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Geriatric Disorders (D Steffens and K Zdanys, Section Editors)

# Pharmacological Treatment of Bipolar Disorder in the Elderly

*Tamar C. Katz, MD, PhD*[1]
*Joanna Georgakas, , B.A.*[2]
*Claire Motyl, , B.A.*[3]
*William Quayle, , B.A.*[3]
*Brent P. Forester, MD, MSc*[4,*]

**Address**
[1]Adult Psychiatry Residency Program, PGY4, Massachusetts General Hospital/ McLean Hospital, Belmont, MA, USA
[2]Geriatric Psychiatry Research Program, McLean Hospital, Harvard Medical School, Boston, MA, USA
[3]Geriatric Psychiatry Research Program, McLean Hospital, Harvard Medical School, Belmont, MA, USA
[*,4]Division of Geriatric Psychiatry, McLean Hospital, 115 Mill Street, Belmont, MA, 02478, USA
Email: brentforester5@gmail.com

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## Opinion Statement

Due to the early age of onset, bipolar disorder is most commonly studied in younger adults, among whom the prevalence is 3.9% in adults aged 18–30 years. Unfortunately, relatively less attention has been paid to the unique needs of older adults with bipolar disorder (OABD), despite clinical complexities that include medical comorbidity, polypharmacy, cognitive decline, and phase of life losses of occupation and social identity. Furthermore, impaired cognitive performance in some older adults may limit the ability to stabilize mood episodes and interfere with the individual's engagement in multi-modal treatment. Many OABD may also struggle with impairments in their independent activities of daily living (IADLs) which can lead to greater psychiatric, medical, psychological, financial, or social sequelae of mood episodes. Further complicating this picture is the fact that most OABD are treated by general psychiatrists or family practitioners due to a worldwide shortage of geriatric psychiatrists. This will become increasingly common as the mean life expectancy continues to increase. It is therefore incumbent on all general practitioners to understand the phases of bipolar disorder and the associated treatment options throughout the lifespan. Treatment of manic or depressive episodes focuses on

symptomatic remission primarily through pharmacotherapy and neurotherapeutics. Management of the maintenance phase focuses on optimizing pharmacotherapy while reducing subclinical symptoms, treating comorbid illness, preventing relapse, and restoring psychosocial functioning and intacts identity through multimodal approaches including psychopharmacology, psychotherapy, diet, and lifestyle modifications. Comprehensive care for OABD is best achieved through close collaboration with the affected individual, the family physician, pharmacist, family members, and social supports.

## Introduction

Despite the extensive body of literature on bipolar disorder, there are few studies that focus specifically on the management of the illness in the geriatric population. To date, there are no published randomized controlled trials (RCTs) that specifically address the treatment of mania, bipolar depression, or maintenance therapy in geriatric cohorts. The International Society for Bipolar Disorders published its first report on older age Bipolar Disorder as recently as 2015 [1••]. Treatment guidelines extrapolated from younger cohorts often fail to consider the unique vulnerabilities of the geriatric population, among them are the following: higher rates of comorbid illness, polypharmacy, increased vulnerability to medication effects, changes in metabolism and metabolic clearance, increased risk of cognitive decline and loss of cerebral tissue volume, difficulty with ADLs, and the long- term effects of bipolar medications on the brain and on general health. Furthermore, among older adults, depressive episodes are more common than manic episodes as the illness progresses, thereby impacting acute management and maintenance medication treatment.

An improved understanding of treating OABD is increasingly important as the prevalence of bipolar disorder in older adults increases worldwide, both in absolute numbers and as a percentage of the general population. The number of persons over age 60 has tripled over the past 50 years and is expected to more than triple again over the next 50 years. According to the International Society for Bipolar Disorders, by 2030, the population over age 60 will grow 3.5 times more rapidly than the general population [1••, 2]. The expected increase in prevalence of OABD will precipitate greater symptom burden among older adults as well as greater systems wide health care costs.

A diagnosis of bipolar disorder currently is associated with 6% of geriatric outpatient visits, 8–10% of geriatric inpatient admissions, and 17% of geriatric psychiatric emergency visits [3, 4]. Bipolar disorder persists well past the sixth decade in many patients, with a prevalence in older adults estimated to be close to 1% [4, 5], or as much as 25% of the population with bipolar disorder [6]. This figure represents a compilation of those with early onset bipolar disorder (primary mania) as well as a late onset variant (secondary mania). Secondary mania, occurring in approximately 10% of OABD [5], is characterized by later onset of first manic episode (in the fifth decade or beyond) and is usually driven by an underlying medical cause. The distinction between primary and secondary mania is an important one as it raises potential differences in pathogenesis and treatment response. Individuals with secondary mania are less likely to have a family history of bipolar disorder and are generally less responsive to lithium [1••]. For all types of bipolar mania, comprehensive treatment involves psychopharmacologic interventions typically with both a mood stabilizer and an atypical antipsychotic. Neurotherapeutic approaches, diet and lifestyle changes, complementary medicine, and psychotherapy may also be beneficial.

# Clinical assessment of older adults with bipolar disorder

The clinical assessment of bipolar disorder in older adults should include an integrated medical and psychiatric approach: a careful history and physical exam with special attention to the natural history and progression of the illness (time of first presentation of mania, number and duration of lifetime episodes,

etc.,). Rating scales, such as the Young Mania Rating Scale (YMRS), are useful tools to help elucidate the type and frequency of symptom burden [7], although there are no mania rating instruments that are geriatric-specific. When possible, collateral information and coordination of care with family members and other caregivers are helpful.

Using this information, a clinician should first attempt to distinguish between primary and secondary mania. Whereas primary mania is typically characterized by the classical image of euphoric mania with expansive mood, flight of ideas, and pressured speech, secondary mania is characterized by mood lability, irritability, inappropriate affect with poor impulse control, delusions, and aberrant motor behavior including physical aggression, restlessness, or perseveration [4, 8].

The etiology of secondary mania is often linked to underlying medical or neurological comorbidities including head injury, tumor, stroke, epilepsy, sleep apnea, Vitamin B12 deficiency, thyroid dysfunction, infectious causes (such as HIV, Lyme, viral encephalitis), toxic ingestions, or medication side effects. Medications associated with secondary mania include corticosteroids, antidepressants, amphetamines, L-DOPA among many others. Toxic ingestions, such as cocaine, have also been known to induce secondary mania [9].

In all cases, a thorough physical and neurological exam should be performed. Recommended labs include a CBC with differential, urinalysis, serum chemistries, liver and renal function, a lipid panel, thyroid stimulating hormone (TSH), and Vitamin D. Underlying medical issues identified through examination and lab testing should be addressed. Medication lists should be carefully reviewed to rule out medication effects as a possible etiology of mood instability and to eliminate drug/drug interactions with new medications that may be prescribed for treatment of the bipolar disorder. Attempts should be made to reduce polypharmacy when possible.

Approximately 30–40% of OABD will present with mixed mood episodes in which patients display symptoms of mania and depression concurrently [10–12]. It is important for physicians to screen for both manic and depressive symptoms because mixed episodes tend to be more severe, of longer duration, and are associated with higher rates of suicide and substance abuse. A careful risk assessment that includes suicidal ideation, risky behaviors, and substance use is essential. Patients who present with mixed episodes are predominantly females.

An important aspect of the workup in older adults includes a cognitive assessment. Cognitive dysfunction is observed in greater than 30% of adults with bipolar disorder and is more severe in late onset BD. Information processing speed and episodic memory are most likely to be impaired even during periods of euthymia. A 2013 study by Wu et al. showed that a lifetime history of bipolar disorder was associated with an increased risk of subsequent dementia, with an adjusted odds ratio of 4.32 [13•]. Possible causes include medication side effects, the effects of recurrent mood episodes on brain anatomy or physiology, comorbid medical illness (such as vascular disease), or other comorbid behaviors associated with mania such as increased substance use [14]. Proposed pathophysiology includes elevated levels of inflammatory cytokines, neurotrophins, mitochondrial dysfunction, and oxidative stress that occur during both manic and depressive episodes [15]. Surprisingly,

cognitive dysfunction has not been shown to correlate with duration of illness or the use of mood stabilizers [16].

# Treatment

Treatment protocols for bipolar disorder vary by phase of illness: mania, depression, or maintenance treatment. For all medications listed below, please refer to Table 1 for further information on dosing, clinical applications, target serum levels, drug-drug interactions, and common side effects.

# Bipolar mania

## Mood stabilizers

Mood stabilizers are typically first-line treatment of mania in older adults. These medications are often used in conjunction with an atypical antipsychotic medication during an acute manic episode. Although published data is limited to open label studies and case reports, lithium and divalproex are the best studied and suggest that efficacy may vary between late and early onset bipolar disorder. A retrospective study by Chen et al. found that lithium was equally effective for both primary and secondary mania [18]; however, others suggest that anticonvulsants have superior treatment efficacy over lithium in late onset mania [17]. A retrospective cohort study of 1388 OABD aged >65 years showed no significant difference between lithium and divalproex users with regard to frequency of hospitalizations, reasons for medical hospitalization, 1-year acute medical health utilization outcomes, or medical comorbidity rates [32•]. Of note, anticonvulsant use in an older adult population was found to increase fracture risk twofold [33].

### Lithium

Lithium is the best studied, first-line treatment, for both mania and depression. A review of retrospective studies found that 66% of patients, manic or depressed, improved on lithium [34]. Because of decreased renal function and the consequent increased risk of toxicity in older patients, lithium dosing in older adults should be 1/3–½ of that used in younger adults [35, 36]. A serum level should be checked after the fifth medication dose though pharmacokinetic changes may increase the time to reach steady state concentration in older adults [34]. In some patients, a higher serum level may be needed (up to 1.0) to attain symptom remission though these patients should be monitored carefully for signs of lithium toxicity, particularly in those with compromised renal function [34]. Signs of lithium toxicity include ataxia, tremor, myoclonus, altered mental status, diaphoresis, palpitations, blurred vision, sedation, nausea, vomiting, and tinnitus [35, 36]. Although there are no absolute contraindications to lithium treatment, caution is advised in patients with significant renal or cardiovascular disease, hyponatremia, concurrent diuretic usage, and dehydration [36].

Kessing et al. have shown that lithium reduces the severity of cognitive impairment in individuals with diagnoses of dementia. Specifically, though rates of dementia among OABD are higher than the general population, this difference normalizes to the same rate as the general population among OABD

**Table 1. Pharmacologic treatment of bipolar disorder**

| Drug | Class | Uses | Dosing | Target serum level | Side effects | Drug/drug nteractions | Additional considerations |
|---|---|---|---|---|---|---|---|
| Lithium | Mood stabilizer | Depression, mania, maintenance | Initial: 150–300 mg/day in 1–2 divided doses. Max dose ~900 mg/day | 0.4–0.8 mEq/L | Mental slowing, polyuria, polydipsia, urinary frequency, renal failure, hyperglycemia, weight gain, peripheral edema, secondary hypothyroidism | NSAIDs, ACEIs, ARBs, certain antibiotics and benzodiazepines | Monitor for toxicity |
| Divalproex sodium | Mood stabilizer | Primary and secondary mania, rapid cycling Maintenance therapy | Initial: 125–250 mg/day, target dose 500–1000 mg/day | 60–100 mcg/L [17], 65–90 most effective [18] | Sedation, nausea, tremor, weight gain, gait disturbance, delirium, hyperammonemia | Interactions occur with carbamazepine, and protein displacement is possible with aspirin, warfarin, digitoxin, and phenytoin [4] | Monitor for toxicity |
| Carbamazepine | Mood stabilizer | Primary and secondary mania, second line | Initial: 100 mg 1–2 times daily, target dose 400–800 mg/day | 6–12 mcg/L | Vertigo, ataxia, dipolopia, nystagmus, blurred vision, cognitive impairment, sedation, and, dizziness [19] | Calcium channel antagonists, cimetidine, terfenadine, and erythromycin [20] | Dose may need to be increased after 4–6 weeks due to CYP3A4 autoinduction [17] |
| Olanzapine | Atypical antipsychotic | Mania, in particular with psychotic features. Maintenance | Initial: 2.5 mg/day, increase by increments of 2.5 mg, max dose 10–15 mg/day in 1–2 doses [20] | | Sedation, weight gain, hyperglycemia, and hypertriglyceridemia. | CYP1A2 inducers or inhibitors affect olanzapine metabolism [21] | Anticholinergic; may worsen anticholinergic symptoms Metabolic effects should be monitored [20, 22] |
| Risperidone | Atypical antipsychotic | Mania, typically with concurrent mood stabilizer | Initial: 0.25–0.5 mg/day, target dose 2–3 mg/day [20, 23] | | Hypotension and dizziness more common in older adults, weight gain, and EPS common in younger adults [24] | CYP2D6 substrate | EPS more common than with other atypical antipsychotics |
| Quetiapine | Atypical antipsychotic | Mania, typically with concurrent mood stabilizer. Bipolar depression monotherapy | Initial: 25–50 mg/day, target dose varies widely from 50–800 mg/day for bipolar mania, and 100–300 mg/day for bipolar depression [20, 23, 25] | | Dry mouth, somnolence, postural hypotension, insomnia, weight gain, and dizziness [25] | Metabolized by CYP3A4 and CYPA4 | |
| Ziprasadone | Atypical antipsychotic | Mania, typically with concurrent mood stabilizer | Initial: 20 mg/day, target dose 80–120 mg/day | | QTc prolongation, falls, orthostasis, sedation, diabetes, and EPS | Metabolized by CYP3A4 | |
| Aripiprazole | Atypical antipsychotic | Mania, adjunctive second-line treatment Maintenance | Initial: 5 mg/day, target dose up to 30 mg/day | | Restlessness, weight gain, sedation [26, 27] | Interacts with drugs that induce or inhibit CYP3A4 and CYP2D6 enzymes [28] | Increased risk of cerebrovascular adverse events in dementia trials |

**Table 1.** (Continued)

| Drug | Class | Uses | Dosing | Target serum level | Side effects | Drug/drug nteractions | Additional considerations |
|---|---|---|---|---|---|---|---|
| Asenapine | Atypical antipsychotic | Mania | Initial: 5 mg/day, target up to 20 mg/day [29, 30] | | GI upset, fatigue, sleep disturbance, reduced salivation, increased dream activity, depression, difficulty concentrating, akathisia, weight gain, sedation [31] | | |
| Lurasidone | Atypical antipsychotic with mood stabilizing properties | Bipolar depression | Initial: 20 mg/day, target dose 40–80 mg, max dose 120 mg | | Fatigue, sedation, akathisia, GI upset, EPS, hypertriglyceridemia, hyperglycemia | Interacts with drugs that induce or inhibit CYP3A4 | Take with food to reduce GI side effects |
| Olanzapine + fluoxetine | Atypical antipsychotic + antidepressant | Bipolar depression | Initial: 2.5 mg/day Olanzapine, target dose 20–30 mg; fluoxetine initial dose 5 mg, target dose 6–12 mg | | See Olanzapine above | See Olanzapine above | See Olanzapine above |
| Lamotrigine | Mood stabilizer | Bipolar depression | Initial: 25 mg/day, target dose 100–200 mg/day in 1–2 divided doses | | Insomnia, fatigue, weight gain, gait instability, muscle spasms. Also risk of Stevens Johnson syndrome or Toxic epidermic necrolysis | Antiretrovirals and antiepileptics | Precise titration protocol to avoid risk of fatal dermatologic reaction \SJS or TEN) |

who use lithium [37], though these results are controversial [34]. Proposed mechanisms include a possible suppressive effect in which lithium suppresses affective instability that may cause deleterious cognitive effects and/or a neuroprotective effect in which lithium may stimulate neurogenesis or upregulate anti-inflammatory markers. Patients taking lithium show increased grey matter volume and increased N-acetyl-aspartate levels (a marker of neuronal viability and function) within several weeks of initiating lithium treatment [38–40]. Lithium dose should be held 24 before ECT to reduce neurocognitive side effects [41].

### Divalproex

Divalproex is the treatment of choice in secondary mania and can be useful in patients with rapid cycling [42]. Divalproex is commonly prescribed in older patients though dosing should be titrated more slowly and serum levels checked with each dose increase as the elimination half-life may be extended due to medication interactions or renal or hepatic impairments associated with aging. [42, 43]. Contraindications include liver disease or significant hepatic impairment and urea cycle disorders. Therefore, levels should be carefully monitored in patients on these medications.

### Carbamazepine

Given limited data in an older population and the risk for drug-drug interactions and neurological side effects, carbamazepine is not considered a first-line treatment for mania in later life, though it may be effective for secondary mania [17]. Carbamazepine is a substrate for and can induce the CYP3A4 enzyme. The dose may need to be increased after the first 3 to 6 weeks due to autoinduction. In addition to the common side effects, rare but serious side effects include agranulocytosis, aplastic anemia, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Blood counts should be monitored closely in patients who develop skin rashes as they may be at greater risk for blood dyscrasias [44]. Carbamazepine should not be used in patients with a history of bone marrow depression.

## Antipsychotics

Studies in adult-aged populations demonstrate efficacy of atypical antipsychotic medications as monotherapy or in combination with a mood stabilizer for acute mania or mixed states. Atypical antipsychotics are preferable to conventional antipsychotics for older cohorts, in particular, due to reduced risk of extrapyramidal side effects that are increasingly common with advancing age (5–6 times greater in older adults compared with an adult population) [45, 46].

In April of 2005, the FDA issued a boxed warning that atypical antipsychotics carry an increased risk of death in elderly patients with dementia, largely as a result of cardiac or infectious conditions [47]. Furthermore, some antipsychotic medications also elevate the risk of cerebrovascular events (CVAEs) in older adults with dementia [20–24, 26, 28–31, 48–57, 58••, 59, 60]. The risk of mortality and CVAEs in older adults with bipolar disorder treated with antipsychotics is less clear. Common side effects include somnolence, orthostatic hypertension, tardive dyskinesia, sedation, weight gain, and gait disturbance. Diabetes has also been linked to treatment using antipsychotics [50]. Close monitoring for metabolic side

effects of this class of medications is recommended. Clinicians should monitor liver function, complete blood counts, glucose, lipid profile, and weight [22].

## Olanzapine

Olanzapine may be used as monotherapy though combination with a mood stabilizer is recommended [23]. CYP1A2 inhibitors, such as fluvoxamine, decrease olanzapine clearance, while inducers, like carbamazepine, increase clearance [21]. Olanzapine is the most anticholinergic of the atypical antipsychotics (with the exception of clozapine), and this may cause or worsen preexisting tachycardia, constipation, urinary hesitancy, and cognitive impairment [34]. Risk of cerebrovascular events is also a concern [20].

## Risperidone

Risperidone is a substrate for CYP2D6, so the dose should be increased if taken in conjunction with an inducer, such as carbamazepine, and should be decreased if taken with an inhibitor, such as fluoxetine or paroxetine [24]. Dose should be titrated more slowly in frail patients as EPS may be more common with risperidone than olanzapine or quetiapine [24].

## Quetiapine

Quetiapine is rarely used as monotherapy for treatment of mania though it is commonly used in conjunction with a mood stabilizer, particularly for treatment of psychotic symptoms. Quetiapine is metabolized by CYP3A4 and CYPA4. Therefore, medications that are potent inhibitors of CYP3A4, such as erythromycin, are likely to raise quetiapine levels, and drugs that induce CYP3A4, such as carbamazepine and phenytoin, will likely decrease quetiapine levels. Quetiapine is less likely to cause EPS as compared to other atypical antipsychotics such as olanzapine and risperidone [51].

## Ziprasidone

Ziprasidone has been used minimally in older adults with bipolar disorder due to limited data and concerns regarding risk for cardiac arrhythmia and should be avoided in individuals with known QTc prolongation and congestive heart failure [23]. Ziprasidone is metabolized by CYP3A4, so inducers of this enzyme, including carbamazepine, reduce ziprasidone levels, whereas CYP3A4 inhibitors increase ziprasidone levels. Advantages of ziprasidone may include lower risk of dyslipidemias, orthostatic hypotension, or sedation [20].

## Aripiprazole

Aripiprazole is not typically used as a first-line treatment for mania though a recent open label prospective trial of aripiprazole therapy in older bipolar patients showed improved efficacy when aripiprazole was used as adjunctive therapy with a mood stabilizer in patients who were suboptimally responsive to prescribed medication treatments [26]. Aripiprazole interacts with drugs that induce or inhibit the CYP3A4 and CYP2D6 enzymes [28]. Therefore, the dose should be doubled when used in conjunction with carbamazepine or other CYP3A4 inducers and

halved when administered with CYP3A4 or CYP2D6 inhibitors [52]. Along with other antipsychotics, aripiprazole also has shown increased risk of cerebrovascular adverse events in dementia trials.

### Asenapine

Several small studies support the use of asenapine in OABD [29–31]. Asenapine is a substrate of CYP1A2; therefore, medications that induce this enzyme will require a higher dose and medications that inhibit it will necessitate a lower dose. More serious side effects include QTc prolongation, orthostasis, EPS, and weight gain [29].

### Benzodiazepines

Benzodiazepines have well documented deleterious effects on cognition and functioning in elderly patients including increased risk of falls and potential increased risk of dementia [53–56]. The risks of dependence are also significant and can lead to medical conditions [20]. Benzodiazepenes should be avoided on a long-term basis, but may have limited utility as adjunctive, short-term treatment for the acute management of severe mania.

## Bipolar depression

Older adults with bipolar disorder who present with depressive symptoms are often misdiagnosed with unipolar depression. Recognition of bipolar disorder through thorough medical and family history and collection of information from collateral sources are crucial as treatment differs significantly from that of unipolar depression. The FDA has approved three agents for the treatment of bipolar depression: (1) lurasidone, (2) quetiapine, and (3) the combination medication olanzapine/fluoxetine. Other antipsychotics have shown little to no efficacy for treating depressive symptoms [57]. The mood stabilizers lithium and lamotrigine have also been shown to be effective. Unlike treatment of bipolar mania which typically requires both an antipsychotic and a mood stabilizer during acute events, bipolar depression may respond to antipsychotics or mood stabilizers as monotherapy. SSRIs as monotherapy should be avoided due to the risk of inducing secondary mania or exacerbating the frequency of mood episodes in individuals with bipolar disorder.

### Atypical antipsychotics

#### Lurasidone

In a post hoc analysis of two double-blind, placebo-controlled trials of lurasidone, Sajatovic et al. (2016) showed that adults over age 55 with bipolar disorder exhibited reduced depressive symptoms compared to placebo [58••]. Monotherapy with lurasidone was effective in reducing symptoms while adjunctive therapy with lithium or divalproex showed

no increased benefit. Common side effects are listed in Table 1 though this medication is generally well tolerated in older adults [58••].

### Quetiapine

In contrast to its adjunctive use in bipolar mania, quetiapine is highly effective as monotherapy for treatment of bipolar depression. Dosing for depression is typically lower than that for mania. In a post hoc analysis of a prospective randomized controlled trial in a mixed-age sample, Sajatovic et al. (2007) found that quetiapine is as efficacious in adults aged 55–65 as in younger adults [59].

### Olanzapine (±fluoxetine)

Olanzapine may be used as monotherapy though it is typically used in conjunction with the SSRI fluoxetine for synergistic effect. Double-blind randomized control trials in mixed-aged subjects ($n = 833$) have shown that fluoxetine plus olanzapine combination treatment is more effective than olanzapine alone or placebo [60]. This effect is unique to fluoxetine and has not been observed with other SSRIs. In addition, those in the fluoxetine plus olanzapine group did not have an increased rate of mania onset compared to those on olanzapine monotherapy. Olanzapine/fluoxetine combination has also been shown to be more effective than lamotrigine in treating bipolar depression in a randomized, double blind trial [61] though increases in adverse events, total cholesterol, triglyceride levels, and weight gain are more common.

## Anticonvulsants/mood stabilizers

### Lithium

Lithium is effective both for treatment of bipolar mania and bipolar depression [62, 63]. Nonetheless, the evidence for lithium efficacy in OABD is almost entirely extrapolated from studies done in younger adult populations. There is no definitive study demonstrating the efficacy of lithium specifically in older patients with bipolar disorder [36]. Dosing, target serum levels, side effects, and drug-drug interactions for treatment of bipolar depression are similar to those for bipolar mania as described above.

### Lamotrigine

Although lamotrigine is approved by the FDA for the prevention of recurrent episodes of mania and depression in individuals with bipolar disorder, lamotrigine has been studied in OABD for the treatment of bipolar depression. In a multi-site, 12-week, open-label trial of lamotrigine in older adults with bipolar disorder (>60 years old), lamotrigine treatment was associated with a decrease in depressive symptoms and an increase in functional status [64•]. Dosing follows a precise titration schedule to avoid the risk of Stevens-Johnson syndrome, a rare but life-threatening rash. A typical titration schedule is as follows: 25 mg/day × 2 weeks, 50 mg/day × 2 weeks, 100 mg/day × 1 week, followed by titration to target dose of 200 mg/day. If treatment with

lamotrigine is ineffective, the patient should be tapered off to avoid withdrawal symptoms.

### Treatment with antidepressants

Though studies have not assessed the use of antidepressant monotherapy for treatment of bipolar depression in older adults, monotherapy with SSRIs and standard antidepressants is not recommended due to the potential risk of inducing mania or rapid cycling [65]. Instead, mood stabilizers are often used in conjunction with antidepressants to offset this risk [66]. Conjunctive therapy, in some instances, has proven more effective than treatment with a mood stabilizer alone [67]. Second generation antipsychotics such as quetiapine, lurasidone, and olanzapine have also been used in conjunction with an antidepressant.

Treatment with antidepressants should be avoided for those who have had poor responses to antidepressants in the past, have had a recent manic episode, or are currently in a mixed episode. If a patient were to develop manic symptoms or enter a mixed episode, abrupt termination of antidepressant treatment is advised [67].

## Management of mixed episodes

Mood stabilizers are considered first line for mixed episodes, particularly divalproex [10–12]. Despite lithium's high level of efficacy for both manic or depressive episodes, it has shown to be less effective for mixed episodes [10–12]. Atypical antipsychotics are often used as adjunctive therapy.

## Maintenance therapy

Following remission of acute mood episodes, psychopharmacologic maintenance therapy is indicated due to the high rates of recurrent mood episodes in the geriatric population. Multiple studies suggest that up to 20% of OABD will experience multiple mood episodes within a 12-month period [42, 68]. A retrospective study of 26 geriatric bipolar patients found that 38% had a lifetime occurrence of at least three mood episodes [69].

### Maintenance therapy following a bipolar manic episode

Per the recommendations of the International Society for Bipolar Disorder (ISBD), patients should be maintained for a period of at least 6 months on the same medications and doses with which they achieved remission [70, 71]. Following a first manic episode in patients treated with both a mood stabilizer and an antipsychotic, it is reasonable to slowly discontinue the antipsychotic following 6 months of stable remission and to continue mood stabilizer monotherapy. In a pooled post hoc analysis of two 18-month randomized control trials in mixed age patients with bipolar disorder, analysis of a subgroup of 98 older patients showed that lithium is more effective than lamotrigine in delaying relapse of manic episodes while lamotrigine is more efficacious in delaying relapse of depression [6, 71, 72]. Patients who have experienced multiple relapses while on a mood stabilizer, or for whom the frequency or

duration of episodes is increasing may require both mood stabilizer and antipsychotic ongoing maintenance therapy.

## Maintenance therapy following a bipolar depressive episode

Patients who have remitted from a depressive episode should be maintained on the same medications and dosages with which they achieved symptom remission [71]. An exception to this is patients who have stably remitted for 6 months with combination olanzapine/fluoxetine treatment. Such individuals should be maintained on olanzapine monotherapy, whereas it is recommended that fluoxetine be tapered off by 10 mg/week to avoid the risk that SSRIs may induce mania or hypomania in euthymic patients though such risk has not been fully substantiated in the literature nor has it been assessed in specifically geriatric cohorts [73]. If symptoms recur, olanzapine should be continued and fluoxetine should be restarted and titrated to the full dose previously used to achieve remission.

## Other considerations of remission

Remitted patients should be monitored frequently for recurrence of symptoms as well as medication side effects and cognitive decline. Continuously, stable patients should be seen at least once every 6 months (1, 67–68).

Some patients may experience intolerable side effects that require medication discontinuation. In these cases, for patients not receiving lithium or lamotrigine, switching to either lithium or lamotrigine would be the drug of choice [62, 63, 64•]. Adjunctive therapy with an antipsychotic, such as aripiprazole or olanzapine may be indicated for maintenance of symptom remission though there are no studies showing clear efficacy of one antipsychotic over another for maintenance therapy among older adults. In cases of discontinuation, the offending medication should be tapered off concurrently with initiating the new medication. Decisions should be made based on side effect profile, drug-drug interactions, medical comorbidities, and patient preference. Per FDA guidelines, lithium, lamotrigine, aripiprazole, and olanzapine are approved agents for maintenance treatment to the exclusion of other mood stabilizers and antipsychotics [23, 45, 52, 62, 63, 64•].

Many older adults with BD suffer from impaired cognition even during periods of euthymia [74]. In a retrospective study, lithium was shown to reduce the incidence of dementia in OABD by 23% in patients who received lithium for 1 year [75••, 76]. Other studies have validated a reduction in neurocognitive disorder in patients treated with lithium [37]. Lithium should therefore be considered a drug of choice for maintenance therapy for those who can tolerate.

In instance of recurrence, medication doses should be optimized. When applicable, serum levels should be checked, such as for lithium or divalproex. Doses may be increased to achieve a higher serum level or higher target dose within the therapeutic range providing that side effects do not interfere. Patients who do not respond within 2–4 weeks for manic symptoms or 8–12 weeks for depressive symptoms are considered to be in a new mood episode and should be managed according to guidelines for acute management as above.

In addition to psychopharmacology, the maintenance phase of the illness is an opportunity for psychoeducation about the importance of adherence to treatment, prodromal symptoms, reducing risk factors (such as substance use),

as well as struggling with identity around the illness. Psychotherapy is highly recommended.

## Neuroimaging studies (and effects of long-term BD on the brain)

Bipolar disorder is characterized as a "neuroprogressive" disease, and cognitive outcomes may be worse for patients who have more bipolar relapses, who have more severe illness, or who are older [77]. Both gray matter loss and white matter abnormalities are associated with the neuropathophysiology of bipolar disorder [77]. A meta-analysis of 98 structural imaging studies in younger adults with bipolar disorder noted lateral ventricle enlargement and increased rate of deep white matter hyperintensities in bipolar patients compared to controls [78]. White matter abnormalities are associated with poorer executive function and cognitive functioning [79]. An MRI study of 54 adults with bipolar disorder (mean age 64.4 years) showed that lower total gray matter and hippocampal volumes were related to bipolar disorder, as was longer exposure to antipsychotics [80••]. In contrast, however, findings from a recent longitudinal study suggest that older bipolar patients do not exhibit volumetric or white matter abnormalities when compared to matched controls, a result that the authors attribute to similar somatic comorbidity burdens [81].

Longer duration of lithium use has been associated with higher white matter integrity in bipolar subjects [82••], and long-term lithium use has been shown to increase gray matter [39]. Lithium treatment is also associated with increased hippocampal volumes [83, 84] and decreased white matter abnormalities [85].

## Neurotherapeutics—electroconvulsive therapy

Electroconvulsive therapy (ECT) is the safest treatment option for elderly patients who cannot tolerate or who respond poorly to medications [86]. ECT is especially indicated in situations where a rapid therapeutic response is needed, for example life-threatening depression and catatonia [87], or inadequate food or fluid intake. ECT has also been shown to be a safe and effective treatment for delirious mania with catatonic features, a severe form of mania to which elderly patients with medical conditions are particularly vulnerable [88]. Recently, robust response rates to ECT were found in depressed, manic, and mixed state patients in a retrospective chart review of 65 bipolar patients [89]. During periods of remission, studies of severely depressed elderly patients showed no significant difference between maintenance ECT and maintenance pharmacotherapy [86].

There are no "absolute" contraindications to ECT, but it is critical to consider risk factors that may increase mortality such as recent myocardial infarction, recent stroke/hemorrhage, chronic obstructive pulmonary disease, asthma, or cerebrovascular malformations among others [90]. Potential risks of ECT include the risks of anesthesia and somatic and cognitive side effects including anterograde memory impairment (41%) and postictal confusion (45%) [91] which are generally transient and reversible [92, 93]. Older adults with underlying neuropsychiatric conditions, such as cognitive impairment, are at a higher risk of developing delirium and confusion following ECT [94]. As a special consideration, lithium should be held for 24–36 h prior to ECT treatment due to its ability to cross the blood brain barrier following ECT, resulting in higher

frequency of adverse events [41, 95].

## Diet and lifestyle

Compared to the general population, standardized mortality ratios for patients with bipolar disorder are 2.5 for men and 2.7 for women [77]. Approximately 2/3 of older adults with bipolar disorder have hypertension [96], 1/4 have coronary artery disease [97], 1/10 have hyperlipidemia [97], and 1/3 have diabetes [96]. About half are obese [98]. The high prevalence of medical comorbidities in the older adult bipolar population necessitates coordinated care between providers to ensure that treatment for one condition does not worsen another; for example, a bipolar patient prescribed duloxetine for diabetic neuropathy may be at increased risk for manic switching [96].

In a recent study of 225 adult patients with rapid-cycling bipolar disorder, endocrine/metabolic illnesses were associated with greater depression severity and poorer treatment outcomes [99]. Each 1-unit increase in BMI decreased the likelihood of treatment response to medication by 7.5% and decreased the likelihood of remission by 7.3% [99]. It has been suggested that Omega-6 heavy diets (found in margarine and oils) may contribute to heart disease, obesity, diabetes, and mental health disorders including bipolar disorder [100]. In contrast, two placebo-controlled, randomized trials of the Omega-3 fatty acids EPA/DHA and EPA (found in fish) demonstrated reductions in bipolar depressive symptoms but no effects on mania [101, 102]. Omega-3 fatty acid supplements (1–2 g/day) may be a reasonable adjunctive treatment for patients with bipolar depression. Exercise has also been shown to improve mood and energy [103].

## Complementary and alternative medicine approaches

Biologics, mind-body interventions, and alternative medicine practices may all serve as important adjuncts in treating older adults with bipolar disorder. The flowering plant St. John's Wort has been shown to be as efficacious as fluoxetine 20 mg in one study of older adults, with minimal adverse effects [104]. However, cases of St. John's Wort-induced mania have been reported [105]. St. John's Wort is contraindicated for older patients on digoxin, warfarin, cyclosporine, HIV protease inhibitors, theophylline, and oral contraceptives due to the risk of drug-drug interaction-induced adverse events or reductions in efficacy of other medications. Similarly, in an open-label study of Coenzyme Q10 (CoQ10) participants showed a significant reduction in MADRS scores from baseline [106].

Light therapy, typically indicated for patients with seasonal affective disorder, may also help alleviate symptoms of bipolar depression [107] though caution should be exercised as some subjects have been reported to develop mixed states [108].

## Psychotherapy

There are no controlled psychotherapy trials in OABD; however as a complement to first-line pharmacological treatment, psychotherapy may improve outcomes for patients with bipolar disorder [109, 110]. Recurrent bipolar depressive episodes are associated with worse psychosocial functioning [111, 112]. Psychotherapy can help older adults navigate expectations concerning mental illness [113], changing social roles and interpersonal losses related to aging [113].

Gerocognitive behavior therapy, which integrates cognitive interventions specialized for older adults with a developmental perspective, promotes stress management, strategies for improving medication compliance, and measures to deal with social consequences of manic or depressive episodes [114]. In some adult studies, interventions which taught bipolar patients to monitor and manage stress and medication adherence reduced recurrence rates [115–118].

## Conclusions

Limitations to the current evidence base demonstrating efficacy and safety of pharmacological and psychotherapy interventions for OABD are considerable. Future treatment studies must include older age cohorts with BD that represent those patients treated in community settings. Representative clinical characteristics of OABD include medical comorbidity, cognitive impairment, polypharmacy, and, increasingly, functional decline. Neurobiological studies to better assess the neuroprogression hypothesis of bipolar disorder will allow for future targeted interventions to delay cognitive and functional decline in our aging patients with bipolar disorder. Finally, health care reform, bringing behavioral health integration into primary care medical settings, represents an opportunity for improved identification and holistic treatment of bipolar disorder in later life.

## Compliance with ethical standards

**Conflict of interest**
Joanna Georgakas declares that she has no conflict of interest.
Claire Motyl declares that she has no conflict of interest.
William Quayle declares that he has no conflict of interest.
Tamar Katz declares that she has no conflict of interest.
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**Human and animal rights and informed consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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