Treatments for Late-Life Bipolar Disorder

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ABSTRACT

Background: Bipolar affective disorder is not uncommon in the elderly; prevalence rates in the United States range from 0.1% to 0.4%. However, it accounts for 10% to 25% of all geriatric patients with mood disorders and 5% of patients admitted to geropsychiatric inpatient units. These patients often present a tremendous treatment challenge to clinicians. They frequently have differing treatment needs compared with their younger counterparts because of substantial medical comorbidity and age-related variations in response to therapy. Unfortunately, the management of geriatric bipolar disorder has been relatively neglected compared with the younger population. There continues to be a scarcity of published, controlled trials in the elderly, and no treatment algorithms specific to bipolar disorder in the elderly have been devised.

Objective: The goal of this article was to review the current literature on both the pharmacologic and nonpharmacologic management of late-life bipolar disorder.

Methods: English-language articles written on the treatment of bipolar disorder in the elderly were identified. The first step in data collection involved a search for evidence-based clinical practice guidelines in the Cochrane Database of Systematic Reviews (up until the third quarter of 2006). Systematic reviews were then located in the following databases: MEDLINE (1966–September 2006), EMBASE (1980–2006 [week 36]), and PsycINFO (1967–September 2006 [week 1]). Additional use was made of these 3 databases in searching for single randomized controlled trials, meta-analyses, cohort studies, case-control studies, case series, and case reports. "Elderly," used synonymously with "geriatric," was defined as individuals aged ≥60 years. However, to take into account ambiguity in the nomenclature, the key words *aged*, *geriatric*, *elderly*, and *older* were combined with words indicating pharmacologic treatments such as *pharmacotherapy*; classes of medications (eg, *lithium*, *antidepressants*, *antipsychotics*, *anticonvulsants*, *benzodiazepines*); and names of selected individual medications (eg, *lithium*, *valproic acid*, *lamotrigine*, *carbamazepine*, *oxcarbazepine*, *topiramate*, *gabapentin*, *zonisamide*, *clozapine*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, *aripiprazole*). These terms were then combined with the diagnostic terms *bipolar disorder*, *mania*, *hypomania*, *depression*, or *bipolar depression*. Finally, the terms *ECT* and *psychotherapy* were also queried in combination with indicators for age and diagnosis. A few articles on "older adults," usually defined as individuals aged 50 to 55 years, were also included. They may allow for possible extrapolation of data to the geriatric population. Additionally, several mixed-age studies were included for similar considerations. Case reports and case series were described for their potential heuristic value.

Results: Unfortunately, there is a considerable dearth of literature involving evidence-based clinical practice guidelines and even randomized controlled trials in elderly individuals with bipolar disorder. Available options for the treatment of bipolar disorder (including those for mania, hypomania, depression, or maintenance) in the elderly include lithium, antiepileptics, antipsychotics, benzodiazepines, antidepressants, electroconvulsive therapy (ECT), and psychotherapy.

Conclusions: The data for the treatment of late-life bipolar disorder are limited, but the available evidence shows efficacy for some commonly used treatments. Lithium, divalproex sodium, carbamazepine, lamotrigine, atypical antipsychotics, and antidepressants have all been found to be beneficial in the treatment of elderly patients with bipolar disorder. Although there are no specific guidelines for the treatment of these patients, monotherapy followed by combination therapy of the various classes of drugs may help with the resolution of symptoms. ECT and psychothera-

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py may be useful in the treatment of refractory disease. There is a need for more controlled studies in this age group before definitive treatment strategies can be enumerated. (*Am J Geriatr Pharmacother.* 2006;4:347–364)

Key words: elderly, geriatric, late life, bipolar disorder, mania, depression, management.

INTRODUCTION

Bipolar affective disorder is not uncommon in the elderly. Prevalence rates in the United States range from 0.1% to 0.4%.[1] However, it accounts for 10% to 25% of all geriatric patients with mood disorders and 5% of all patients admitted to geropsychiatric inpatient units.[2] Most elderly patients with bipolar disorder present with a combination of manic and depressive symptoms.[3] These patients may also appear delirious.[4] Geriatric patients with bipolar disorder also have higher rates of comorbid alcohol use disorders, dysthymia, generalized anxiety disorder, and panic disorder than elderly patients without bipolar disorder.[5]

From an economic standpoint, Bartels et al[6] indicated that elderly bipolar patients use mental health services more than elders with unipolar mood disorders. Depp et al[7] reported age differences in patterns of health care use: elderly patients with bipolar disorder were less likely than younger patients with bipolar disorder to use inpatient, outpatient, and emergency department psychiatric care but more likely to use case management and conservator services. The mortality rate for both mixed-age bipolar patients and patients with late-life bipolar disorder is higher than that of the general population.[8]

Major risk factors for the development of late-life bipolar disorder are neurologic illness, cerebrovascular disease, and a family history of affective disorders.[9–11] Young et al[12] found that elderly manic patients were much more likely to have greater cortical sulcal widening and lateral ventricle–brain ratio scores compared with younger subjects and that the cortical sulcal widening was associated with onset of illness at a later age.

There is some evidence that the prognosis for the elderly with bipolar disorder is worse than in their younger counterparts.[13] Elderly bipolar patients often have incomplete response to treatment, recurrent episodes of illness, and higher mortality rates than the younger population. Suicide rates are the highest of all age groups in the elderly, and bipolar disorder is also associated with a high risk of suicide. Elderly patients with bipolar disorder who are treated with mood stabilizers and antidepressants, however, appear to be at significantly reduced risk of attempting suicide ($P = 0.047$).[14]

Recently, a pilot study of standardized treatment in geriatric bipolar disorder was completed.[15] The study was small (N = 31), prospective, and open-label. The mean follow-up period was 398 days, and patients were treated with standardized treatment pathways for bipolar disorder. The mean percentage of "well days"—defined as scores of ≤10 on both the 17-item Hamilton Rating Scale for Depression and the Young Mania Rating Scale—was 72.5%. The authors of the study concluded that treating older adults with bipolar disorder under standardized treatment protocols was feasible. However, only 10% of the participants experienced sustained recovery, even with standardized treatment regimens.[15]

Unfortunately, there continues to be limited data on the treatment for late-life bipolar disorder.[16] The data that are available suffer from a lack of adequate randomized, placebo-controlled studies. It is difficult, therefore, to arrive at any definitive conclusions regarding the management of this disorder. Given this complicated scenario, clinicians tend to depend on anecdotal evidence, case reports, and expert opinion rather than on reliable data. This often leads to inadequate treatment response, unacceptable adverse-effect rates, and frustration in dealing with these patients.

In this article, we summarize the data available on the treatment of late-life bipolar disorder. This will help clinicians use the data in an appropriate manner, thereby improving the quality of their patient care.

MATERIALS AND METHODS

Data Sources

English-language articles written on pharmacologic and nonpharmacologic treatments, including electroconvulsive therapy (ECT) and psychotherapy, for bipolar disorder in the elderly were identified. The first step in data collection involved a search for evidence-based clinical practice guidelines in the Cochrane Database of Systematic Reviews (up until the third quarter of 2006). Systematic reviews were then located in the following databases: MEDLINE (1966–September 2006), EMBASE (1980–2006 [week 36]), and PsycINFO (1967–September 2006 [week 1]). Additional use was made of these 3 databases in searching for single randomized controlled trials and other high-quality evidence from meta-analyses, cohort studies, case-control studies, case series, and case reports. In rare instances, the full text could not be obtained (usually for older articles), and data were instead obtained from abstracts.

Selection Criteria

There is considerable confusion in the literature concerning the age cutoff for "elderly." In this review, elderly was defined as being aged ≥60 years. However, to take into account ambiguity in the nomenclature, the key words *aged*, *geriatric*, *elderly*, and *older* were combined with words indicating pharmacologic treatments such as *pharmacotherapy*; classes of medications (eg, *lithium*, *antidepressants*, *antipsychotics*, *anticonvulsants*, *benzodiazepines*); and names of selected individual medications (eg, *lithium*, *valproic acid*, *lamotrigine*, *carbamazepine*, *oxcarbazepine*, *topiramate*, *gabapentin*, *zonisamide*, *clozapine*, *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, *aripiprazole*). These terms were then combined with the diagnostic terms *bipolar disorder*, *mania*, *hypomania*, *depression*, or *bipolar depression*. Finally, the terms *ECT* and *psychotherapy* were also queried in combination with indicators for age and diagnosis.

Preference was given to evidence-based reviews, meta-analyses, and randomized, placebo-controlled trials. When evidence was lacking, individual clinical trials were examined. A few articles on "older adults," usually defined as individuals aged 50 to 55 years, were also included. They may allow for possible extrapolation of data to the geriatric population. Several mixed-age studies were included for similar considerations. Case reports and case series were described for their potential heuristic value.

RESULTS

There is a considerable dearth of literature involving evidence-based clinical practice guidelines and even randomized controlled trials in elderly individuals with bipolar disorder. In general, psychiatric illness in the geriatric population has not been well studied. Because of the lack of data regarding the treatment of geriatric patients with bipolar disorder, the existing evidence is largely derived from extrapolations from "mixed-age" or "older" patient studies, case series, and case reports.

Table I provides an overview of the various mood stabilizers used in bipolar disorder treatment; **Table II** and **Table III** summarize information regarding antipsychotic agents, antidepressants, and benzodiazepines, respectively.[17]

Lithium

Lithium is considered a first-line treatment for bipolar disorder.[18] However, based on our literature review, there are no published, randomized, placebo-controlled trials of lithium in the elderly. Recommendations for clinical use have been based on extrapolations from pharmacokinetic studies, anecdotal reports from mixed-age populations, and clinical experience in geriatric psychiatry.[19]

Although there has been some suggestion that lithium may be less effective in geriatric patients, supportive evidence for this assumption is lacking. Most studies appear to indicate that lithium is equally efficacious in all age groups.[20] Despite this, a recent study showed that prescription patterns are shifting in favor of valproic acid over lithium for elderly patients with bipolar disorder.[21]

In terms of acute therapeutic outcomes with lithium, Young et al[16] reviewed 4 studies each involving >10 elderly patients. The total number of older adult (aged 50–55 years) and elderly (age ≥60 years) patients in the trials was 137. Overall, 66% of patients improved on lithium within a 2- to 10-week time frame. Lithium dosages were not reported. In 3 of the studies, the lithium levels ranged between 0.3 and 2.0 mEq/L.

It is well established that lithium's pharmacokinetics are substantially altered by age. Although the absorption of lithium is generally unchanged in the elderly,[22] its kinetics may be influenced by a number of factors, including reduced volume of distribution and reduced renal clearance. These changes can cause an increase in the concentration–dose ratios. The volume of distribution is decreased in the elderly due to increased adipose tissue, decreased skeletal muscle mass, and decreased total body water.[19] Furthermore, lithium is eliminated renally. Because renal clearance is reduced in older adults, its elimination half-life is longer than in younger adults (28–36 vs 24 hours).[23,24] Therefore, it has been suggested that the elderly may require lower dosages and serum levels.[22]

The effects of other medical conditions on the pharmacokinetics of lithium in the elderly are less well defined. Reduced lithium clearance is expected in patients with hypertension, congestive heart failure, and renal dysfunction. Larger lithium maintenance doses are usually required in obese compared with nonobese patients.[19] In terms of drug interactions, the most clinically significant ones are associated with agents that are commonly used in the geriatric population. For example, thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, and NSAIDs all increase serum lithium concentrations.[19] Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of lithium toxicity when they are used in conjunction with each other. Finally, sodium deficiency—caused by

Table I. Overview of mood stabilizers used in the treatment of bipolar disorder.[17]

Medication	Dosage	Selective Adverse-Effect Profile	Drug–Drug Interactions
Lithium: No RCTs in geriatric bipolar disorder. Four positive geriatric open-label case series.	0.4–0.7 mEq/L	Common: Weight gain, memory loss, ataxia, fine hand tremor, polyuria. Serious: Coma, increased intracranial pressure, seizure, arrhythmias, diabetes insipidus, hypothyroidism.	Lithium concentration increases with ACE inhibitors, thiazide and loop diuretics, NSAIDs, SSRIs, hypertension, congestive heart failure, renal dysfunction, and sodium deficiency.
Divalproex sodium: No RCTs in geriatric bipolar disorder. Four positive retrospective studies.	65–90 μg/mL	Common: Nausea, somnolence, parkinsonism, weight gain, hair thinning. Serious: Coma, liver failure, pancreatitis, thrombocytopenia.	Acetylsalicylic acid increases valproic acid concentration. Phenytoin and carbamazepine decrease valproic acid concentrations. Valproic acid increases concentrations of phenobarbital, phenytoin, lamotrigine, tricyclic antidepressants, and warfarin.
Carbamazepine: No RCTs in geriatric bipolar disorder.	4–12 μg/L	Common: Dizziness, sedation, cognitive deficits, rashes. Serious: Nephrotoxicity, hepatitis, arrhythmias, porphyria, bone marrow depression, SLE, SJS, TEN, SIADH.	Calcium channel antagonists, cimetidine, terfenadine, and erythromycin.
Lamotrigine: Retrospective review of 2 mixed-age RCTs.	25–400 mg/d	Common: Dizziness, sedation, headache, ataxia, rash (0.3%). Serious: SJS, blood dyscrasias, TEN, liver failure.	Lamotrigine increases concentration of carbamazepine. Lamotrigine decreases concentration of valproic acid. Lamotrigine concentration is increased by valproic acid. Lamotrigine concentration is decreased by carbamazepine.
Oxcarbazepine: No RCTs in geriatric bipolar disorder.	150–1200 mg/d	Common: Nausea, dizziness, somnolence. Serious: Hyponatremia, SJS, TEN.	Phenytoin, phenobarbital, carbamazepine, and verapamil reduce oxcarbazepine concentration. Oxcarbazepine increases phenytoin concentration. Oxcarbazepine decreases lamotrigine and topiramate concentrations.
Gabapentin: Two positive geriatric, open-label case series of augmentation for bipolar depression.	100–5400 mg/d	Common: Somnolence, ataxia, dizziness. Serious: Seizure, SJS.	Minimal interaction potential due to lack of hepatic enzyme induction or inhibition. Excreted by the kidneys.
Topiramate: One positive geriatric, open-label case study of augmentation for bipolar depression.	25–400 mg/d	Common: Somnolence, cognitive deficits, paresthesias, weight loss. Serious: Blood dyscrasias, hypohidrosis, dyspnea, hepatitis, hyperammonemia, nephrotoxicity, pancreatitis.	Minimal drug interactions and limited hepatic metabolism with low protein binding.
Zonisamide: No RCTs in geriatric bipolar disorder.	100–400 mg/d	Common: Drowsiness, loss of appetite, dizziness, headache, nausea, agitation/irritability. Serious: Renal stones, SJS, TEN, fulminant hepatic necrosis, agranulocytosis, aplastic anemia.	Phenytoin, phenobarbital, and carbamazepine induce the metabolism of zonisamide. The metabolism of zonisamide is inhibited by ketoconazole, cyclosporine, miconazole, and fluconazole.

RCTs = randomized controlled trials; ACE = angiotensin-converting enzyme; SSRIs = selective serotonin reuptake inhibitors; SLE = systemic lupus erythematosus; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; SIADH = syndrome of inappropriate antidiuretic hormone.

Table II. Overview of antipsychotic agents used in the treatment of bipolar disorder.[17]

Medication	Dosage	Adverse-Effect Profile
Clozapine: One positive geriatric open-label case series of clozapine augmentation in bipolar I disorder.	25–800 mg/d	Common: Weight gain, sedation, postural hypotension, hypersalivation, urinary retention, constipation. Serious: Agranulocytosis, blood dyscrasias, myocarditis, hepatitis, pancreatitis, ileus, pulmonary embolism, seizure, NMS.
Risperidone: One positive geriatric open-label case series.	0.5–4 mg/d	Common: Postural hypotension, EPS, weight gain. Serious: CVA, NMS, priapism, seizure, thrombocytopenic purpura, hyperprolactinemia.
Olanzapine: No RCTs in geriatric bipolar disorder.	2.5–20 mg/d	Common: Postural hypotension, dose-dependent EPS, diabetes mellitus, weight gain, hyperlipidemia. Serious: CVA, NMS, seizure.
Quetiapine: No RCTs in geriatric bipolar disorder.	50–800 mg/d	Common: Hypotension, EPS, diabetes mellitus, weight gain, hyperlipidemia. Serious: Leukopenia, NMS, seizure, hepatitis.
Aripiprazole: No RCTs in geriatric bipolar disorder.	2.5–30 mg/d	Common: Sedation, weight gain, anticholinergic effects. Serious: NMS, hypotension, seizure.

NMS = neuroleptic malignant syndrome; EPS = extrapyramidal symptoms; CVA = cerebrovascular accident; RCTs = randomized controlled trials.

Table III. Overview of antidepressants and benzodiazepines used in the treatment of bipolar disorder.[17]

Medication	Adverse-Effect Profile
SSRIs: One positive RCT in adults and elderly with bipolar depression.	Common: Nausea, diarrhea, insomnia, sexual dysfunction. Serious: Depression worsening, hypomania, hyponatremia, seizure, suicidal thinking and behavior, bleeding.
TCAs: No RCTs in geriatric bipolar disorder.	Common: Anticholinergic and orthostatic effects, sedation, weight gain, sexual dysfunction. Serious: Agranulocytosis, blood dyscrasias, arrhythmias, mania, CVA, hepatitis, depression worsening, hypertension, myocardial infarction, seizure.
Benzodiazepines: No RCTs in geriatric bipolar disorder.	Common: Falls due to gait disturbances or ataxia; cognitive impairment; sedation; risk of dependence. Serious: Variable.

SSRIs = selective serotonin reuptake inhibitors; RCT(s) = randomized controlled trial(s); TCAs = tricyclic antidepressants; CVA = cerebrovascular accident.

diet, drugs, or other factors—can increase lithium reabsorption and concentrations.[20]

Controversy exists regarding the optimal serum lithium levels in older adults. A target serum lithium level in the range of 0.4 to 0.7 mEq/L for older adults with bipolar disorder has been recommended.[22] Several studies have indicated that elderly patients require 25% to 50% lower dosages than younger patients.[20] However, the determination of appropriate serum levels should be influenced by age, medical status, tolerability, and frailty.[18]

The therapeutic benefits of lithium may be modified in the elderly. The adverse effects observed in younger adults are also seen in older patients. According to 1 retrospective chart review, there was no significant difference between elderly and adult patients with regard to the overall incidence of adverse effects, but there was a significantly greater incidence ($P < 0.02$) of moderate to severe adverse effects in the elderly.[25] Typical adverse events associated with lithium include gastrointestinal distress, nausea, vomiting, weight gain,

cognitive impairment, ataxia, fine hand tremor, cerebellar dysfunction, renal impairment, polyuria, polydipsia, diabetes insipidus, hypothyroidism, electrocardiogram (ECG) changes, rash, acne, and psoriasis.[18]

The neurotoxic effects of lithium are characterized by confusion, disorientation, memory loss, ataxia, and akathisia. Neurotoxicity may occur in the elderly at levels considered therapeutic in the adult population.[19] Underlying neurologic disorders, specifically those presenting with episodic confusion, dementia, or extrapyramidal symptoms (EPS), can be associated with an increased incidence of chronic mania, poorer response to lithium, and more frequent and severe neurotoxicity.[26] In a retrospective study of 114 elderly patients, delirium was the most common adverse effect of lithium treatment (19.3%) over 7.5 years. The mean serum lithium level was 0.5 mmol/L. Variables significantly associated with experiencing adverse effects included male sex and higher serum lithium levels.[27] Recovery from lithium-induced neurotoxicity may also be prolonged in patients who are very old or who have underlying clinical or subclinical brain disease.[28]

Tremor is an additional neurologic adverse effect of lithium. It may be bothersome to some patients and can result in treatment noncompliance. Both the prevalence and severity of fine hand tremor appear to increase with age.[29] Its prevalence varies from 40% to 58%.[25,30] Lithium-induced tremor may diminish with a reduction in dosage and serum concentration. However, in geriatric patients, other causes of tremor should be considered if it does not lessen after a reduction in dosage.[20]

Lithium can cause ECG alterations in geriatric patients. Specifically, reports have indicated a high frequency of ECG T-wave morphologic changes.[31] Therapeutic and toxic levels of lithium have occasionally been associated with serious cardiac dysfunction. Of particular concern have been cases of sinus node dysfunction, sinoatrial block, and the appearance or aggravation of ventricular irritability. The incidence of cardiac complications may increase with age.[31] In 1 case report, a 33-year-old woman demonstrated sinoatrial node block, which resolved in <24 hours with discontinuation of lithium.[32] In another report, a 44-year-old woman with no history of heart disease developed a high-grade atrioventricular block and bradycardia that was reversed by discontinuing lithium.[33] Roose et al[34] reported that 58% of elderly patients on maintenance lithium therapy had ECG abnormalities consisting of arrhythmias and conduction defects. It is recommended that patients who are at risk have periodic ECG investigations.[20]

Lithium also affects several other organ systems. It antagonizes thyroid function. In a survey of 148 elderly outpatients, 32% were on thyroxine or had elevated thyroid-stimulating hormone levels.[35] In another study of 46 psychiatric outpatients aged 50 to 84 years, polyuria, polydipsia, weight gain, and edema occurred in 46%.[36]

Lithium toxicity can be life-threatening. Its most dramatic manifestations involve the central nervous system and the kidneys. Some of the effects can be permanent. In a case-control study involving 10,615 elderly patients continuously treated with lithium, 4% were admitted at least once over 10 years for lithium toxicity.[37] Interestingly, the risk of lithium toxicity was dramatically increased when a loop diuretic or an ACE inhibitor had been started within the previous month. Neither thiazide diuretics nor NSAIDs were significantly associated with hospitalizations for lithium toxicity. Of the patients hospitalized, 15% were treated in a critical care unit, 3% underwent dialysis, and 5% died before discharge.[37]

Antiepileptic Drugs

The availability of newer antiepileptic drugs for clinical use has greatly multiplied over the last few years. This development has expanded the treatment options for bipolar disorder. However, only a few of them have been approved by the US Food and Drug Administration (FDA) for the treatment of bipolar disorder. Valproate has been FDA approved for the treatment of manic episodes associated with bipolar disorder, while lamotrigine is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, and mixed episodes) in patients treated for acute mood episodes with standard therapy. Carbamazepine has also shown efficacy in treating acute mania, and carbamazepine extended-release capsules are indicated for the treatment of acute manic and mixed episodes associated with bipolar I disorder. Newer anticonvulsants such as oxcarbazepine, zonisamide, levetiracetam, and phenytoin may offer some promise. However, gabapentin and topiramate do not appear to be efficacious in treating acute mania, and their utility in bipolar depression and prevention of mood episodes has not been fully studied.[38]

Based on our literature review, there do not appear to be any published, controlled studies with these medications that focus on late-life bipolar disorder. Recommendations for clinical use have been based on extrapolations from pharmacokinetic studies, anecdotal reports from mixed-age populations, and clinical expe-

rience in geriatric psychiatry. Valproate and carbamazepine reportedly are the most widely prescribed agents for bipolar disorder in the elderly.[18]

Valproic Acid

Valproic acid has been shown to be effective in the acute treatment of bipolar disorder in several studies. Young et al[16] reviewed 5 studies, 4 of which were retrospective and involved elderly manic patients taking valproate. A total of 137 patients were observed. The dosages ranged from 250 to 2250 mg/d. Valproate concentrations ranged from 25 to 120 μg/mL. Overall, 59% of patients met criteria for improvement. In a case series of 6 patients, 5 improved with valproate alone or in combination with other agents.[39] Another retrospective study, involving 59 patients, found similar response rates between valproate (75%) and lithium (82%) in the treatment of mania in older adult and elderly patients when therapeutic levels were achieved.[40] Even though valproate is being used more frequently in the geriatric population, 1 retrospective chart review concluded that its use did not lead to significant changes in length of hospital stay or in Global Assessment of Functioning outcome measures.[41]

Although controlled studies have not been completed, valproate in combination with lithium may be helpful for geriatric patients with rapid cycling bipolar disorder.[42] The combination may also be beneficial for elderly patients who are only partially responsive to lithium monotherapy.[42,43]

In terms of pharmacokinetics, age-associated changes involve decreased protein binding and decreased albumin levels. Valproic acid is mostly bound to albumin, resulting in an increase in the free (unbound) fraction of the drug. Because the unbound fraction of the drug is pharmacologically active, elderly patients may require lower dosages.[20] The elimination half-life may be prolonged as well, due to the greater volume of distribution in the aged.[44] Chen et al[40] have therefore suggested a lower therapeutic range for elderly patients on the order of 65 to 90 μg/mL.

Valproic acid is extensively metabolized in the liver. It is a weak inhibitor of drug oxidation. Serum concentrations of drugs that undergo oxidative metabolism (eg, phenobarbital, phenytoin, tricyclic antidepressants) may be increased.[20] Other significant drug–drug interactions in the elderly include the concomitant use of acetylsalicylic acid, which can increase the free fraction of valproate,[45] or warfarin. Valproic acid and its metabolites displace warfarin from its binding site on albumin, thereby increasing the unbound fraction of the drug.[46] The total valproate concentration–dose ratio is decreased by phenytoin and carbamazepine.[16] Valproate also inhibits the metabolism of lamotrigine.[16]

The most common adverse effects associated with valproate semisodium are gastrointestinal symptoms, somnolence, and weight gain. Other adverse effects include hair thinning, thrombocytopenia, and elevated liver enzyme levels.[18] Patients with urea cycle disorders may develop hyperammonemic encephalopathy.[18] Pancreatitis occurs in <1% of patients and is usually seen in younger patients, early in treatment. The risk of hepatic failure also appears to be lessened with increased age.[47]

Valproate has been associated with parkinsonism in elderly patients. In 1 case report, a 66-year-old woman with a bipolar disorder developed parkinsonism after taking valproate for 3 years.[48] Approximately 5 weeks after she stopped taking the drug, the parkinsonism improved. It appears that parkinsonism as an adverse effect of valproate occurs mainly in patients aged >50 years who have been on valproate for a long period of time. Once the medication is discontinued, parkinsonian symptoms decrease within a few months. The authors of the case report maintain that parkinsonism as an adverse effect of valproate is very likely to occur in patients with bipolar disorder. The mechanism whereby this occurs, however, is unclear.[48]

Lamotrigine

In 2003, lamotrigine received FDA approval for the maintenance treatment of bipolar disorder based on the results of 2 positive trials.[49,50] Lamotrigine was shown to stabilize mood by delaying the time to treatment for a mood episode. The results indicated that lamotrigine was an effective, well-tolerated maintenance treatment for bipolar disorder, particularly for prophylaxis of depression, although it was less effective than lithium for time to intervention in mania.[51] Additionally, in a small, 4-week, randomized, double-blind, clinical trial, lamotrigine was as effective as lithium in the treatment of 30 inpatients with bipolar disorder hospitalized for acute mania.[52]

Lamotrigine has not been well studied in the geriatric population. A small, open-label, uncontrolled case series involving 5 women with bipolar disorder reported that 3 of the 5 improved after 6 weeks when lamotrigine was added to either lithium or valproate.[53] The mean age of the patients was 71.5 years. The 3 patients who improved had rapid cycling bipolar disorder. The drug was well tolerated, and no rashes were noted. Another case report suggested that lamotrigine may have a role in

the replacement of ECT in treatment-refractory bipolar depression.[54]

In a more recent review, Sajatovic et al[55] retrospectively examined the response to lamotrigine, lithium, and placebo in older (aged ≥55 years) adults with bipolar I disorder who participated in 2 mixed-age, maintenance studies examining time to intervention for an emerging mood episode (manic/hypomanic/mixed or depressed) and drug tolerability. The data from 98 older adults (lamotrigine, n = 33; lithium, n = 34; placebo, n = 31) were examined. The mean modal total daily doses were lamotrigine 240 mg and lithium 750 mg. The authors found that lamotrigine, but not lithium, significantly delayed the time to intervention for any mood episode, compared with placebo (lamotrigine vs placebo, $P = 0.011$; lithium vs placebo, $P = 0.122$; lamotrigine vs lithium, $P = 0.245$). The median time to intervention for a mood episode was 201 days for lamotrigine, 138 days for lithium, and 98 days for placebo. When analyses were adjusted for index mood, no significant differences were found (lamotrigine vs placebo, $P = 0.084$; lithium vs placebo, $P = 0.184$; lithium vs lamotrigine, $P = 0.210$). Lamotrigine, but not lithium, significantly delayed time to intervention for a depressive episode (lamotrigine vs placebo, $P = 0.011$; lithium vs placebo, $P = 0.779$; lamotrigine vs lithium, $P = 0.011$). Median time to intervention for depression was 149 days for lithium and 182 days for placebo but was not calculable for lamotrigine because <50% of patients relapsed to depression. Analyses adjusted for index mood showed that results for the lamotrigine group reached statistical significance (lamotrigine vs placebo, $P = 0.021$). Lithium, but not lamotrigine, significantly delayed the time to intervention for mania/hypomania/mixed symptoms compared with placebo (lithium vs placebo, $P = 0.034$; lamotrigine vs placebo, $P = 0.233$; lamotrigine vs lithium, $P = 0.350$). Median time to intervention for mania was 236 days (34 weeks) for placebo but was not calculable for the lithium and lamotrigine groups. When analyses were adjusted for index mood, no significant differences were found. A disproportionate number of patients in the analysis came from the study with an index episode of depression (lamotrigine, n = 24; lithium, n = 26; placebo, n = 21) compared with an index episode of manic/hypomanic/mixed symptoms (lamotrigine, n = 9; lithium, n = 8; placebo, n = 10). When older adults judged currently or recently depressed were examined separately, a significantly longer time to intervention for a mood episode was observed with lamotrigine, but not lithium, compared with placebo (lamotrigine vs placebo, $P = 0.029$; lithium vs placebo, $P = 0.319$; lamotrigine vs lithium, $P = 0.113$). Lamotrigine was also superior to placebo and lithium for time to intervention for depression in the depressed subgroup, but no significant treatment effect was observed for time to intervention for mania. When older adults entered the study recently manic/hypomanic/mixed, no significant effect was observed for any treatment on any efficacy measure.

Overall, these older adults reported more adverse events with lithium treatment (85%) than with lamotrigine (82%).[55] Of adverse events occurring in ≥10% of patients, those more common with lithium than lamotrigine included diarrhea, headache, nausea, infection, amnesia, dizziness, dyspraxia, xerostomia, tremor, fatigue, and influenza. Only back pain was more common with lamotrigine. The overall incidence of rash was similar between treatment groups (lamotrigine, n = 1 [3%]; lithium, n = 2 [6%]; placebo, n = 0 [0%]). In the randomized phase, no cases of serious rash were reported. The overall incidence of weight loss (<4%), weight gain (<6%), mania (<9%), and depression (<4%) reported as adverse events was similar between treatment groups. Most adverse events were mild to moderate in intensity and resolved without sequelae. No serious adverse events with an incidence of ≥10% were reported in any treatment group. The proportion of patients that withdrew from the study because of adverse events was highest in the lithium group. Adverse events leading to premature withdrawal were reported in 18% of lamotrigine-treated patients, 29% of lithium-treated patients, and 13% of patients in the placebo group.[55]

Lamotrigine appears to be well tolerated in the long term. It is metabolized in the liver and has little influence on the pharmacokinetics of other agents, although it may increase plasma concentrations of the active metabolite of carbamazepine during concomitant administration.[56] Carbamazepine also lowers the concentrations of lamotrigine in the blood. Lamotrigine and valproate should be used cautiously when administered together, since valproate doubles the plasma level of lamotrigine, and lamotrigine decreases the concentration of valproate by 25%.[53]

The most common adverse effects in 1 study of 463 mixed-age adults were headache, insomnia, nonserious rash, tremor, and somnolence. Nonserious rash presented in 7% of the lamotrigine group compared with 2% of the placebo group ($P < 0.05$).[50] In another study, the incidence of rash associated with hospitalization among adults treated with lamotrigine was 0.3%. The incidence of cases reported as possible Stevens-

Johnson syndrome was 0.1% for adult patients. Incidence of rash may be increased in pediatric populations, with high initial dose, rapid dose titration, and concomitant use of valproate.[57]

Compared with the other antiepileptic agents, lamotrigine has a favorable cognitive profile. One study showed improvement of cognitive activation after introducing treatment.[58]

Carbamazepine

Based on our literature review, there are no published, controlled trials of carbamazepine that focus on late-life bipolar disorder. However, carbamazepine extended-release capsules have recently been approved by the FDA for the treatment of acute manic and mixed episodes associated with bipolar I disorder.

Studies in mixed-aged populations have proposed that carbamazepine is inferior to lithium in the long-term treatment of bipolar disorder.[59] However, it has also been suggested that patients with nonclassical features may profit more from prophylaxis with carbamazepine. Carbamazepine appears to be inferior to valproate in the treatment of acute mania in a mixed-age population.[60]

Carbamazepine induces the metabolism of drugs that are metabolized by the liver.[18] It is highly protein bound. Carbamazepine metabolism is autoinduced in the elderly, as in younger patients. Because of the autoinduction process, it may become necessary to increase carbamazepine dosages over the first 3 to 6 weeks of treatment to maintain a steady drug level. Targeted serum levels are generally 4 to 12 μg/L. Possible drug–drug interactions with carbamazepine include calcium channel antagonists, cimetidine, terfenadine, and erythromycin.[18]

The most common adverse effects of carbamazepine are neurologic in origin. They include dizziness, sedation, vertigo, ataxia, diplopia, nystagmus, blurred vision, and cognitive impairment. These effects are dosage related, transient, and often reversible with dosage reduction.[20] Cognitive adverse effects may be particularly problematic in the elderly.[61] Other adverse effects include alteration of the normal regulation of antidiuretic hormone (vasopressin), leading to hyponatremia.[20]

Carbamazepine has quinidine-like properties. It has been associated with bradycardia and atrioventricular conduction delays. Kasarskis et al[62] observed these potentially life-threatening bradyarrhythmias or atrioventricular conduction delays mainly in elderly women. The patients had had either therapeutic or modestly elevated carbamazepine serum levels.

Rashes are common with carbamazepine therapy, as are mild blood dyscrasias such as mild leukopenias.[63] Carbamazepine-induced rashes have been shown to occur in 12% of adult psychiatric patients, while leukopenia has occurred in 7% of adults. Severe rashes and blood dyscrasias, such as aplastic anemia and agranulocytosis, are rare, however. The incidence of drug-induced blood dyscrasias increases with advanced age. It has been suggested that elderly psychiatric patients treated with carbamazepine who develop skin rashes should receive vigilant monitoring of blood counts, as there may be an association with carbamazepine-induced rashes and blood dyscrasias.[63]

Other Anticonvulsants

Information regarding other anticonvulsants (eg, oxcarbazepine, gabapentin, topiramate, zonisamide) in geriatric patients is limited, at best, to case reports.

Oxcarbazepine's chemical structure is similar to that of carbamazepine, but its metabolism is different, and it appears to have fewer adverse effects.[64] Oxcarbazepine is rapidly reduced to 10,11-dihydro-10-hydroxy-carbazepine (monohydroxy derivative [MHD]), which is the clinically relevant metabolite of oxcarbazepine. Oxcarbazepine and MHD exhibit linear pharmacokinetics with no autoinduction. Elimination half-lives in healthy volunteers were 1 to 5 hours for oxcarbazepine and 7 to 20 hours for MHD. Longer elimination half-lives have been reported in elderly volunteers. Mild to moderate hepatic impairment does not appear to affect MHD pharmacokinetics. Renal impairment does affect the pharmacokinetics of oxcarbazepine and MHD. The interaction potential of oxcarbazepine is relatively low. However, enzyme-inducing antiepileptic drugs such as phenytoin, phenobarbital, or carbamazepine can slightly reduce the concentrations of MHD. Verapamil may moderately decrease MHD concentrations. Oxcarbazepine appears to increase concentrations of phenytoin and to decrease trough concentrations of lamotrigine and topiramate.[64] In 1 study, the 4 most common adverse events experienced by elderly patients taking oxcarbazepine were vomiting (19%), dizziness (17%), nausea (17%), and somnolence (15%). In addition, it was noted that elderly patients taking concomitant natriuretic drugs were more likely to develop serum sodium levels <135 mEq/L.[65]

Gabapentin received FDA marketing approval for seizures in 1993. No controlled studies have been conducted in geriatric bipolar disorder. In a small case series, 7 elderly patients, each in a manic episode, were treated with gabapentin. All 7 patients experienced improvement in manic symptoms, with minimal to no adverse effects. They received gabapentin in combina-

tion with antipsychotic medications, and in 1 case in combination with valproate.[66] In another open-label trial, 5 geriatric patients with bipolar depression, who were already on a combination of lithium and valproate, had gabapentin added to their drug regimen.[67] One patient had remission of her depressive episode. Gabapentin was well tolerated. A placebo-controlled study in 117 adults failed to demonstrate that gabapentin was an effective adjunctive treatment when administered to outpatients with bipolar disorder.[68]

Gabapentin is not metabolized in humans. It is not protein bound, nor does it induce liver enzymes. This diminishes the likelihood of drug interactions with other antiepileptic agents and drugs such as oral contraceptives. Although gabapentin is an analogue of the neurotransmitter γ-aminobutyric acid (GABA), which does not cross the blood–brain barrier, gabapentin penetrates the central nervous system. Its activity is seemingly distinct from GABA-related effects. Mild adverse events, most commonly somnolence, fatigue, ataxia, and dizziness, have been reported in ~75% of patients.[69]

Topiramate is FDA approved as an adjunctive treatment of epilepsy in adults and children. Although results have been mixed, 4 randomized clinical trials have not supported the efficacy of topiramate as an antimanic agent.[38] Based on our literature review, there do not appear to be any trials that have focused on the use of this agent for the treatment of late-life bipolar disorder. In 1 case report, a 65-year-old white man with mania improved after topiramate was added as adjunctive therapy to valproate, olanzapine, and lorazepam.[70]

Topiramate has little hepatic metabolism, low protein binding, and few drug interactions.[71] It has been associated with weight loss. In 1 randomized, double-blind, placebo-controlled study involving 385 participants from a mixed-age population, topiramate produced significantly greater weight loss than placebo at all dosages ($P < 0.05$ after week 4).[72] The percentage of total weight lost varied between 4.8% and 6.3% at week 24 of the trial. The most frequent adverse events were related to the central or peripheral nervous system. They included paresthesia, somnolence, and difficulty with memory, concentration, and attention.[72] Topiramate has been associated with a higher incidence of cognitive adverse events than other antiepileptic agents. In 1 study of 596 mixed-age patients, 41.5% reported a cognitive adverse event.[73]

Zonisamide received FDA approval for epilepsy in 2000. An initial study showed efficacy in bipolar mania.[74] In a retrospective chart review, zonisamide appeared to be effective as an adjunctive agent for bipolar depression.[75] Six out of 12 patients improved. The mean dose used was 236 mg/d. Two patients discontinued therapy due to sedation. Adverse effects associated with zonisamide principally involve the central nervous system and include drowsiness and altered thinking. There is also an increased risk of kidney stones.[76]

Antipsychotic Agents

The number of options for the acute treatment of bipolar disorder is rapidly increasing. In the past, therapeutic options for acute mania were limited to lithium, valproate, and typical antipsychotics, although among the typical agents only chlorpromazine is FDA approved for the treatment of the manifestations of the manic type of manic-depressive illness. However, the last several years have seen new evidence for the utility of atypical antipsychotics in the treatment of acute mania and for maintenance therapy. Traditional antipsychotic agents have held special risks for the elderly because the likelihood of developing medication-induced EPS and tardive dyskinesia increases with age. Atypical antipsychotics appear to have much lower rates of EPS and tardive dyskinesia, and may therefore be a better choice for geriatric patients.[77]

Additionally, antipsychotics, especially low-potency agents, have anticholinergic effects. These can contribute to tachycardia, constipation, urinary hesitancy/obstruction, and cognitive impairment. α_1-Receptor antagonism by antipsychotic drugs may cause orthostatic hypotension, which in turn can contribute to falls. Currently, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole are atypical agents approved by the FDA for bipolar disorder. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are FDA approved for the treatment of acute manic and mixed episodes associated with bipolar disorder. Olanzapine is also indicated as a monotherapy for maintenance treatment of patients with bipolar disorder. The combination of olanzapine or risperidone with lithium or valproate is indicated for the short-term treatment of acute mixed or manic episodes associated with bipolar I disorder. IM olanzapine is also indicated for the treatment of agitation associated with schizophrenia and bipolar I mania. Olanzapine and fluoxetine HCl combination capsules have been approved for the treatment of depressive episodes associated with bipolar disorder. Unfortunately, published controlled studies of atypical antipsychotic agents in the elderly are lacking, and information regarding these agents has been extrapolated from mixed-age populations.[78]

Several concerns have been raised regarding the use of atypical antipsychotic agents in the elderly. Any

potential benefit from these agents must now be balanced against the risks associated with their use. The FDA has placed a black box warning on all atypical agents cautioning of increased mortality in elderly patients with dementia-related psychosis. There appears, in trials, to be a risk of death in drug-treated patients of between 1.6 to 1.7 times that seen in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was ~4.5%, compared with a rate of ~2.6% in the placebo group. Most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature.[79] A meta-analysis published in April 2005[80] reported results consistent with the FDA's report. No drug appeared to be individually responsible for the effect but rather each contributed to the overall effect. Although these trials did not involve elderly patients with bipolar disorder, it appears likely that the risks reported by the FDA can be extrapolated to occur with the use of these medications in the elderly for any condition.

Another difficulty with atypical antipsychotic agents has centered around their effects on weight gain, dyslipidemia, and hyperglycemia. These adverse effects are part of the metabolic syndrome.[81] The National Cholesterol Education Program has defined the metabolic syndrome as ≥3 of the following 5 characteristics: abdominal obesity (waist circumference >102 cm [40 inches] in males or >88 cm [35 inches] in females); fasting triglycerides >150 mg/dL; fasting high-density lipoprotein cholesterol <40 mg/dL in males and <50 mg/dL in females; blood pressure >130/85 mm Hg; and fasting blood glucose >110 mg/dL.[82] The metabolic syndrome results in insulin resistance and atherogenic dyslipidemia, and it can contribute to type 2 diabetes mellitus and cardiovascular disease.[82] Straker et al[81] studied 89 psychiatric inpatients who were taking at least 1 second-generation antipsychotic. No control group was used. The prevalence of the metabolic syndrome among the general US population is 22.8% in men and 22.6% in women. However, in the study by Straker et al, 29.2% of the patients met criteria for the metabolic syndrome. The syndrome was significantly associated with older age, higher body mass index, and higher values for each of the individual criteria for the metabolic syndrome. The age range used in the study to delineate "older age" was not given. The study suggested that patients treated with second-generation antipsychotic agents are at higher risk for developing the metabolic syndrome than the general population.[81]

In a recent study of 367 psychiatric inpatients treated with second-generation antipsychotic agents, 37.3% had the metabolic syndrome.[82] Patients aged >79 years were excluded, and it was not clear how many elderly patients were included. Besides confirming the high prevalence of the metabolic syndrome in patients taking atypical antipsychotic agents, the data also indicated that the metabolic syndrome doubles the 10-year risk of coronary heart disease (CHD) events in the population studied compared with the rest of the cohort. The age- and race-adjusted 10-year risk of CHD events in men was 11.5% versus 5.3%, and 4.5% versus 2.3% in women, respectively. Although controversy exists about the relative contribution of individual antipsychotic agents, the data suggest that clozapine and olanzapine are associated with greater risks than risperidone and quetiapine, which have greater risks than aripiprazole and ziprasidone.[82] Although these studies were of mixed-age populations comprising mainly patients with either schizophrenia or bipolar disorder atypical antipsychotic agents could pose significant risks for elderly patients, who often have medical comorbidity, by elevating their risk of CHD events. The data indicate that older age is significantly associated with the metabolic syndrome and that there is a 2-fold increase in the predicted 10-year CHD risk in patients with the metabolic syndrome treated with second-generation antipsychotic agents.

In terms of specific agents, the use of clozapine has been limited to treatment-refractory conditions because of its potential for serious adverse reactions. Shulman et al[83] assessed the efficacy of clozapine in 3 elderly men with bipolar I disorder (most recent episode manic with psychotic features). The patients were refractory or intolerant to treatment with lithium, valproate, benzodiazepines, and traditional neuroleptics both alone and in combination. Scores on the Clinical Global Impressions scale improved with clozapine, from a mean of 6.3 pretreatment to 2.0 posttreatment. There were no significant drops in granulocyte counts, and patients had sustained improvement, on average, over 11 months. The risk of agranulocytosis is between 0.3% and 1.0% in the younger population. This risk appears to be increased for older adults.[84] Other adverse effects that are of concern in the elderly include sedation, postural hypotension, anticholinergic effects, and increased risk for seizures.

Risperidone is approved by the FDA for bipolar mania. It was found to be effective in elderly bipolar patients in 1 case series.[85] Adverse effects of concern in the aged include postural hypotension, dose-dependent EPS, and hyperprolactinemia.[86] Risperidone has minimal effects on weight.[87] There also is no effect on QT dispersion, although it does prolong the QT interval.[88]

The use of both risperidone and olanzapine may be associated with increased rates of cerebrovascular adverse events, including stroke and transient ischemic attacks. In 4 placebo-controlled trials, which lasted 1 to 3 months and involved >1200 patients with Alzheimer's disease or vascular dementia, cerebrovascular adverse events were twice as common in the risperidone-treated group (4%) as in the placebo group (2%).[89] However, there has been some controversy regarding this apparent increased risk for stroke. A recent retrospective study found that older adults with dementia who were taking atypical antipsychotic agents had a risk of ischemic stroke similar to those taking typical antipsychotics.[90]

Olanzapine, quetiapine, ziprasidone, and aripiprazole are FDA approved for use in acute bipolar mania. Based on our literature review, there appear to be few reports of use of these agents specific to elderly bipolar disorder patients. Olanzapine, like risperidone, may be associated with an increased risk of cerebrovascular events.[91] One case report found it to be effective in the treatment of stuporous catatonia in an 85-year-old bipolar patient.[92] In 1 open-label study, quetiapine, when given within the recommended dosage range, had a benign EPS profile, with potentially greater tolerability and comparable efficacy to risperidone in older outpatients (aged 60–80 years) with psychotic disorders.[93] Aripiprazole has demonstrated reduction of both positive and negative symptoms of schizophrenia.[94] It lacks any significant EPS, tardive dyskinesia, sedation, weight gain, anticholinergic effects, or corrected QT prolongation in elderly patients with schizophrenia or schizoaffective disorder. It appears to be a safe and effective medication for elderly patients.[94] However, trials in geriatric elderly patients with bipolar disorder have yet to be completed.

Benzodiazepines

Studies are lacking regarding the benefits of adjunctive use of benzodiazepines in elderly patients. In 1 open-label study in a mixed-age population, the authors compared the effect of clonazepam supplementation for treatment of unipolar depression and bipolar depression.[95] In the unipolar depression group, 84.2% of the subjects fulfilled the response criteria, which was at least an 80% reduction in the Hamilton Rating Scale for Depression score. However, in the bipolar depression group, only 10.5% responded.[95] In another study of 34 patients, involving mostly adults, clonazepam was either given as monotherapy or, as in the case of lithium nonresponders, as adjunctive therapy to evaluate its effectiveness in the prophylaxis of affective disorder.[96] The goal of the study was to evaluate the use of this compound as a mood stabilizer. Patients with unipolar depression had significantly fewer depressive episodes after initiation of treatment with clonazepam (P = 0.026), while patients with bipolar disorder did not benefit from the therapy.[96]

Potential benefits must be weighed against risks in the elderly. Significant adverse effects that may be associated with benzodiazepine use in the elderly include falls, cognitive impairment, sedation, and impairment of driving skills. Long-term use of benzodiazepines should be discouraged because of the risk of dependence, which can be a serious problem in the elderly. Unrecognized and untreated benzodiazepine dependence can lead to serious medical complications.[97]

Antidepressants

Strategies for antidepressant cotherapy in elderly patients with bipolar disorder have not yet been devised. A recent study reviewed evidence from randomized controlled trials on the efficacy and safety of antidepressants in the short-term treatment of bipolar depression.[98] The trials involved patients aged up to 70 years; 75% of the patients were receiving a concurrent mood stabilizer or an atypical antipsychotic. The rate of switching to mania or hypomania for tricyclic antidepressants was 10%; for all other antidepressants it was 3.2%; and for placebo it was 4.7%. The conclusion was that antidepressants are effective in the short-term treatment of bipolar depression. The trial data did not suggest that switching is a common early complication of treatment with antidepressants.[98] Others have noted antidepressant-associated mania in late life occurs most often with tricyclic antidepressants.[99] Thus, it may be prudent to use an SSRI rather than a tricyclic antidepressant as first-line treatment.[98]

Schaffer et al[100] conducted a population-based retrospective cohort study of 1072 elderly (aged ≥66 years) outpatients with bipolar disorder who had been dispensed an antidepressant prescription. The control group consisted of 3000 elderly bipolar patients who were not taking any antidepressants. SSRIs accounted for 68% of the antidepressant prescriptions, while tricyclics, serotonin and norepinephrine reuptake inhibitors, and other antidepressants comprised the remainder. The principal finding was that elderly bipolar patients who were prescribed an antidepressant were significantly less likely to be admitted for mania than elderly bipolar patients who were not taking an antidepressant. Antidepressant use was also associated with a nonsignificant decreased rate of hospitalization for depression.[100]

Electroconvulsive Therapy

ECT is a highly effective intervention in the treatment of acute mania as well as depression. The use of ECT has had a resurgence in the past few years. This has been especially true in the elderly, in whom ECT has been frequently demonstrated to be a safe and effective intervention.[101] The decision to use ECT in an elderly patient is complex and should be based on the patient's illness, risks of treatment compared with alternative or no treatment, and both the patient's and family's wishes.[101] Approximately 80% of patients with mania who receive ECT show remission or marked clinical improvement.[102] In the treatment of elderly patients with depression, there appears to be no significant difference between unilateral and bilateral ECT, either in improvement or in the number of treatments needed. Postictal recovery times and memory impairment are greater, however, with bilateral ECT as compared with unilateral ECT.[103,104]

ECT is generally well tolerated by geriatric patients. It is the treatment of choice for elderly patients with mania who are intolerant of, or refractory to, pharmacologic management or who have a severe behavioral disturbance that necessitates a rapid response.[20] The mortality rate associated with ECT has been reported to be 0.01%.[101,105,106] Geriatric patients develop more medical problems in the course of ECT that require medical treatment or temporary discontinuation of treatment than do younger controls.[105] In 1 study, complications occurred in 35% of the elderly patients as opposed to 18% of a younger age group.[106] The most important of these were cardiovascular in nature. The risk for complications was found to be increased in the very old, those in poor general health, and those taking multiple medications, especially cardiovascular agents. There was no relationship between either complications and outcome or between complications and the number or laterality of treatments.[106] Despite the increased frequency of adverse events in the aged, the majority of medical problems that occur are reversible.[105]

Psychotherapy

Bipolar disorder is often only partially treated by medications. This has led to recent developments in the adjunctive psychological treatment of this disorder. A recently published review examined outcome studies of psychological interventions reported since 1990.[107] The interventions included psychoeducation, cognitive-behavioral therapy (CBT), interpersonal and social rhythm therapy, and psychoanalytic therapy. The research indicated that a range of psychological approaches appeared to benefit people with bipolar disorder. The clearest evidence was for individual CBT, which had an impact on symptoms, social functioning, and risk of relapse. Unfortunately, many of the studies were uncontrolled and of poor quality. They were also restricted to younger adults, and so it remains unclear how elderly patients would respond to psychotherapeutic interventions.[107]

DISCUSSION

Although randomized controlled trials addressing the treatment of late-life bipolar disorder are lacking, current data suggest that anticonvulsants such as valproate and lamotrigine may be of benefit and better tolerated as mood stabilizers than lithium in the elderly.[18] Lithium may require lower target serum levels, on the order of 0.4 to 0.7 mEq/L,[22] along with 25% to 50% lower dosages in the elderly than in younger patients.[20] Additionally, while there does not appear to be a significant difference between elderly and adult patients in overall incidence of adverse effects, elderly patients appear to suffer a greater incidence of moderate to severe effects than younger patients.[25] For these reasons, divalproex sodium and atypical antipsychotics could be first-line drugs for the treatment of mania in the elderly.[16] Elderly patients will need slower titration of these drugs and a more conservative dosage regimen. Those patients with comorbid brain disease may require even lower doses. Carbamazepine is considered a second-line agent for the treatment of manic episodes, as it causes more hematologic toxicity and drug interactions than divalproex sodium. The role of other anticonvulsant agents in the treatment of late-life mania is still unclear. Although there are no specific treatment guidelines, clinical experience indicates that the initial trial should last at least 3 to 4 weeks. If monotherapy fails, the addition of an atypical antipsychotic, an anticonvulsant, or lithium may help with resolution of symptoms.

Atypical antipsychotic agents in geriatric patients may be associated with increased mortality. There appears to be a risk of death 1.6 to 1.7 times that seen in patients receiving placebo. Most of the deaths have been either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature,[79] and no drug appears to be individually responsible for this effect.[80] Although the black box warning concerns patients treated for dementia-related psychosis, these risks could be extrapolated to occur with other uses of atypical antipsychotic agents in the elderly. It has also been noted that atypical antipsychotics can contribute to the metabolic syndrome,

with 1 study reporting that 29.2% of the patients taking these medications met the criteria for this condition.[81] Finally, there is a 2-fold increase in the predicted 10-year CHD risk in patients with the metabolic syndrome treated with second-generation antipsychotic agents.[82] Potential benefit from atypical antipsychotics must be balanced against the risks associated with their use.

In the treatment of bipolar depression, monotherapy with a mood stabilizer is reasonable, given the advantages of monotherapy in elderly patients. Lithium can either be used as a primary agent or in combination with an antidepressant, an anticonvulsant, or an atypical antipsychotic agent. Lamotrigine may also be useful in the treatment of bipolar depression, both as monotherapy, or in combination with an antidepressant, another anticonvulsant, lithium, or an atypical antipsychotic agent. Antidepressants appear to be effective in the short-term treatment of bipolar depression. However, it may be prudent to use an SSRI rather than a tricyclic antidepressant, since tricyclic antidepressants have been associated with higher switch rates.[98]

In terms of maintenance therapy after acute treatment of a manic, hypomanic, or mixed episode, first-line options include valproate, lithium, or olanzapine. Safety issues, as noted earlier, warrant careful consideration of olanzapine for potential long-term treatment. For maintenance treatment after an acute depressive episode, lamotrigine as monotherapy or in combination with another mood stabilizer may be used. Lithium is a second-line option. In older adults (aged >55 years), lamotrigine significantly delayed the time to intervention for any mood episode compared with both placebo and lithium. Lamotrigine, but not lithium, also significantly delayed time to intervention for a depressive episode while lithium, not lamotrigine, significantly delayed the time to intervention for mania.[55] Finally, while antidepressants currently have no role in maintenance treatment for depression, in 1 retrospective study, elderly bipolar outpatients who were prescribed an antidepressant were significantly less likely to be admitted for mania than elderly bipolar patients not taking an antidepressant. Antidepressant use was also associated with a nonsignificant decreased rate of hospitalization for depression.[100]

ECT may be useful in patients with pharmacotherapy-refractory disease and in those who need rapid resolution of symptoms due to suicidality or self-neglect. However, no data are available that compare ECT and pharmacotherapy in elderly patients.

Psychotherapy in combination with medications may be useful in patients with partial resolution of symptoms and in those patients with complicated psychosocial issues that are hindering their treatment.

Pharmacotherapy that has been efficacious for mania or bipolar depression should be continued for at least 6 to 12 months.[16] If the symptoms are in remission for >12 months, slow discontinuation of adjunctive medications such as antidepressants, antipsychotics, or anti-anxiety agents can be attempted while the patient is under close supervision. The optimal duration of mood stabilizer treatment in cases of late-life bipolar disorder is still not known.[16] Unfortunately, most elderly patients with bipolar disorder do not experience sustained recovery. In 1 study, only 10% did, even with standardized regimens.[15]

The Texas Implementation of Medication Algorithms has proposed evidence-based acute and maintenance strategies for the treatment of bipolar I disorder.[108] Additionally, the American Psychiatric Association has completed a Practice Guideline for the Treatment of Patients with Bipolar Disorder.[109] Neither of these guidelines focus on or make treatment recommendations for the geriatric patient population, however. Geriatric patients often have significant medical comorbidity and age-associated changes in their response to treatment. It may be that agents often used safely in adults—such as lithium or atypical antipsychotics—may not play as large a role in the treatment of bipolar disorder in the elderly due to risks of increased toxicity or other safety concerns.

The current review addresses the treatment of bipolar disorder in the elderly. It has several limitations, including the paucity of randomized controlled trials for the treatment of late-life bipolar disorders. There could also be publication bias, as negative trials may not be made available, and selection bias.

CONCLUSIONS

Bipolar disorder is not uncommon in late life. The presence of bipolar disorder in late life is associated with increased use of case management and conservator services. Although the data for the treatment of late-life bipolar disorder are limited, some commonly used treatments—including lithium, divalproex sodium, carbamazepine, lamotrigine, atypical antipsychotics, and antidepressants—have all shown some efficacy in the treatment of elderly patients with bipolar disorder. There are no specific guidelines for the treatment of these patients, but monotherapy followed by combination therapy of the various classes of drugs may help with the resolution of symptoms. ECT and psychotherapy may be useful in the treatment of refractory disease. There is a

need for more controlled studies in this age group before definitive treatment strategies can be enumerated.

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