Geriatric bipolar disorder: Treatment of mania and major depression

AUTHORS: Martha Sajatovic, MD, Peijun Chen, MD, MPH, PhD
SECTION EDITORS: Paul Keck, MD, Kenneth E Schmader, MD
DEPUTY EDITOR: David Solomon, MD

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INTRODUCTION

The treatment of older bipolar patients differs from the treatment of younger patients [1]. Up to 25 percent of all bipolar patients are older [2], and the absolute number of geriatric bipolar patients is expected to increase as the world's population ages over the next several decades [3,4].

This topic reviews the acute treatment and prognosis of geriatric bipolar disorder. The epidemiology, pathogenesis, clinical features, assessment, diagnosis, general principles of treatment, and maintenance treatment of geriatric bipolar disorder are discussed separately, as are the epidemiology, clinical features, diagnosis, acute treatment, and maintenance treatment of bipolar disorder in mixed-age patients.

- (See "Geriatric bipolar disorder: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Geriatric bipolar disorder: General principles of treatment".)
- (See "Geriatric bipolar disorder: Maintenance treatment".)
- (See "Bipolar disorder in adults: Epidemiology and pathogenesis".)
- (See "Bipolar disorder in adults: Clinical features".)
- (See "Bipolar disorder in adults: Assessment and diagnosis".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar major depression in adults: Choosing treatment".)

- (See "Bipolar disorder in adults: Choosing maintenance treatment".)

DEFINITION OF GERIATRIC BIPOLAR DISORDER

The minimum age used to define geriatric bipolar disorder is generally 60 years [5-7]. However, some authorities use an age cut-off of 50, 55, or 65 years [8,9]. The International Society for Bipolar Disorders Task Force on Older-Age Bipolar Disorder recommends that older age bipolar disorder include patients ≥50 years [5].

Geriatric bipolar disorder includes both aging patients whose mood disorder presented earlier in life and patients whose mood disorder presents for the first time in later life [1,10]. The International Society for Bipolar Disorders Task Force uses the term “older age bipolar disorder” instead of “geriatric bipolar disorder” [5].

Bipolar disorder in both geriatric and younger patients is characterized by episodes of major depression (table 1), mania (table 2), and hypomania (table 3) [11]. The clinical features and diagnosis of geriatric bipolar disorder are discussed separately. (See "Geriatric bipolar disorder: Epidemiology, clinical features, assessment, and diagnosis".)

TREATMENT

General principles — The general principles and issues that are involved in treating geriatric bipolar disorder include:

- Goal of treatment
- Initial evaluation
- Level of care
- Pharmacologic issues
- Monitoring
- Adjunctive psychotherapy
- General medical comorbidity
- Managing nonresponse
- Making referrals

These general principles are discussed in detail separately. (See "Geriatric bipolar disorder: General principles of treatment".)

Mania and hypomania — Pharmacotherapy is generally used for geriatric mania and hypomania. Despite clinical differences between these types of mood episodes, they are treated with the same medications [12-14]. For refractory mania, electroconvulsive therapy (ECT) can be beneficial.

First-line medications — Relatively few high-quality studies of pharmacotherapy for acute geriatric mania and hypomania have been conducted [15]. Based upon randomized trials in mixed-age adults and other studies in older patients, first-line medications for acute geriatric mania and hypomania include, in order of preference, lithium, valproate, olanzapine, and quetiapine [1,6,7,9,16-20]. However, it is reasonable to use these drugs in a different order.

Lithium, valproate, olanzapine, and quetiapine have demonstrated efficacy compared with placebo in mixed-age adults. Only one head-to-head trial, which compared lithium with divalproex, has been conducted in patients with late-life mania; the results indicate that the benefit of each drug is substantive and generally comparable [6].

In addition, lithium, valproate, olanzapine, and quetiapine are each suitable for maintenance treatment (maintenance treatment typically consists of the regimen that successfully treated the acute mood episode) [7,21]. Other factors that help determine the choice of a specific drug for acute treatment include past response to medications, psychotic symptoms (eg, grandiose delusions), side effect profiles, comorbid general medical conditions, potential for drug-drug interactions, patient preference, and cost. As an example, lithium is frequently avoided in patients with renal disease and valproate is avoided in patients with hepatic or pancreatic disease, whereas second- (and first-) generation antipsychotics increase the risk of hyperglycemia in older diabetic patients [22]. In addition, patients with psychotic features typically receive an antipsychotic. Study results suggest that clinicians can generally expect that approximately 50 to 80 percent of older adults with mania will respond to a first-line treatment [6,17,23,24].

The efficacy of lithium, olanzapine, quetiapine, and valproate for acute mania and hypomania in mixed-age adults is discussed separately, as are the adverse effects. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

- **Lithium** – In older bipolar patients, lithium is usually started at 150 mg once or twice daily and increased every one to five days as tolerated [6,7,25,26]. The half-life of lithium increases to approximately 28 to 36 hours as patients get older; older patients thus generally require smaller doses to reach and maintain a steady serum level than do younger patients. Multiple treatment guidelines for older adults with bipolar disorder note

that relatively low doses are frequently sufficient to achieve therapeutic serum concentrations [27,28].

The target dose is determined by 12-hour serum trough levels that should be drawn five to seven days after each dose increase. The therapeutic range for serum lithium concentrations in older adults with bipolar disorder is lower than that used for other adults [9,19,20,28]. We suggest the following serum concentrations, which come from the International Society for Bipolar Disorders consensus practice guidelines for maintenance treatment in geriatric bipolar disorder and are based upon age [7]:

- Patients 60 to 79 years old – 0.4 to 0.8 mEq/L (0.4 to 0.8 mmol/L)
- Patients 80 years and older – 0.4 to 0.7 mEq/L (0.4 to 0.7 mmol/L)

Other guidelines also suggest that a minimum concentration of 0.4 mEq/L is sufficiently efficacious for some older adults with mania and can help avoid adverse effects and toxicity [28]. (By contrast, several guidelines state that the minimum concentration for mixed-age adults is 0.6 mEq/L.) In one randomized trial that studied lithium for patients with acute late-life mania (mean age 68 years), the average serum concentration was approximately 0.8 mEq/L [6].

Target doses greater than 900 to 1200 mg per day are rarely required, and some patients 80 years or older may achieve therapeutic serum lithium levels with doses as low as 225 to 300 mg per day [29]. A randomized trial that studied lithium for acute late-life mania found that the mean daily dose was 780 mg/day [6], and a prospective observational study of 56 geriatric bipolar patients who recovered from their mood episode with lithium found that the mean daily dose was 689 mg [16]. Practice guidelines often recommend that clinicians dose lithium to achieve serum levels at the lower end of the therapeutic range; however, for partial responders, the dose should be increased to achieve higher levels within the therapeutic range [27]. Lithium serum concentrations and laboratory testing in mixed-age adults are discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects".)

Lithium side effects observed in older bipolar patients include [1]:

- Ataxia
- Cognitive impairment
- Gastrointestinal distress
- Goiter and hypothyroidism
- Peripheral edema
  Polyuria

- Polydipsia
- Rash
- Tremor
- Weight gain
- Worsening of arthritis

The risk of hypothyroidism increases as age increases. In addition, the risk of chronic kidney disease secondary to lithium appears to be greater in older patients than younger patients by virtue of chronic exposure. Additional information about lithium side effects is discussed separately. (See "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Managing lithium adverse effects' and "Lithium and the thyroid" and "Renal toxicity of lithium".)

Lithium toxicity may also occur; common signs of toxicity include ataxia, impaired attention and delirium, gastrointestinal distress (eg, vomiting), and tremor [7]. Older patients are at greater risk for acute lithium toxicity than younger patients. Absorption of lithium is usually not changed by aging, but excretion is typically less in the elderly because the glomerular filtration rate is decreased [30]. In addition, older patients generally have a low volume of lithium distribution caused by reductions in lean body mass and total body water. The risk of toxicity is also increased by general medical comorbidities that are common in older patients, such as dehydration, heart failure, hyponatremia, and renal dysfunction. Additional information about lithium toxicity, including management, is discussed separately. (See "Lithium poisoning".)

Drug-drug interactions can diminish renal clearance of lithium and thus increase the risk of adverse effects and toxicity because lithium has a narrow therapeutic index. As an example, concomitant administration of lithium with angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or thiazide diuretics can raise serum lithium concentrations. Specific interactions of lithium with other medications may be determined by using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Evidence supporting the use of lithium as first-line treatment for mania and hypomania includes a nine-week randomized trial that compared lithium with divalproex in older patients who presented with bipolar I manic, hypomanic, or mixed episodes (n = 224) [6]. The mean serum concentration of lithium was 0.76 mEq/L (0.76 mmol/L) and of divalproex was 74 mcg/mL. In addition, rescue treatment with lorazepam (maximum 3 mg/day) was permitted; patients unresponsive to lorazepam received risperidone (0.5 to 2 mg once or twice daily). The primary study findings included the following:

- Response (reduction of baseline symptoms ≥50 percent) was comparable with lithium and divalproex (79 and 73 percent of patients), as was remission (70 and 63 percent of patients).

  However, improvement of mania rating scale scores was moderately larger with lithium than divalproex. A subgroup analysis found that greater improvement with lithium occurred in patients who were more severely ill at baseline; for patients with less severe illness at baseline, improvement was comparable for the two drugs.

- Any use of rescue treatment with lorazepam or risperidone was comparable in patients who received lithium or divalproex (61 and 51 percent). In addition, daily use of risperidone was comparable for the two groups. However, daily use of lorazepam occurred in fewer patients who received lithium than divalproex (10 versus 20 percent).

- All-cause attrition among patients who received lithium or divalproex was comparable (51 and 44 percent), and tolerability was generally comparable as well.

Other evidence supporting the use of lithium includes randomized trials in mixed-age adults that indicate maintenance treatment with lithium can prevent suicide and observational studies that suggest lithium has neuroprotective properties and is associated with a reduced risk of developing neurocognitive disorders. (See "Suicidal ideation and behavior in adults" and "Geriatric bipolar disorder: Maintenance treatment", section on 'Cognitive impairment' and "Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects", section on 'Mechanism of action'.)

- **Valproate (Divalproex)** – Valproate is usually started at 125 to 500 mg per day in older bipolar patients and increased by a dose equal to the starting dose every one to five days [6,31]. The target dose is generally determined by 8- to 12-hour serum trough levels of both total and free valproate, which should be drawn two to five days after each dose increase. When 24-hour extended-release preparations are administered in the morning, trough levels are drawn the following morning before the next daily dose [32]. When 24-hour extended-release preparations are administered at bedtime, levels are drawn 18 to 24 hours later, prior to the next dose. We suggest that valproate be dosed to achieve a total serum level of 65 to 100 mcg/mL, although some older patients will not tolerate the higher ranges [33,34]. The half-life and free-plasma fraction of valproate may increase with age [17], and older patients generally require smaller doses to reach and maintain a steady serum level than do younger patients. The target dose is generally 500 to 1500 mg per day [25,31]. A randomized trial that studied divalproex for acute late-life mania found

that the mean daily dose was 1200 mg/day, and the mean serum concentration was 74 mcg/mL [6]. In a prospective observational study of 76 geriatric bipolar patients who recovered from their mood episode with valproate, the mean daily dose was 956 mg per day [16].

Common side effects in older geriatric bipolar patients include gastrointestinal distress, sedation, weight gain, and hand tremor [35,36]. Additional information about valproate side effects (table 4) is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Valproate or divalproex' and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Valproate'.)

Evidence of efficacy includes a randomized trial that compared divalproex with lithium in patients with late-life mania (n = 224) [6]. The benefit of the two drugs was substantive and comparable for most outcomes, but for a few other outcomes, lithium was superior to divalproex; additional details of the study are discussed above in the present section, under the bullet point “Lithium.” In addition, a post-hoc, pooled analysis of three randomized trials lasting three weeks found that in 45 acutely manic older patients, symptoms improved more with valproate than placebo (not tested statistically) [24].

- **Olanzapine** – Olanzapine is usually started at 2.5 to 5 mg once daily in older bipolar patients [16,25]. The dose is then increased every two to five days by increments equal to the starting dose, to reach the target dose of 5 to 15 mg per day. For patients who neither respond to 15 mg per day nor are troubled by side effects, the dose may be increased up to 20 mg per day.

  Olanzapine can cause sedation and falls, as well as metabolic problems such as weight gain, dyslipidemia, hyperglycemia, and diabetes (table 5) [1,20]. Olanzapine may also cause electroencephalographic abnormalities and constipation [20]. In addition, second-generation antipsychotics are associated with an increased risk of death in older patients treated for dementia-related psychosis (primarily due to cardiovascular events or infections) [20,37]; some authorities believe this risk may extend to late-life bipolar disorder [38]. A retrospective registry study examined the risk of mortality in older veterans who were treated for bipolar disorder with newly prescribed medications; after adjusting for the probability (propensity) to receive each medication, based upon potential confounding factors such as general medical and psychiatric comorbidity and use of concomitant medications, the analyses found that the mortality rate during the first six months of treatment was approximately two times greater in patients who received olanzapine or risperidone than valproic acid [39].

Evidence of efficacy includes a pooled analysis of three randomized trials (61 acutely manic older patients) lasting three weeks, which found that symptoms improved more with olanzapine than placebo (not tested statistically) [24]. This is consistent with the finding that olanzapine is efficacious in younger patients [40].

- **Quetiapine** – In older bipolar patients, quetiapine is usually started at 12.5 to 25 mg once daily or 25 to 50 mg per day in two divided doses [16,25]. The dose is then increased every two to five days by increments equal to the starting dose to reach the target dose of 100 to 300 mg per day, taken in two divided doses. For patients who neither respond to 300 mg per day nor are troubled by side effects, the dose may be increased up to 800 mg per day [23]. However, many patients will not tolerate higher doses due to sedation and orthostasis.

  Common side effects observed in older manic patients treated with quetiapine include dry mouth, sedation, postural hypotension and dizziness, dyslipidemia, hyperglycemia, and weight gain [1,23]. Studies in mixed-age patients suggest that the metabolic problems occur less frequently with quetiapine than olanzapine (table 5). Fall risk may be increased in elderly people with sedation and postural hypotension; a slower dose titration may minimize these adverse effects [20]. In addition, second-generation antipsychotics are associated with an increased risk of death in older patients treated for dementia-related psychosis [20,37]; some authorities believe this risk may extend to late-life bipolar disorder [38].

  Evidence of efficacy includes a pooled analysis of two 12-week randomized trials that compared quetiapine with placebo in mixed-age manic patients [23]. In the subgroup of 59 older patients, symptoms improved more with quetiapine (modal dose 550 mg per day) than placebo. This was consistent with the finding that quetiapine was superior to placebo in younger patients. Among older patients, withdrawal from treatment due to adverse effects occurred in more patients who received quetiapine than placebo (25 versus 10 percent).

For geriatric bipolar patients who do not respond to treatment with one first-line medication within four weeks of reaching the target dose, or do not tolerate the drug, we suggest tapering and discontinuing the failed medication over one to two weeks at the same time that another first-line medication is started and titrated up. (Response is defined as substantial improvement in the number, intensity, and frequency of symptoms.) The failed medication is generally tapered by the same amount for each dose decrease. As an example, quetiapine 300 mg per day is decreased by 50 mg per day, every one to three days.

Second-line medications — Geriatric manic and hypomanic episodes often do not respond to treatment with two to four monotherapy trials of first-line medications [17,23,24].

Preferred approach — For treatment-resistant geriatric manic and hypomanic episodes that do not respond to two to four monotherapy trials of first-line medications, we prefer combining lithium or valproate with a second-generation antipsychotic for four weeks, based upon randomized trials in mixed-age adults. However, lithium plus valproate is a reasonable alternative. In one randomized trial that initially compared lithium with divalproex as monotherapy in patients with late-life mania or hypomania (n = 224), roughly 15 percent required add-on risperidone (up to 2 mg twice daily) [6].

We generally use a medication combination consisting of:

- Lithium plus risperidone, quetiapine, or olanzapine, or
- Valproate plus risperidone, quetiapine, or olanzapine

However, there is no evidence of superior efficacy for any specific combination in treating manic and hypomanic episodes. Selecting a combination is thus guided by side effect profiles, potential drug-drug interactions, comorbid general medical conditions, patient preference, and cost. Specific medication interactions that can occur may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

For resistant geriatric bipolar patients receiving lithium or valproate monotherapy for manic or hypomanic episodes, we add risperidone, quetiapine, or olanzapine to their regimen [20]. For resistant patients receiving quetiapine or olanzapine monotherapy, we add lithium or valproate to their regimen. The dose and side effects of lithium, valproate, risperidone, quetiapine, and olanzapine are discussed separately. (See 'First-line medications' above and "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)

Resistant geriatric bipolar patients who do not respond to or tolerate one medication combination should be treated with a second medication combination. Generally, lithium is switched to valproate or vice versa. As an example, for patients who do not respond to lithium plus risperidone, quetiapine, or olanzapine within four weeks of therapy at target doses, we suggest tapering and discontinuing lithium at the same time that valproate is started and titrated up. Lithium is generally tapered over one to two weeks by the same amount for each dose decrease (eg, lithium 900 mg per day is decreased by 300 mg per day, every one to three days).

Conversely, for resistant geriatric patients who do not respond to valproate plus risperidone, quetiapine, or olanzapine within four weeks of reaching target doses, we suggest tapering and

discontinuing valproate at the same time that lithium is started and titrated up. Valproate is generally tapered over one to two weeks by the same amount for each dose decrease (eg, valproate 1000 mg per day is decreased by 250 mg per day, every one to three days).

Although the antipsychotic (risperidone, quetiapine, or olanzapine) is generally continued at the same dose when lithium is switched to valproate (or vice versa), it is also reasonable to switch the antipsychotic after lithium has been switched to valproate (or vice versa). The antipsychotic is generally tapered over one to two weeks by the same amount for each dose decrease (eg, olanzapine 15 mg per day is decreased by 5 mg per day, every one to three days), and at the same time, the new antipsychotic is started and titrated up.

The efficacy of medication combinations is discussed separately in the context of mixed-age adults with severe manic episodes. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Severe manic episodes'.)

Subsequent approach — For treatment-resistant geriatric bipolar patients who do not respond to or tolerate medication combinations (see 'Preferred approach' above), we suggest aripiprazole, asenapine, risperidone, or ziprasidone as monotherapy or as add-on therapy with lithium or valproate for four weeks [16,25,41-44]. The choice to prescribe aripiprazole, asenapine, risperidone, or ziprasidone as monotherapy or add-on therapy is based upon the efficacy and tolerability of lithium or valproate in prior treatment trials. The administration of these drugs is as follows:

- **Aripiprazole**
  - Starting dose 2.5 to 5 mg once daily
  - Target dose 5 to 15 mg once daily
  - Maximum dose 30 per day
- **Asenapine**
  - Starting dose 5 mg once or twice daily
  - Target dose 10 mg twice daily
  - Maximum dose 20 mg per day
- **Risperidone**
  - Starting dose 0.5 to 1 mg once daily or in two divided doses
  - Target dose 1 to 4 mg once daily or in two divided doses
  - Maximum dose 6 mg per day

- **Ziprasidone**
  - Starting dose 20 mg once daily or 40 mg per day in two divided doses
  - Target dose 80 to 120 mg per day, in two divided doses
  - Maximum dose 160 mg per day

To reach the target dose of aripiprazole, asenapine, risperidone, or ziprasidone monotherapy, we suggest increasing the dose every two to five days by increments equal to the starting dose. At the same time, both drugs of the failed regimen are concurrently tapered and discontinued over one to two weeks. Each failed medication is decreased by the same amount each time the dose is decreased. As an example, if the patient is receiving lithium 900 mg per day and olanzapine 10 mg per day, lithium is decreased by 300 mg per day every one to three days, and olanzapine by 5 mg every one to three days.

To reach the target dose of aripiprazole, asenapine, risperidone, or ziprasidone as add-on therapy, we suggest increasing the dose every two to five days by increments equal to the starting dose. At the same time, the failed antipsychotic (eg, olanzapine or quetiapine) is concurrently tapered and discontinued over one to two weeks.

The use of aripiprazole, asenapine, risperidone, or ziprasidone for mania and hypomania is based upon randomized trials in mixed-age adults. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'First-line monotherapy'.)

In addition, low-quality evidence in older adults with mania or hypomania, as well as our clinical experience, suggests that these four drugs may be helpful:

- Aripiprazole – A 12-week prospective observational study of two older patients with mania who were treated with adjunctive aripiprazole (mean dose roughly 10 mg/day) found that both patients improved substantially [45].

- Asenapine – Multiple prospective observational studies suggest that asenapine may be helpful [42,43]. As an example, in a study of 25 older patients with mania who completed three weeks of treatment with asenapine (10 mg twice daily), remission occurred in 56 percent [44].

- Risperidone – A case series of two geriatric patients hospitalized with bipolar mood episodes with mixed features found that adjunctive risperidone (mean dose 1.5 mg twice daily) was associated with marked improvement in one patient and no improvement in the other patient [46].

- Ziprasidone – There do not appear to be any published studies regarding the benefit of ziprasidone in older bipolar patients [19,20].

Second-generation antipsychotics are associated with an increased risk of death in older patients treated for dementia-related psychosis (primarily due to cardiovascular events or infections) [20,37]; some authorities believe this risk may extend to late-life bipolar disorder [38]. Information about other side effects (table 5) of aripiprazole, asenapine, risperidone, and ziprasidone is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Second-generation' and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

Other options — Adjunctive memantine may be useful for geriatric mania. An eight-week randomized trial compared valproate plus memantine with valproate plus placebo in older patients with acute mania (n = 58) [47]. Improvement of mania was greater with adjunctive memantine.

Refractory patients — Based upon clinical experience, geriatric mania and hypomania generally respond to treatment with first-line or second-line medications. For refractory manic episodes that do not respond to four to eight medication trials, we prefer ECT. However, several reasonable alternatives are available, such as first-generation antipsychotics.

Preferred approach — For refractory patients whose manic episodes do not respond to four to eight medication trials, we suggest ECT [1,38].

ECT is generally safe and there are no absolute contraindications, even in patients whose general medical status is compromised [48]. However, safety concerns regarding ECT necessitate preprocedure medical consultation. Adverse effects include cardiopulmonary events, aspiration pneumonia, fractures, dental and tongue injuries, headache, nausea, and cognitive impairment. Medical consultation prior to ECT is discussed separately. (See "Medical evaluation for electroconvulsive therapy".)

Electrode placement and other aspects of ECT technique for treating geriatric bipolar disorder have not been standardized. Thus, ECT is typically administered with the same technique used for other indications and is generally given three times per week on alternating days. Most patients regardless of indication remit with 6 to 12 treatments, but some patients may require 20 or more. Additional information about ECT is discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

Although there is little direct evidence for the antimanic efficacy of ECT in geriatric patients [1,49], several high-quality studies suggest that ECT is effective for mixed-age manic patients. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Mania'.)

Baseline cognitive status in older patients should be assessed prior to commencing ECT, especially if bilateral ECT is used, because ECT may cause cognitive impairment [5]. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Adverse cognitive effects'.)

Alternative approach — A reasonable alternative to ECT for refractory geriatric mania or hypomania is a trial with a first-generation antipsychotic, carbamazepine, levetiracetam, gabapentin, or clozapine.

- **First-generation antipsychotic** – Among first-generation antipsychotics, we suggest haloperidol, which is started at a dose of 0.5 to 2.0 mg daily, and increased every three to five days by the same amount to a target dose of 5 mg daily, and a maximum of 10 mg per day. Compared with second-generation antipsychotics, first-generation antipsychotics are more likely to cause extrapyramidal symptoms and tardive dyskinesia, and their incidence increases with age [38]. In addition, first-generation antipsychotics are associated with an increased risk of death in older patients treated for dementia-related psychosis [37]; some authorities believe this risk may extend to late-life bipolar disorder [38]. Evidence for the efficacy of haloperidol includes a network meta-analysis of randomized trials in mixed-age patients with manic or mixed (concurrent manic and depressive symptoms) episodes; haloperidol was more effective than many other antimanic agents. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'First-line monotherapy'.)

  Additional information about the dose and side effects (table 5) of first-generation antipsychotics is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'First-generation' and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects", section on 'Side effects'.)

- **Carbamazepine** – Carbamazepine is started at 100 mg once or twice per day, and is increased every three to five days by the same amount [25,31,50]. The target dose is generally determined by 12-hour serum trough levels that should be drawn three to five days after each dose increase. Based upon clinical experience, we suggest that carbamazepine be dosed to achieve a serum level of 4 to 12 mcg/mL, which is typically achieved with a dose of 400 to 800 mg per day in two divided doses. A study of 12 geriatric

bipolar patients who recovered from their mood episode with carbamazepine found that the mean daily dose was 608 mg per day [16]. Adverse effects in geriatric bipolar patients include sedation, ataxia, blurred vision, nystagmus, and leukopenia, or more rarely agranulocytosis [31]. Additional information about the dose, side effects (table 4), and efficacy of carbamazepine is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Carbamazepine'.)

- **Levetiracetam** – Levetiracetam may possibly benefit geriatric bipolar patients with refractory mania or hypomania. A case series of six older bipolar patients found that adjunctive levetiracetam (median dose 500 mg per day) improved manic symptoms and was well tolerated [51]. Additional information about the adverse effects of levetiracetam (table 4) is discussed separately. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Levetiracetam'.)

- **Gabapentin** – Gabapentin may perhaps help late-life refractory mania or hypomania. A case series of seven hospitalized geriatric bipolar patients who were treated with antipsychotics found that adjunctive gabapentin (mean daily dose 600 to 1200 mg) improved manic symptoms and was well tolerated [52]. Additional information about the adverse effects of gabapentin (table 4) is discussed separately. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Gabapentin'.)

- **Clozapine** – Another alternative to ECT for geriatric patients with refractory mania or hypomania is clozapine. The usual starting dose is 12.5 or 25 mg per day, which is increased by the same amount every day to 25 mg twice per day. Subsequently, the dose is increased by 25 mg per day every day as tolerated, to a target dose of approximately 150 mg twice per day.

  One concern with clozapine in older patients is fall risk related to sedation and postural hypotension. In addition, second-generation antipsychotics are associated with an increased risk of death in older patients treated for dementia-related psychosis (primarily due to cardiovascular events or infections) [20,37]; some authorities believe this risk may extend to late-life bipolar disorder [38]. Clozapine can also cause agranulocytosis and white blood cell counts need to be monitored. Evidence of its efficacy includes a case series of three refractory manic, geriatric patients who responded to clozapine (25 to 112.5 mg per day) [53]. Additional information about the administration, adverse effects, and efficacy of clozapine is discussed separately. (See "Bipolar mania and hypomania in adults:

Choosing pharmacotherapy", section on 'Other options' and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Bipolar major depression — Geriatric bipolar major depression is typically treated with pharmacotherapy because it is easier to administer, more widely available, and more acceptable to patients compared with ECT. However, refractory patients may benefit from ECT.

First-line treatment — We suggest lurasidone or quetiapine as first-line treatment for geriatric bipolar depression, based upon analyses of results for geriatric patients enrolled in randomized trials conducted with mixed-age adult bipolar patients [54,55]. Clinicians can expect that approximately 40 to 50 percent of patients will respond to lurasidone or quetiapine, based upon study results.

- **Lurasidone** – The starting dose of lurasidone in older bipolar patients is 20 mg once daily in the evening; lurasidone is taken with a meal (eg, >350 calories) to limit gastrointestinal side effects. The dose can be increased every two to seven days by increments of 20 mg per day to optimize effectiveness. The target dose range is 20 to 120 mg/day. In a six-month prospective observational study of 141 older patients who were treated with lurasidone, the mean daily dose was 65 mg [56].

  Adverse effects of lurasidone include insomnia, diarrhea, somnolence, akathisia, fatigue, vomiting, nasopharyngitis, and muscle spasms. In addition, second-generation antipsychotics are associated with an increased risk of death (primarily cardiovascular events or infections) in older patients treated for dementia-related psychosis [37]; some authorities believe this risk may extend to late-life bipolar disorder [38].

  The efficacy of lurasidone for bipolar major depression was demonstrated in a six-week randomized trial with mixed age patients (n = 505, 18 to 75 years old) [57]. In the subgroup of patients aged 55 years and older (n = 88), remission occurred in more patients who received lurasidone than placebo (38 versus 15 percent) [55]. In addition, discontinuation of treatment due to adverse effects was 7 percent in both groups. Afterwards, 55 of the older patients were treated with lurasidone in a prospective, observational extension study lasting six months; the drug remained effective and was well tolerated [56].

- **Quetiapine** – In older bipolar patients, quetiapine is usually started at 12.5 to 25 mg once daily or 25 to 50 mg per day in two divided doses [16,25]. The dose is then increased every two to five days by increments equal to the starting dose to reach the target dose of 100 to 300 mg per day, taken in two divided doses. For patients who neither respond to 300 mg per day nor are troubled by side effects, the dose may be increased up to 600 mg per day [54].

In geriatric patients with bipolar major depression, quetiapine commonly causes dry mouth, sedation, dizziness, constipation, dyslipidemia, hyperglycemia, and weight gain [1,54]. In addition, second-generation antipsychotics are associated with an increased risk of death (primarily cardiovascular events or infections) in older patients treated for dementia-related psychosis [37]; some authorities believe this risk may extend to late-life bipolar disorder [38].

Evidence of efficacy includes a pooled analysis of two, eight-week randomized trials that compared quetiapine with placebo in mixed-age patients with bipolar major depression [54]. In the subgroup of 72 older patients, remission occurred more often with quetiapine 300 or 600 mg per day than placebo (45 and 48 versus 28 percent of patients). Although the differences between active treatment and placebo were not statistically significant, the results were consistent with the finding in younger patients that remission occurred significantly more often with quetiapine 300 or 600 mg than placebo. Among the older patients, withdrawal from treatment was comparable for quetiapine 300 mg per day and placebo (29 versus 30 percent of patients), but was greater for quetiapine 600 mg per day than placebo (48 versus 30 percent).

Additional information about using quetiapine to treat bipolar depression is discussed separately in the context of mixed age patients. (See "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics", section on 'Quetiapine'.)

Treatment resistance — Geriatric bipolar major depression may not respond to treatment with lurasidone [55] or quetiapine [54]. For these treatment-resistant patients, we suggest switching to a second-line drug regimen, consisting of lamotrigine, fluoxetine plus olanzapine, lithium, or valproate [1,38]. No head-to-head trials have compared the efficacy of these drugs for treating geriatric bipolar depression. The choice thus depends upon prior response to medications, side effect profiles, comorbid general medical conditions, potential for drug-drug interactions, patient preference, and cost. Randomized trials in mixed-age patients indicate that lamotrigine, fluoxetine plus olanzapine, lithium, or valproate are efficacious. (See "Bipolar major depression in adults: Choosing treatment" and "Bipolar major depression in adults: Efficacy and adverse effects of second-generation antipsychotics" and "Bipolar major depression in adults: Efficacy and adverse effects of antidepressants".)

To switch drugs, lurasidone or quetiapine is tapered and discontinued over one to two weeks while at the same time a new drug regimen is started and titrated up. We generally taper lurasidone or quetiapine by the same amount for each dose decrease. As an example, quetiapine 300 mg per day is decreased by 50 mg per day, every one to three days.

The starting dose of lamotrigine in older bipolar patients is 25 mg per day for two weeks [25,58]. The dose is then increased to 25 mg twice daily for the next two weeks. Thereafter, the dose can be increased by 25 to 50 mg per day, once a week for each increase. This slow titration reduces the risk of serious and life-threatening skin rashes, such as Stevens-Johnson syndrome. The target dose is usually 100 to 200 mg per day, taken in two divided doses. A study of 41 geriatric bipolar patients who recovered from their mood episode with lamotrigine found that the mean daily dose was 163 mg per day [16].

Evidence for the efficacy of adjunctive lamotrigine (mean daily dose 151 mg per day) includes a 12-week, open-label study in 57 geriatric patients with bipolar major depression [58]. Baseline depressive symptoms and psychosocial functioning improved significantly and remission occurred in 57 percent. Withdrawal from treatment due to adverse events occurred in 11 percent; side effects included benign rash, reduced or increased sleep duration, weight loss or weight gain, fatigue, and unsteady gait.

Fluoxetine plus olanzapine can efficaciously treat bipolar major depression [59]. A randomized trial (n = 437 mixed-age adults) found that remission occurred in more patients who received fluoxetine plus olanzapine than placebo (49 versus 25 percent) [60]. For geriatric patients, we suggest starting fluoxetine at 10 mg per day and increasing the dose by the same amount every four weeks, to a target dose of 20 mg per day. Possible side effects include sedation, insomnia, weight loss or weight gain, abnormal bleeding, bone loss, and fractures. Given its long half-life, fluoxetine should be used carefully in older adults. Although use of other antidepressants is not supported by high-quality evidence, we have successfully used either escitalopram 10 to 20 mg per day or venlafaxine 37.5 mg to 225 mg per day. The dose and side effects of olanzapine are discussed elsewhere in the topic, and additional information about fluoxetine is discussed separately. (See 'First-line treatment' above and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Lithium [61] and valproate [62] can each effectively treat geriatric bipolar major depression. The dose and side effects of lithium and valproate are discussed elsewhere in this topic. (See 'First-line medications' above.)

For geriatric bipolar depression that does not respond to treatment with one second-line medication regimen within four to eight weeks of reaching the target dose, we suggest tapering and discontinuing the failed regimen over one to two weeks at the same time that another second-line regimen is started and titrated up. The failed regimen is generally tapered by the same amount for each dose decrease. As an example, lamotrigine 150 mg per day is decreased by 50 mg per day, every one to three days. For patients who discontinue fluoxetine plus olanzapine, both drugs are tapered concurrently.

Refractory major depression — Geriatric bipolar major depression often does not respond to pharmacotherapy [54,58,62]. For refractory patients whose depression does not respond to three to five medication trials, we suggest ECT [38]. Evidence supporting the use of ECT includes studies in mixed age bipolar patients. (See "Bipolar disorder in adults: Indications for and efficacy of electroconvulsive therapy", section on 'Bipolar major depression'.)

Although an open-label study with 20 geriatric bipolar patients suggested that adjunctive aripiprazole may possibly improve depressive symptoms [45], we generally do not use it. Two randomized trials in mixed-age adults (n = 374 and 375) with bipolar major depression each found that remission with aripiprazole monotherapy was no better than placebo, and that aripiprazole caused more akathisia, insomnia, nausea, fatigue, restlessness, and dry mouth [63].

RECOVERY FROM MOOD EPISODES (PROGNOSIS)

Prognostic factors that are consistently associated with poor response to treatment in late life bipolar disorder include poor adherence, comorbid substance use disorders, and comorbid neurologic disorders [5].

Geriatric bipolar patients generally recover from their mood episodes and appear to do so more often than younger patients. As an example, the Systematic Treatment Enhancement Program for Bipolar Disorder found that recovery from mood episodes occurred in significantly more geriatric patients than younger patients (78 versus 67 percent) [16].

Geriatric bipolar disorder with late-onset (age 50 years or more) may have a better short-term prognosis than earlier-onset bipolar disorder that has persisted into later life [64]. An observational study found that time to remission of manic or mixed (concurrent manic and depressive symptoms) episodes was shorter for 141 late-onset patients compared with 323 earlier-onset patients (40 versus 56 days) [65].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Bipolar disorder".)

INFORMATION FOR PATIENTS

Information for patients (patient education) is discussed separately. (See "Geriatric bipolar disorder: General principles of treatment".)

SUMMARY AND RECOMMENDATIONS

- The minimum age used to define geriatric bipolar disorder is generally 50 to 60 years. The clinical features of geriatric bipolar disorder differ from those of younger patients in that cognitive impairment and comorbid general medical illnesses are more common in geriatric patients, whereas comorbid anxiety and substance use disorders are less common in geriatric patients. (See 'Definition of geriatric bipolar disorder' above and "Geriatric bipolar disorder: Epidemiology, clinical features, assessment, and diagnosis", section on 'Clinical features'.)

- The general principles and issues involved in treating geriatric bipolar disorder include the following: goal of treatment, initial evaluation, level of care, pharmacologic issues, monitoring, adjunctive psychoeducation, general medical comorbidity, managing nonresponse, and making referrals. (See "Geriatric bipolar disorder: General principles of treatment".)

- For geriatric patients with acute mania or hypomania, we suggest monotherapy with lithium, valproate, olanzapine, or quetiapine, rather than other medications (**Grade 2C**). Factors that help determine the specific choice include past response to medications, psychotic symptoms, side effect profiles, comorbid general medical illnesses, potential for drug-drug interactions, patient preference, and cost. Our order of preference is lithium, valproate, olanzapine, and quetiapine. Patients who don't respond to or tolerate one drug are switched to another drug. (See 'First-line medications' above.)

- Geriatric manic and hypomanic episodes that do not respond to lithium, valproate, olanzapine, or quetiapine are treated with a combination of lithium or valproate plus risperidone, quetiapine, or olanzapine. (See 'Second-line medications' above.)

- For geriatric patients with bipolar major depression, we suggest initial treatment with lurasidone or quetiapine rather than other drugs (**Grade 2B**). (See 'First-line treatment' above.)

- For treatment of geriatric bipolar major depression that does not respond to lurasidone or quetiapine, we suggest lamotrigine, olanzapine plus fluoxetine, lithium, or valproate, rather than other drugs. (See 'Treatment resistance' above.)

- For geriatric patients with mania that is refractory to treatment with four to eight medication trials, and for patients with refractory bipolar major depression that is refractory to three to five medication trials, we suggest ECT rather than additional pharmacotherapy trials (**Grade 2B**). (See 'Refractory patients' above and 'Refractory major depression' above.)

- Geriatric bipolar patients appear to recover from their mood episodes more often than younger patients. (See 'Recovery from mood episodes (prognosis)' above.)

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