Dose	Adverse Drug Reactions
	Baseline or initial visit	q1–2wk	q3mo	q6mo	Annually	At dose change		
BMP	X		X*	X^	X^		Lithium concentration: 0.4–1.2 mEq/L (ideally obtained at least 8–12 hr after the last dose because trough concentrations are preferred)	GI upset, confusion, polyuria/polydipsia, weight gain, muscle spasms, tremor, metallic taste, hypothyroidism, leukocytosis, alopecia, hypercalcemia (monitor in older patients and women)
CBC	X				X		Lithium concentration 4 or 5 days after initiation, any changes in dose, or addition of interacting drugs such as diuretics, ACEIs, or NSAIDs. Thereafter, monitor every 6–12 mo, or as clinically indicated	Serious: Lithium toxicity (ataxia, tremor, nausea, diarrhea, blurred vision, confusion, seizures, coma; can be lethal at > 3.5 mEq/L), renal impairment, nephrogenic diabetes insipidus
TSH	X			X	X		Starting: 300 mg BID Titration: Increase by 300 mg/wk Maintenance: 900–1800 mg/day divided BID/QID	
hCG	X						In general, an increase of 300 mg of lithium will result in an increase of 0.2 mEq/L	
ECG (age > 40 or CV risk factors)	X							
Lithium concentration	X	X		X		X		

X* = during first 6 mo of therapy or after significant drug changes; X^ = in stable patients.

BMP = basic metabolic panel; CV = cardiovascular; hCG = human chorionic gonadotropin; LFT = liver function test; q = every; QID = four times daily; TSH = thyroid-stimulating hormone.

recommendations are similar to those in the BAP guidelines, which also recommend SGAs – specifically quetiapine, lurasidone, and olanzapine. We will discuss preferential clinical scenarios for each drug in each section that follows; however, treatment selection should always be individualized on the basis of patient factors such as current and prior medication use and response, personal preference, and each medication's adverse effect profile.

SGAs in Bipolar Depression

Currently, four SGAs carry an FDA indication for the treatment of bipolar depression, as outlined in Table 4: cariprazine, lurasidone, quetiapine, and olanzapine. However, the indication for olanzapine requires coadministration with fluoxetine. Quetiapine and lurasidone are both recommended as first-line treatment in the BAP guidelines. In clinical trials, quetiapine 300 mg/day has had ideal efficacy in bipolar depression. An advantage of the SGAs approved for bipolar depression

Table 7. VPA Monitoring and Clinical Pearls

Laboratory Tests	Monitoring Frequency			Therapeutic Concentration and Dose	Adverse Drug Reactions
	Baseline	q3mo	q6mo		
CBC	X		X	VPA concentrations: 50–125 mcg/mL	GI upset, nausea, vomiting, sedation, dizziness, weight gain, tremors
LFTs	X	X[a]	X	Starting dose: divalproex ER 500 mg QHS (VPA 250 mg BID or TID)	Serious: Pancreatitis, hepatotoxicity, thrombocytopenia, ototoxicity, hyperammonemia (lethargy, mental status changes)
hCG	X			Titration: Increase by 250–500 mg/day every 2 or 3 days Maintenance: 750–3000 mg/day In mood disorders, VPA concentrations may not correlate with clinical efficacy, but do correlate with adverse effects. Ideally, trough concentrations should be obtained 4–7 days after initiation or dosage change Trough concentrations to be obtained before the morning dose. Obtain free concentrations if hypoalbuminemia	
VPA concentration	Not routinely monitored for efficacy in bipolar disorder; for safety, can be checked (range 50–125 mcg/mL)				

[a]During first 6 mo of therapy.
QHS = every night at bedtime; VPA = valproic acid.

is their relatively more rapid onset of action. Both quetiapine and lurasidone showed improvement in the first week compared with placebo in clinical trials. This may be advantageous in patients who require a rapid clinical response, such as patients who may be at an increased risk of suicide. In contrast, it may take significantly longer for lamotrigine to show an adequate response because of its titration schedule. Not all SGAs can be used equally in bipolar depression, and only SGAs with an FDA indication for the treatment of bipolar depression should be selected. Aripiprazole, which is commonly used as an adjunct therapy for major depressive disorder and is recommended by guidelines for the treatment of bipolar mania and bipolar maintenance, has data analyses showing it to be ineffective in bipolar depression. Because of this lack of positive response in clinical trials, as well as its adverse effect profile of akathisia, insomnia, and restlessness, aripiprazole is not recommended for use in bipolar depression (Thase 2008).

All SGAs carry a risk of causing or worsening metabolic syndrome and should therefore be used cautiously

in patients with existing diabetes or those with risk factors for developing diabetes. Baseline laboratory values, including fasting blood glucose, lipids, and weight, should ideally be obtained before initiating therapy and rechecked after 3 months. See Table 5 for more details on SGA monitoring (ADA 2004).

Patients taking SGAs should also be monitored for EPS, including akathisia. The incidence of EPS varies with each SGA, with lurasidone's package insert stating an incidence of akathisia of up to 22%, whereas quetiapine has an incidence of 5%. Patients should be monitored for signs and symptoms of akathisia during each visit. This can be assessed by asking the patient directly about these symptoms, as well as using the Barnes Akathisia Rating Scale. Other EPS include drug-induced tremors and pseudoparkinsonism, both of which tend to occur at higher dosages of SGAs. Risperidone is one of the SGAs with a higher incidence of tremors, particularly at higher dosages.

Patient-specific factors such as administration time and necessity of food should also be considered when selecting an SGA. Lurasidone and ziprasidone need to be taken with food for optimal absorption. More sedating SGAs such as quetiapine and olanzapine should be administered in the evening or at bedtime, particularly if the patient experiences significant sedation.

Lamotrigine in Bipolar Depression

Lamotrigine is recommended by both the CANMAT and BAP guidelines for the treatment of bipolar depression. Despite its lack of an FDA indication, lamotrigine has strong evidence for use in bipolar depression. Lamotrigine improves depressive symptoms in patients with bipolar disorder compared with placebo. Data analyses appear to point to a larger response for lamotrigine in patients with more severe baseline depressive symptoms (Geddes 2009). In addition, lamotrigine has been beneficial when used together with lithium or quetiapine in clinical trials (Young 2010; van der Loos 2009). These data, together with lamotrigine's favorable adverse effect profile, including minimal effect on weight and good tolerability, make it a first-line option in the guidelines.

One of lamotrigine's main limitations is the need for a slow and gradual titration schedule because of the risk of Stevens-Johnson syndrome (SJS), a severe skin reaction (Table 8). The recommended titration for lamotrigine starts at 25 mg daily for 2 weeks, increasing to 50 mg daily for 2 weeks, then 100 mg daily for 1 week, and then at week 6, it can be titrated to 200 mg daily, though it is also suggested to alternatively increase to 150 mg daily first for 1–2 weeks for tolerability. Because most patients with bipolar disorder require 100–200 mg daily of lamotrigine, it takes at least 4 weeks before even achieving a therapeutic dose. Doses exceeding 200 mg are not effective in bipolar disorder, though they are sometimes used for other indications.

Patients may already be taking valproic acid or carbamazepine when starting lamotrigine; therefore, drug interactions should be considered when initiating lamotrigine. A lower initial dose of lamotrigine, together with a different titration schedule, is recommended if a patient is taking lamotrigine and valproic acid concomitantly; conversely, a higher initial dose of lamotrigine is recommended for patients taking carbamazepine, phenytoin, or phenobarbital. Alternatively, if patients are taking lamotrigine concurrently with valproic acid or carbamazepine and either is discontinued, the lamotrigine dose should be adjusted accordingly.

In addition, estrogen-containing oral contraceptives decrease lamotrigine concentrations. Because lamotrigine does not have a narrow therapeutic window in the treatment of bipolar disorder, this interaction between oral contraceptives and lamotrigine concentrations may not have a large clinical effect; however, the patient's response should be considered (Ng 2009).

Because of the need for a gradual titration to avoid SJS, lamotrigine is not ideal in patients looking for faster symptomatic relief. In addition, the slow titration schedule makes lamotrigine less than ideal for use in acute mania, given that rapid stabilization is often needed in this setting. Because of the risk of SJS, if a patient misses more than 5 days of lamotrigine, the manufacturer recommends restarting the dose at 25 mg and titrating it to match the original titration schedule. Therefore, focusing on patient adherence is extremely important when counseling a patient taking lamotrigine.

Role of Antidepressants in Bipolar Depression

The role of antidepressants in the treatment of bipolar depression has evolved over time. Historically, it was thought that antidepressants should only be used in conjunction with a mood stabilizer in the treatment of bipolar depression, given that this would perhaps minimize the risk of switching a patient to a manic episode. However, in larger randomized controlled trials, adding an antidepressant to a mood stabilizer conferred no additional benefit, nor did the results show an increase in the risk of treatment-emergent affective switch (Sachs 2007).

Although historically, using antidepressants in bipolar disorder has not been considered clinically appropriate, data analyses support their use in certain clinical situations (Young 2000). These situations include patients with comorbid anxiety or other psychiatric conditions for whom antidepressant medications are effective (Ott 2018). In epidemiologic studies, patients with bipolar disorder have a 3-fold increase in anxiety disorders compared with the general population, with a lifetime prevalence of 75% (Pavlova 2015; Merikangas 2007). This points to the degree of comorbidity between anxiety disorders and bipolar disorder and the complexity of treating both disorders at the same time.

Patients with bipolar disorder may report a prior response to a certain antidepressant; therefore, antidepressants can be considered for these patients. The guidelines mirror these

Table 8. Lamotrigine Monitoring and Clinical Pearls

Laboratory Tests	Monitoring Frequency		Therapeutic Concentration and Dose	Adverse Drug Reactions
	Baseline	Annually		
BMP	X	X	Drug concentrations not routinely monitored	Rash, sedation, vision changes (blurry, double), dizziness, headache, tremor, insomnia, fatigue, nausea, vomiting, GI upset, poor coordination
LFTs	X	X	**Specific titration to avoid SJS (must be followed):** 25 mg daily × 2 wk 50 mg daily × 2 wk 100 mg daily × 1 wk 200 mg daily thereafter	Serious: SJS, toxic epidermal necrolysis
			Drug interactions: With VPA, start at a **lower** lamotrigine dose (25 mg QOD)	Most life-threatening rashes occur in the first 2–8 wk of starting treatment
			With **carbamazepine**, use a **higher** lamotrigine dose (50 mg/day). **Follow specific instructions in package insert**	

BMP = basic metabolic panel; LFT = liver function test; QOD = every other day; SJS = Stevens-Johnson syndrome; VPA = valproic acid.

recommendations. If antidepressants are used for bipolar depression, they should be used as an adjunct to other mood stabilizers or SGAs.

When prescribing an antidepressant, the risk of switching to a manic episode should be considered. Data analyses show that although there may be an increased risk when using antidepressants as monotherapy in bipolar depression (HR 2.83; CI, 1.12, 7.19), there does not appear to be an increased risk of treatment-emergent affective switch when antidepressants are used in conjunction with a mood stabilizer (Viktorin 2014; Sachs 2007). In fact, a large study using the Swedish national registry showed no increased risk of switching to mania during the first 3 months of treatment when antidepressants were used in conjunction with mood stabilizers, and there was a decreased risk of switching to mania during months 3–9 of treatment (Viktorin 2014). Caution should still be used when prescribing antidepressants to patients with bipolar disorder and should ideally only be done in conjunction with a mood stabilizer. Data analyses point to selective serotonin reuptake inhibitors and bupropion having a lower risk of treatment-emergent switch than serotonin-norepinephrine reuptake inhibitors such as venlafaxine (Leverich 2006).

Role of Lithium in Bipolar Depression

Lithium is recommended as a first-line treatment for bipolar depression in the CANMAT guidelines and as a second-line option in the BAP guidelines. Lithium has good efficacy in bipolar depression and decreases suicide risk. Studies have shown about a 10% reduction in suicide attempts and about a 20% reduction in deaths by suicide (Benard 2016). The CANMAT guidelines recommend that if lithium is used, a trough lithium concentration of 0.8–1.2 mEq/L should be targeted. However, intolerability, drug-drug interactions, and therapeutic drug monitoring, together with its narrow therapeutic window, may potentially make lithium less than ideal for some patients.

In pregnancy, lithium can cause a congenital heart defect, particularly with exposure in the first trimester, known as Ebstein anomaly. However, the absolute risk of Ebstein anomaly is considered minimal, and experts recommend that treatment not be withheld solely because of this concern if lithium is the most suitable medication for the patient. For planned pregnancies, it is safest to avoid the use of lithium during the first trimester, if possible. Because of physiologic changes during pregnancy, pregnant women may require more frequent therapeutic concentration monitoring (Larsen 2015).

MAINTENANCE TREATMENT OF BIPOLAR DISORDER

Once patients have been stabilized from either acute mania or a depressive episode, they enter the maintenance phase of treatment. In this phase, the main goal of therapy is to prevent either a manic episode or a depressive episode. This differs from in the acute phases of bipolar disorder, in which the goal of therapy is to control the current symptoms of either mania or depression.

Review of Guideline Recommendations for Bipolar Maintenance

See Table 3 for an outline of the recommended treatments for bipolar maintenance. Most treatment options are monotherapy with SGAs or other mood stabilizers. As much as possible, clinicians should strive for this goal of monotherapy for the maintenance of bipolar disorder because it will decrease the potential of adverse effects and cost and help patients adhere to treatment. Once a patient is in the maintenance treatment phase, adherence to and tolerability of medications should be emphasized because patients will require chronic treatment to prevent future manic or depressive episodes. Patients may require lower dosages of the medications used during their manic or depressive phase. Some data analyses suggest that a lower lithium concentration of 0.6–0.8 mEq/L is adequate for some patients during bipolar maintenance (Malhi 2017). Clinicians should use judgment and weigh the risk of adverse effects from medications to avoid the risk of a psychiatric relapse.

Considerations in the Older Population During Maintenance Phase

In older adult patients, the potential for worsening chronic conditions should be considered when selecting medications for bipolar disorder. For example, SGAs may worsen preexisting type 2 diabetes or Parkinson disease. If an SGA is needed in a patient with Parkinson disease, quetiapine is the best choice because of its low binding affinity for dopamine receptors. Table 5 highlights which SGAs carry a higher risk of worsening metabolic conditions. This information should be considered when selecting an SGA in a patient at risk of diabetes.

In older adults who are already prone to chronic kidney disease, lithium should be used cautiously. This is particularly true in patients with already existing diminished renal function, given that lithium is eliminated entirely by the kidneys. Lithium should be initiated at a low dose and slowly titrated in patients with a CrCl of 30–80 mL/minute/1.73 m^2. Lithium is not recommended in patients with a CrCl less than 30 mL/minute/1.73 m^2. After long-term chronic use, lithium causes hypothyroidism and nephrogenic diabetes insipidus. In older adults, it may be prudent to monitor lithium concentration and renal functioning every 3 months instead of every 6 months (Rej 2018). In addition, if a clinician observes a change in a patient's renal function, a lithium concentration should be reassessed, since these two laboratory values are closely related.

In older adults, a lower goal for therapeutic lithium drug concentrations may also be reasonable. One study suggests that a lithium concentration of 0.8–1.0 mEq/L is adequate in the treatment of bipolar mania in older adults (Young 2017). Although this is a very narrow window, the results of this study point to the potentially unnecessary higher therapeutic window of up to 1.2 mEq/L. As mentioned earlier, data analyses also support a lower lithium concentration during the maintenance phase of 0.6–0.8 mEq/L (Malhi 2017).

Valproic acid and derivatives do not require renal adjustment. However, valproic acid is not recommended in mild to moderate hepatic disease and is contraindicated in severe hepatic impairment. The lamotrigine package insert states that no dose adjustment is needed in renal disease, but simply that decreased dosages may be sufficient and effective. There are some recommendations to decrease the dosage in moderate to severe hepatic impairment. Overall, lamotrigine may be safer in older adult patients with complicating comorbidities.

Drug-drug interactions should also be considered when selecting agents for patients with bipolar disorder. Drug-drug interactions should be considered in all treatment stages, but this is particularly important when considering a medication that a patient may be taking chronically for maintenance. Lithium is prone to many drug-drug interactions with agents commonly used in older populations, such as ACEIs, ARBs, and thiazide diuretics. All three of these common antihypertensive agents can increase lithium concentrations. Therefore, extreme caution should be taken and monitoring done when adding or removing these agents because of their impact on lithium concentrations. In addition, NSAIDs can increase lithium concentrations. Because NSAIDs can easily be purchased OTC and are often taken chronically by older patients, proper counseling should be provided. Because of lithium's narrow therapeutic index, drug-drug interactions can significantly change lithium concentrations. Valproic acid can cause protein-binding interactions as well as CYP2C9 inhibition, which can be significant in older adults. One interaction of this type is with warfarin, in which the combination of valproic acid and warfarin can cause a supratherapeutic INR. Valproic acid also has a drug-drug interaction with lamotrigine, in which valproic acid increases lamotrigine concentrations through inhibition of glucuronidation. Lamotrigine undergoes metabolism through glucuronidation and is therefore prone to drug-drug interactions with phenytoin, lopinavir, ritonavir, carbamazepine, and phenobarbital (Ng 2009). Although we did not discuss carbamazepine in detail, carbamazepine is recommended by both the CANMAT and BAP guidelines as a second-line agent for

Patient Care Scenario

A 67-year-old man (height 68 inches, weight 79 kg [175 lb]) presents to your primary care clinic after a recent discharge from the hospital. His home drugs before admission included metoprolol succinate 50 mg by mouth daily, aspirin 81 mg by mouth daily, losartan 100 mg by mouth daily, amlodipine 5 mg by mouth daily, tamsulosin 0.4 mg by mouth daily, metformin 1000 mg by mouth twice daily, dulaglutide 1.5 mg subcutaneously weekly, and venlafaxine XR 150 mg by mouth daily.

The hospital summary notes that the patient brought himself to the hospital because he was experiencing chest pain and had not slept for several days. His wife had been out of town for a week, which resulted in poor self-care and reduced oral intake. He had reportedly stopped all medications during the previous 14 days because he stated on admission that he did not want to take them on an empty stomach. He also noted that he was sleeping less and staying up late to read the news. During hospitalization, he was argumentative with the staff and hyperverbal and had grandiose behaviors. During his hospital stay, he was reinitiated on his home medications, as well as quetiapine 150 mg twice daily. His home medications and quetiapine were continued at discharge.

Today, 3 weeks after hospital discharge, he has fatigue and increased appetite. He reports that his fasting blood glucose readings have been elevated this past week (range 130–180 mg/dL). His symptoms reported during hospitalization appear to have resolved. Although the patient reports having similar symptoms when he was in his 40s and 50s, they had not happened for a "long time." He states that he has depression most of the time, which is why he takes an antidepressant. However, he admits he does not feel the venlafaxine works well because he often still has bouts of depression. The patient's laboratory values from 1 month ago, before hospital admission, were as follows: A1C 7.2%, SCr 1.4 mg/dL, AST 20 U/L, and ALT 25 U/L. His weight is now 77 kg (170 lb). What changes could be made to address the patient's concern while preventing the episodes that led to his hospitalization?

ANSWER:

The patient appears to report previous manic symptoms several years ago but endorses recent depressive symptoms. This is not unusual for patients with bipolar disorder because they will spend significantly more time experiencing depressive symptoms than manic symptoms. According to patient reports, he still has "bouts of depression" despite taking venlafaxine. The lack of adequate response to venlafaxine, together with his previous manic symptoms, clearly shows the need for a mood stabilizer instead of an antidepressant. This lack of response to an antidepressant, as well as his presenting symptoms and psychiatric history, point to a possible bipolar disorder diagnosis.

Because this patient was not having an adequate response to venlafaxine but the agent was reinitiated in the hospital, it would be reasonable to taper off venlafaxine. A slow taper is reasonable because the patient has been taking venlafaxine for many years and is likely to have withdrawal symptoms if it is discontinued abruptly. In fact, his abrupt discontinuation of all of his medications may have contributed to this manic episode because this phenomenon has been discussed in the literature.

The events leading to his hospitalization indicate a more recent acute manic episode. As such, he was appropriately initiated on treatment for an acute manic episode while an inpatient. Without a clear history of recent or past mood stabilizer use before hospitalization and with the clear need for a mood stabilizer, quetiapine was continued at discharge to serve in this capacity.

Although quetiapine is an adequate medication for maintenance treatment of bipolar disorder, this patient now has increased sedation and increased appetite, as well as blood glucose elevations. Treatment options at this time are as follows.

- Changing quetiapine to a different SGA for bipolar maintenance and with a lower risk of worsening metabolic syndrome. These other SGAs include aripiprazole and asenapine. The patient should be monitored for any additional changes in his glucose concentration and weight. Both aripiprazole and asenapine can also cause significant akathisia. The patient should be monitored for signs and symptoms of akathisia.
- Changing to lamotrigine. Lamotrigine is relatively well tolerated, is recommended for bipolar maintenance, and has a low potential for drug interactions as well as a low rate of metabolic adverse effects.
- Changing to valproic acid. Although valproic acid is a first-line agent and the patient has no contraindications, the potential for weight gain, drug interactions, and tolerability issues may limit its use.
- Changing to lithium. However, lithium would not be ideal at this time because of the patient's renal function, as well as a drug-drug interaction with losartan.

1. Ng F, Mammen OK, Wilting I, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord 2009;11:559-95.
2. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20:97-170.
3. Narayan V, Haddad PM. Antidepressant discontinuation manic states: a critical review of the literature and suggested diagnostic criteria. J Psychopharmacol 2011;25:306-13.

Patient Care Scenario

A 55-year-old woman presents to the primary care clinic with ongoing symptoms of depression. She states that, almost every day, she feels a lack of motivation and desire to do anything. She also reports feeling sad and is tearful during the visit. She is accompanied by her husband, who states that she has hardly gotten out of bed the past few weeks. They report that the symptoms of depression have been ongoing for about 3 months but have gotten worse over the past month. She has had a diagnosis of bipolar disorder since she was in her 20s.

She reports having taken medications on and off since then and, most recently, has taken lamotrigine 200 mg by mouth daily for the past 5 years. During these 5 years, she has occasionally had some symptoms of depression, but they had never been this severe or lasted this long. Another clinician prescribed aripiprazole for her about a month ago. However, the patient has not responded, and she has mild symptoms of akathisia. Her current psychiatric medications are lamotrigine 200 mg by mouth daily and aripiprazole 15 mg by mouth daily. Other medications include lisinopril 20 mg by mouth daily and atorvastatin 10 mg by mouth daily. Her renal and liver function are within normal limits and stable. What would be the best pharmacologic approach to treating this patient's current bipolar depression?

ANSWER:

The patient is not currently being treated appropriately for bipolar depression. She has taken lamotrigine 200 mg daily for many years for bipolar maintenance and was relatively well controlled until the past 3 months, when she had a relapse of depressive symptoms. The other clinician's choice to add aripiprazole was inappropriate because aripiprazole has no evidence to support its use in bipolar depression. Aripiprazole should be discontinued and another medication initiated in its place. There is no need to taper aripiprazole because the patient has not been taking it very long. In addition, she is experiencing akathisia, and aripiprazole is not currently providing any psychiatric benefit for the patient; therefore, another medication should be initiated in its place.

The decision to add on another medication to lamotrigine or change to a different medication can be challenging in this scenario. Ideally, a new agent will be added on, and if the patient responds, lamotrigine can begin to be tapered and patient response can be assessed. Changing lamotrigine is not preferred because response is not guaranteed from the new agent; therefore, whatever effectiveness the patient was experiencing psychiatrically from lamotrigine may be lost. Appropriate treatment options for this patient include:

- Adding quetiapine XR 50 mg once daily and titrating it to a usual target dose of 300 mg daily. Although the package insert states that 300 mg can be reached by day 7, patients often need a longer titration because of intolerability, mainly sedation. However, the XR formulation of quetiapine generally causes less sedation than the immediate-release formulation. Quetiapine would be a good addition for this patient because it is indicated for bipolar depression and could improve the patient's symptoms within a few weeks.
- Adding lithium 300 mg twice daily, assessing a lithium concentration in 4 or 5 days, and adjusting the dose accordingly. Lithium is recommended by both the CANMAT and BAP guidelines in the treatment of bipolar depression. The patient has no contraindications to lithium treatment. However, lithium requires more monitoring, and this patient is taking an ACEI, which could cause higher lithium concentrations. Higher lithium concentrations could be accounted for after the first lithium concentration is obtained and adjusted accordingly.
- Adding lurasidone 20 mg once daily and titrating it every week up to 120 mg/day. This would be equivalent to quetiapine as far as efficacy but would have a different adverse effect profile. Although lurasidone has less sedation than quetiapine, its incidence of akathisia is similar to that of aripiprazole, which the patient could not tolerate because of akathisia. Lurasidone carries a lower risk of metabolic adverse effects, which could be favorable for this patient.

All of these options are reasonable for this patient. Ideally, the patient should be consulted and involved in the treatment decision to improve medication adherence. She should be informed of the risk-benefit of each treatment option and allowed to have input on the final decision.

1. Finley PR. Drug interactions with lithium: an update. Clin Pharmacokinet 2016;55:925-41.
2. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20:97-170.

Patient Care Scenario

A 59-year-old woman who has been cared for by pharmacy services for chronic disease state management for several years arrives for a routine follow-up. At this visit, her hands and forearms are trembling, particularly when she reaches into her bag to get her medication vials. When the pharmacist mentions the tremors to her, she states that she also began noticing them about 2 months ago and that some of her friends have mentioned them as well.

Her current medications include insulin glargine 40 units subcutaneously once daily, risperidone 2 mg by mouth in the morning and 4 mg in the evening, amlodipine 10 mg by mouth once daily, exenatide 10 mcg subcutaneously twice daily, metformin 1000 mg by mouth twice daily, and atorvastatin 80 mg by mouth once daily. Her diabetes is well controlled, with a current A1C of 6.4%. Her A1C has been consistently below 7% for the past 2 years. She is overweight with a current BMI of 29.8 kg/m^2. Her bipolar disorder has been stable longer than the pharmacist has known her. She established care in this clinic over 5 years ago and was already taking the same dose of risperidone at that time. She has not had any depressive or manic episodes since being a patient of this clinic. The care team assesses that the tremor is drug induced from risperidone and would like a recommendation from the pharmacist on the best plan of action to keep her psychiatrically stable.

ANSWER:

Extrapyramidal symptoms occur with SGAs. Drug-induced tremors are particularly common with risperidone at the higher doses this patient is taking. Although the tremor could be treated with a medication such as an oral benztropine, this treatment might not be ideal because it could cause additional adverse effects. Anticholinergics used to treat EPS can cause significant adverse effects of constipation, dry mouth, sedation, and confusion, which can be particularly troublesome in the older adult population. Additional treatment options for this patient include:

- **Reducing the dose of risperidone. Her current dose of 6 mg/day is at the maximal recommended daily dose. The risperidone dose could be tapered slowly by 0.5 mg to 1 mg per month, and she could be reassessed at each visit for relapse of psychiatric symptoms as well as for improvement in tremor. Potentially, even a small reduction in risperidone to 4 mg/day could reduce the tremors without compromising her psychiatric symptoms.**
- **Changing to a different mood stabilizer that has good efficacy in bipolar maintenance and has a lower incidence of drug-induced tremors. Quetiapine, asenapine, aripiprazole, and lamotrigine are reasonable options. Quetiapine causes the fewest EPS of the SGAs. Although aripiprazole and asenapine do not have a high incidence of drug-induced tremors, they can cause akathisia. All SGAs carry a risk of worsening a patient's diabetes control. Lamotrigine could be ideal because it does not cause EPS; also, it is recommended by the guidelines for bipolar maintenance and has no significant drug-drug or drug-disease interactions in this patient scenario.**

If a patient is changed to a different mood stabilizer, a cross-taper should be performed. Ideally, the new mood stabilizer should be initiated and titrated to an effective dose at the same time as the outgoing mood stabilizer is being tapered. A helpful online tool for treating these types of clinical scenarios is available at www.switchrx.com.

1. Grande I, Bernardo M, Bobes J, et al. Antipsychotics switching in bipolar disorder: a systematic review. Int J Neuropsychopharmacol 2014;17:497-507.
2. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20:97-170.

bipolar mania and bipolar maintenance. Carbamazepine is also prone to drug-drug interactions as a CYP inducer.

CONCLUSION

Bipolar disorder is a chronic condition with three distinct phases: mania, depression, and maintenance. Clinicians in the ambulatory care setting are most likely to encounter patients in the depressive phase of bipolar disorder. The clinical presentation of bipolar depression does not differ from unipolar presentation, except for the prior history of manic symptoms. Therefore, it is important that clinicians conduct a thorough interview to assess for prior psychiatric history.

The CANMAT and BAP guidelines highlight the different medications used in the three different phases of bipolar disorder. See Tables 1–3 for a review of the medications used in these three phases. In general, the SGAs play a role in the treatment of all phases of bipolar disorder, though only cariprazine, lurasidone, olanzapine, and quetiapine have indications for bipolar depression. See Table 4 for a review of the FDA indications of all the medications discussed in this chapter. Other mood stabilizers, such as lithium, valproic acid, and lamotrigine, also play a role in the treatment of bipolar disorder.

Clinicians should also be aware of how to treat the maintenance phase of bipolar disorder, given that this could be particularly important in the older adult population because of drug-drug and drug-disease state interactions. Although mania is not as common in the ambulatory care setting or in the older adult population, clinicians should still be aware of its presentation, as well as potential contributing factors, such as medications that may cause drug-induced mania. Clinicians

Practice Points

- **Bipolar disorder is a psychiatric condition that often requires lifelong treatment. Each phase of the disorder (mania, depression, and maintenance) is approached differently, and different drugs are effective for different phases.**
- **Bipolar depression does not differ in presentation from unipolar depression, but treatment is different. The SGAs quetiapine, olanzapine, cariprazine, and lurasidone all have FDA indications for the treatment of bipolar depression.**
- **A thorough history-taking is crucial to properly assess for bipolar disorder. The MDQ is a valuable tool that can be used in the ambulatory care setting.**
- **In older populations presenting with a first onset of manic or depressive symptoms, other causes should be ruled out, including drug-induced mood symptoms.**
- **Patient-specific factors, such as other comorbid medical conditions, drug-drug interactions, and personal preferences, should be considered when selecting an agent for long-term maintenance treatment of bipolar disorder.**

should consider drug-drug interactions and comorbid conditions, particularly in older patients. This is important in all phases of bipolar disorder, but even more so in the maintenance phase, given that patients often require lifelong therapy.

REFERENCES

American Diabetes Association (ADA), American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care 2004;27:596-601.

American Psychiatric Association (APA). Bipolar and related disorders. In: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: APA, 2013. Accessed June 11, 2020.

Benard V, Vaiva G, Masson M, et al. Lithium and suicide prevention in bipolar disorder. Encephale 2016;42:234-41.

Buoli M, Esposito CM, Godio M, et al. Have antipsychotics a different speed of action in the acute treatment of mania? A single-blind comparative study. J Psychopharmacol 2017;31:1537-43.

Celano CM, Freudenreich O, Fernandez-Robles C, et al. Depressogenic effects of medications: a review. Dialogues Clin Neurosci 2011;13:109-25.

Dome P, Rihmer Z, Gonda X. Suicide risk in bipolar disorder: a brief review. Medicina (Kaunas) 2019;55:403.

Finley PR. Drug interactions with lithium: an update. Clin Pharmacokinet 2016;55:925-41.

Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br J Psychiatry 2009;194:4-9.

Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016;30:495-553.

Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530-7.

Keck PE, Orsulak PJ, Cutler AJ, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. J Affect Disord 2009;112:36-49.

Larsen ER, Damkier P, Pedersen LH, et al. Use of psychotropics drugs during pregnancy and breast-feeding. Acta Psychiatr Scand Suppl 2015;445:1-28.

Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006;163:232-9.

Malhi GS, Gessler D, Outhred T. The use of lithium for the treatment of bipolar disorder: recommendations from clinical practice guidelines. J Affect Disord 2017;217:266-80.

Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64:543-52.

Mitchell PB, Goodwin GM, Johnson GF, et al. Diagnostic guidelines for bipolar depression: a probabilistic approach. Bipolar Disord 2008;10:144-52.

Ng F, Mammen OK, Wilting I, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord 2009;11:559-95.

Ott CA. Treatment of anxiety disorders in patients with comorbid bipolar disorder. Ment Health Clin [Internet]. 2018;8:256-63.

Pavlova B, Perlis RH, Alda M, et al. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry 2015;2:710-7.

Rej S, Herrrmann N, Gruneir A, et al. Blood lithium monitoring practices in a population-based sample of older adults. J Clin Psychiatry 2018;79:17m12095

Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007;356:1711-22.

Schaffer A, Cairney J, Veldhuizen S, et al. A population-based analysis of distinguishers of bipolar disorder from major depressive disorder. J Affect Disord 2010;125:103-10.

Skjelstad DV, Malt UF, Holte A. Symptoms and signs of the initial prodrome of bipolar disorder: a systematic review. J Affect Disord 2010;126:1-13.

Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol 2008;28:13-20.

van der Loos MLM, Mulder PGH, Hartong EGTM, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:223-31.

Viktorin A, Lichtenstein P, Thase ME, et al. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry 2014;171:1067-73.

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20:97-170.

Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry 2010;71:150-62.

Young LT, Joffe RT, Robb JC, et al. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry 2000;157:124-6.

Young RC, Mulsant BH, Sajatovic M, et al. GERI-BD: a randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. Am J Psychiatry 2017;174:1086-93.

Self-Assessment Questions

1. A woman with recently diagnosed bipolar disorder worries about her prognosis. She would like to know what to expect from her new diagnosis. Which one of the following symptoms is this patient most likely to experience for a greater percentage of her lifetime?

   A. Sadness
   B. Euphoria
   C. Psychosis
   D. Grandiosity

2. A 65-year-old man presents with symptoms of decreased motivation, trouble sleeping, depressed mood, and irritability over the past month. His significant other states that the patient has had symptoms like this since he was in his 20s and 30s and is concerned that he may have an undiagnosed bipolar disorder. Which one of the following screening tools would best assess for previous symptoms of mania in this patient?

   A. Patient Health Questionnaire-9
   B. Mood Disorder Questionnaire (MDQ)
   C. Abnormal Involuntary Movement Scale (AIMS)
   D. Mini-Mental State Examination

3. A 55-year-old man presents with acute manic symptoms. He is hyperverbal and has not slept in 3 days. The patient has good insight and is aware of his need for medications. He and his wife have come to their primary care clinic in hopes of starting a medication that works quickly and helps avoid a hospitalization. His current home drugs include carvedilol 6.25 mg twice daily, lisinopril 20 mg once daily, spironolactone 25 mg daily, ranitidine 150 mg twice daily, and aspirin 81 mg daily. Which one of the following is best to recommend initiating for this patient?

   A. Lithium 300 mg twice daily
   B. Divalproex sodium 250 mg once daily
   C. Asenapine 10 mg twice daily
   D. Lamotrigine titrated according to the package insert

4. A woman is seeking treatment for bipolar depression. She states that several trials of antidepressants have failed and that she would like to try "something different." Her main concerns are weight gain and worsening of her type 2 diabetes. Which one of the following is best to recommend for this patient?

   A. Quetiapine
   B. Lurasidone
   C. Lithium
   D. Lamotrigine

5. A 60-year-old man is being treated in your clinic for bipolar disorder. The disorder was first diagnosed when he was age 20, and he has had several episodes requiring medical intervention throughout his life. He claims to always have responded quickly to medications. He is currently maintained on quetiapine 300 mg daily. He denies ever having any psychotic symptoms during his manic episodes and denies any comorbid substance use. Which one of the following patient factors makes most increases this patient's risk of recurring bipolar disorder episodes?

   A. Younger age at onset
   B. Lack of psychotic features
   C. No history of substance use
   D. Quick response to medications

6. A 64-year-old man presents with mania for the first time. His partner reports that these symptoms began abruptly and are out of character for him. His medical history is significant for HIV, multiple sclerosis, hypertension, and coronary artery disease. The psychiatrist asks for your help in ruling out other possible causes of mania in this patient. Which one of the following would be best to rule out in this patient?

   A. Hypothyroidism
   B. Neurosyphilis
   C. Interferon-induced mania
   D. Efavirenz-induced mania

7. A 62-year-old woman has been well controlled psychiatrically on lithium 900 mg/day for several years. Her primary care provider is concerned about her many comorbidities, which include hypothyroidism (TSH 1.2 mU/L), type 2 diabetes (A1C 8.8%), hypertension (last blood pressure 128/78 mm Hg), osteoarthritis, gastroesophageal reflux disease, and nonalcoholic fatty liver disease. Her lithium concentration is 0.4 mEq/L. Which one of the following is best to recommend for this patient?

   A. Continue the current lithium dose.
   B. Decrease the lithium dose to 600 mg/day.
   C. Change to quetiapine.
   D. Change to lamotrigine.

8. A 55-year-old woman has been stable on lithium for bipolar disorder. She recently developed hypertension, and her primary care provider would like to initiate an antihypertensive. Which one of the following antihypertensives would be the most compatible for this patient while taking lithium?

   A. Lisinopril
   B. Hydrochlorothiazide
   C. Amlodipine
   D. Spironolactone

9. A 62-year-old man is brought to the ED by his spouse after not having slept for several days. She reports that he has been staying up all night working in the garage, which is unusual for him. Today, he began to talk about seeing people walking across the house that she did not see. Which one of the following most likely precipitated this patient's symptoms?

    A. Prednisone 50 mg by mouth daily
    B. Temazepam 30 mg daily by mouth at bedtime
    C. Aripiprazole 15 mg by mouth daily
    D. Zonisamide 50 mg by mouth twice daily

10. A 50-year-old man is brought in by his partner with symptoms of grandiosity, elated mood, and rapid speech, and he has not slept for 3 days. He is not currently taking any medications but reports having taken a psychotropic before, whose name he cannot recall. His partner states that the patient has not had symptoms like this for many years. The couple is trying to avoid hospitalization and would like a medication that works quickly in hopes of avoiding a trip to the hospital. The patient's medical history is significant for hypertension, hypertriglyceridemia, and obesity. Which one of the following is the best initial treatment to recommend for this patient?

    A. Fluoxetine 10 mg daily
    B. Lamotrigine 25 mg daily
    C. Asenapine 5 mg twice daily
    D. Olanzapine 10 mg daily

11. A 55-year-old man is transitioning to divalproex sodium for bipolar maintenance because of intolerability to his previous medications. The psychiatrist asks for the pharmacist's advice on how best to monitor this patient. Which one of the following laboratory values is best to obtain at baseline for this patient?

    A. TSH
    B. SCr
    C. Fasting blood glucose
    D. LFTs

12. A patient presents to your clinic for the treatment of depression. She has several symptoms, including a depressed mood, loss of interest in activities, decreased energy, and passive suicidal ideations. She does not report any past symptoms of mania. Which one of the following is most suggestive of bipolar disorder in this patient?

    A. Two prior depressive episodes
    B. Decreased appetite
    C. Age younger than 25 at first onset of symptoms
    D. Absence of psychotic features

13. A 56-year-old man with a longstanding history of bipolar disorder comes to your clinic with current depressive symptoms. He takes divalproex sodium 500 mg twice daily (valproic acid concentration 102 mcg/mL). The patient reports good adherence to this medication. He has taken divalproex sodium for several years and tolerates it well. He has not tried other medications in the past. He is feeling very depressed and has not slept for several days. He is feeling anxious because of these symptoms and would like something that works relatively quickly. Which one of the following is best to recommend adding to this patient's regimen?

    A. Aripiprazole
    B. Quetiapine
    C. Lamotrigine
    D. Lithium

14. A patient presents with symptoms of decreased energy, decrease appetite, inability to sleep for more than a few hours despite wanting to sleep, sadness, and irritability. He reports these symptoms have been occurring for the past month and were preceded by a period of mania. He is currently having suicidal ideations, which are very bothersome to him. He reports a prior suicide attempt about 5 years ago. He is not currently taking any other medications and has a nonsignificant medical history. Which one of the following is best to recommend for this patient?

    A. Lamotrigine
    B. Lithium
    C. Divalproex
    D. Aripiprazole

15. An older woman with a longstanding history of bipolar disorder has been maintained on lithium 300 mg twice daily for several years. However, in the past few years, her renal function has declined to a CrCl of 25 mL/minute/1.73 m^2. She tried aripiprazole in the past but developed significant akathisia. She has also tried quetiapine, but she gained too much weight with it and felt tired all the time. Her other medications include warfarin 2.5 mg daily, lisinopril 10 mg daily, and amlodipine 5 mg daily. Which one of the following is best to recommend for this patient?

    A. Decrease the lithium dose.
    B. Change lithium to valproic acid.
    C. Change lithium to lamotrigine.
    D. Change lithium to lurasidone.