Epidemiology, Etiology, and Treatment of Geriatric Mania

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Few prospective studies have focused on elderly patients with mania, despite the rapidly aging population and the difficulties encountered in treating older patients with manic symptoms. Retrospective studies generally have found that the number of new cases of mania and the prevalence of mania in the population decrease with age, although there is evidence to contradict this widely held belief. The diagnosis of mania in the elderly is confounded by the overlap of manic symptoms with other syndromes that occur with aging, including dementia, delirium, and medical illnesses. The treatment of mania is more difficult in the elderly, and new treatments such as the atypical antipsychotics and the anticonvulsants take on a more important role in treatment regimens for older patients.

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EPIDEMIOLOGY

Few studies accurately estimate the incidence and prevalence of late-life mania. Early studies completed before the development of standardized criteria such as the *Diagnostic and Statistical Manual of Mental Disorders* criteria[1] do not adequately delineate bipolar and unipolar disorders and the distinction between schizophrenia and mania. The overlap of manic symptoms with the clinical presentation of organic disorders such as neurosyphilis and dementia (e.g., agitation, psychosis, confusion) also makes the historical prevalence rates of mania in elderly populations difficult to interpret.

Geriatric patients with chronic mental illnesses are more likely to reside in nursing homes, state hospitals, and other residential settings, and these settings are typically underrepresented in epidemiologic studies. In some studies, these rates are estimated from retrospective chart reviews rather than from prospective interviews or standardized interviews of reliable informants. Diagnosing mania in the elderly is extremely difficult even with trained observers, and this task is made more difficult in nursing home patients with cognitive difficulties.

The most recent study of psychiatric disorders in the community, the National Comorbidity Survey,[2] did not include the elderly. The Epidemiologic Catchment Area (ECA) study[3] found that none of the 900 elderly community residents sampled met criteria for bipolar disorder. Researchers generally believe that the incidence of mania declines with age[4–7] and that the prevalence of mania in the elderly is significantly lower than the 1% prevalence found in the general adult population. However, some estimates of the prevalence of mania in elderly psychiatric patients are as high as 19%,[8–10] with the prevalence in nursing home patients estimated at approximately 10%.[11]

The survival of young patients with mania would also affect the prevalence rate in elderly patients. The long-term outcome of patients with mania was examined in a 1973 study.[12] The investigators followed 393 patients in a naturalistic study that was conducted before the advent of modern pharmacologic treatments for mania. In the 10-year follow-up, all but 2 patients relapsed, and the duration of manic and depressive episodes was remarkably stable. The time interval between episodes decreased until approximately the fifth episode and then remained relatively constant. Untreated mania, at least over 10 years, is therefore a chronic relapsing disorder.

Other researchers have shown that there is an increased incidence of new-onset mania in older adults. Goodwin et al.[13] found 2 peak periods for the onset of mania in women, one early in adult life and the second when women reach their fifth decade, at approximately the time of menopause. In contrast, some researchers have demonstrated that men show an increased incidence of mania into the eighth and ninth decades of life.[14,15] These numbers are based on survival rates, and the absolute number of elderly men and women with new-onset mania may be lower than that seen in younger populations.

The increased incidence of mania with age as well as the chronic relapsing course would lead to an expected increase, not the observed decline, in the prevalence of mania with age. Apart from an accurate diagnosis, which

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clearly would have the greatest impact on prevalence rates, the true prevalence may decrease because of decreased survival rates in elderly patients compared with younger patients with mania. Suicide rates for patients with chronic relapsing mania have been estimated to be as high as 20%. There also is evidence that mania in the elderly, particularly when the onset of mania is late in life, has a poor prognosis because of comorbid medical conditions. Geriatric mania patients demonstrate more neurologic abnormalities (e.g., neurologic soft signs, ataxia) and cognitive disturbances such as confusion and disorientation.[16–21] In one study, elderly manic patients were shown to have an increased cumulative mortality over 10 years compared with geriatric depressed patients (70% vs. 30%).[22]

ETIOLOGY

Many older patients with late-onset mania have clinical characteristics of "secondary mania," or mania that is associated with a medical illness. Krauthammer and Klerman,[23] and later, Stasiek and Zetin,[24] contrasted patients with idiopathic or primary mania with those whose onset of mania was associated with a medical disorder (e.g., neoplasm, cerebrovascular accident) or medication (e.g., antidepressant, oral steroid). They found that patients with secondary mania were older at the onset of their disorder and had fewer family members with a diagnosis of mania.

Patients with idiopathic late-onset mania also have fewer first-degree relatives with mania than patients with mania that begins early in life.[25–30] The onset of mania may therefore be influenced, in part, by both genetic and environmental factors. One environmental factor important in the onset of mania is neurologic disease. In 1989, Stone[17] retrospectively reviewed the charts of older manic patients with comorbid organic cerebral disease and found that these patients had fewer family members with affective disorders compared with manic patients without comorbid neurologic disorders. Snowdon[21] found that approximately half of manic patients with no history of comorbid neurologic disease had a family history of affective disorders. Only 15% of manic patients with a neurologic disorder before the onset of mania had a family history of affective disorder. Patients with genetic loading for bipolar disorder experience the onset of symptoms earlier in life, and environmental factors (e.g., neurologic disease) may be more important in late-onset mania.

Neuroimaging has provided a link between mania and cerebrovascular accidents, particularly of the right hemisphere.[31–34] An increase in cerebrovascular risk factors[35] and subtle evidence of cerebrovascular disease on neuroimaging (e.g., periventricular white matter disease and subcortical hyperintensities)[36] have also been found in patients with late-onset mania. These cerebrovascular changes can occur in younger patients with mania,[37] and it would be simplistic to define early-onset mania as genetic and late-onset mania as secondary to medical conditions. What is important to consider is the fact that because geriatric mania is so often associated with medical conditions, specifically neurologic disease, the clinical presentation, course, and treatment may differ from those associated with mania that begins in early adulthood.

The Clinical Presentation of Geriatric Mania

As outlined above, in contrast to younger patients, elderly patients with mania are more likely to present with evidence of neurologic disorders. Clinical symptoms include confusion, disorientation, and distractibility.[19] In routine clinical practice, an elderly patient with manic symptoms may be misdiagnosed as having dementia with agitation. The following case illustrates the overlap of mania and dementia.

A 20-year-old patient becomes increasingly agitated and difficult to manage. When you enter the ward, he immediately comes up to you and asks you to dance. He never stops talking and stays up all night without tiring during the day. He exposes himself to the female patients and masturbates in the dayroom. He wanders in and out of other patients' rooms, sometimes getting into fights and mumbling obscenities. When you try to redirect him, he curses and spits in your face. On the Mini-Mental State Examination, the patient scores 15/30. He states that the date is "Christmas day and the day Christ is born." He cannot do serial 7's or memory testing. He is not cooperative and becomes belligerent during the testing.

This patient has typical manic symptoms of agitation, mood lability, insomnia, irritability and fighting with staff, inappropriate sexual conduct, and psychosis. The treatment in this case is relatively straightforward and involves first treating the patient with a combination of antipsychotics and mood stabilizers such as anticonvulsants or lithium and then gradually weaning him off the antipsychotics.

Now consider the same case, but change the age of the patient to 75 years.

A 75-year-old patient becomes increasingly agitated and difficult to manage. Although the 75-year-old has the same symptoms as the younger patient, the 2 patients probably would be diagnosed very differently. The older patient with agitation and cognitive problems quite likely would be diagnosed with dementia only. If the patient had a history of a cognitive decline prior to hospitalization, demonstrated neurologic abnormalities on examination (e.g., gait ataxia, frontal release signs), and showed key findings on magnetic resonance imaging (e.g., periventricular white matter hyperintensities and mildly enlarged ventricles), the chances of a dementia diagnosis would increase. Yet, all of these findings could occur in mania, particularly if the mania had developed over a period of months and had been untreated, or if the mania had been preceded by an undiagnosed depression and profound psychomotor retardation.

Table 1. Potential Causes of Secondary Mania[a]

Medical disorders
Anemia
Hyperthyroidism
Vitamin B_{12} deficiency
Influenza
Niacin deficiency
Medications/treatments
Antidepressants, electroconvulsive therapy, lithium toxicity
Benzodiazepines
Amphetamines, cocaine
Captopril, enalapril
Estrogen and calcium replacement
Neurologic disorders
Alzheimer's disease
Vascular dementia
Basal artery aneurysm
Cerebrovascular accident (particularly right hemisphere)
Encephalitis
Epilepsy
Multiple sclerosis
Wilson's disease
Normal pressure hydrocephalus
Neurosyphilis
Parkinson's disease
Pick's disease
Sydenham's chorea
Tourette's disorder
Traumatic brain injury
Tumors

[a]Based on Van Gerpen et al.[41]

Table 2. Symptoms of Depression and Delirium in the Elderly

Agitated depression
Psychomotor agitation
Decreased sleep
Poor concentration
Dysphoric mood and irritability
Suicidal behavior
Psychosis
Delirium
Psychomotor agitation
Decreased sleep
Disorganized thinking
Confusion
Distractibility
Rambling speech
Poor judgment
Psychosis

There are several case reports of elderly patients with bipolar disorder being diagnosed with dementia and responding to medications used to treat mania with a clearing of their cognitive and affective disorders.[38–40]

The differential diagnosis in elderly patients with agitation and psychosis should also include late-onset delusional disorder, schizophrenia, delirium, and agitated depression. The medical workup initially should focus on identifying potential causes of secondary mania (Table 1) and include a neurologic examination, blood chemistries, measures of calcium and magnesium, liver function tests, complete blood count with platelets, thyroid panel, Venereal Disease Research Laboratory screening, measures of vitamin B_{12} and folate, toxicology screen, urinalysis, electrocardiogram (ECG), and (if clinically indicated) tests of serum levels of medications, lumbar puncture, and neuroimaging.

Both delirium and agitated depression have symptoms that overlap with mania and agitated dementia (Table 2), and older patients with mania often have mixed symptoms. Irritability and depressive thought content may be more prominent than euphoria, leading to diagnosis of depression rather than mania.[19]

THE TREATMENT OF MANIA IN THE ELDERLY

The treatment of the agitated demented patient and the treatment of the elderly patient with mania are similar and include the use of antipsychotics and anticonvulsants as first-line agents. However, in certain clinical situations, the pharmacologic strategies may be quite different. For example, although trazodone, buspirone, and progesterone are used to treat patients with agitated dementia, these medications would not be effective in treating manic symptoms. Similarly, a patient with treatment-resistant mania may respond to electroconvulsive therapy (ECT) or newer anticonvulsants such as lamotrigine that have not been shown to be effective in dementia with agitation.

Antipsychotic Medications

The initial treatment of an agitated manic patient usually includes antipsychotics and benzodiazepines as adjunctive therapy. The traditional antipsychotics (e.g., haloperidol, chlorpromazine) have not been demonstrated to be effective in the long-term treatment of mania in the elderly, and there are no double-blind trials comparing different antipsychotic agents in this population. Once acute symptoms have resolved, continuing to treat elderly bipolar patients with traditional antipsychotic medications puts them at high risk for long-term side effects such as tardive dyskinesia (TD). In some studies of elderly patients receiving traditional neuroleptics, the risk of developing TD increased with age, and prevalence rates of TD in the community have approached 20%.[42,43] Elderly patients are also more sensitive to the anticholinergic effects and orthostatic hypotension associated with low-potency antipsychotics (e.g., thioridazine) and the extrapyramidal side effects of high-potency neuroleptics (e.g., haloperidol). In an acutely agitated patient, these side effects may exacerbate the side effects of other medications, leading to urinary retention, constipation, blurred vision, tachycardia, and the risk of falling. In general, low doses of the high-potency antipsychotics are preferred (e.g., haloperidol, 0.5 mg i.m. or p.o.). However, these medications carry the risk of dystonic reactions and severe parkinsonian symptoms that may not be tolerated by elderly patients. Thus, the traditional antipsychotics are used infrequently as the sole subacute therapy for manic patients.

Table 3. Common Side Effects of Lithium[a]

Neurologic
Mental slowing
Ataxia
Tremor
Cerebellar abnormalities
Renal
Urinary frequency
Renal failure (rare)
Cardiac (all more common in the elderly)
Sinus node dysfunction
Sinoatrial block
Bundle-branch block
Ventricular arrhythmia
Myocardial injury
Endocrine
Nontoxic goiter (10%)
Increase in fasting blood glucose
Gastrointestinal
Dose-related nausea
Gastric irritation
Diarrhea
Significant weight gain
Dermatologic
Possible worsening of a number of chronic skin conditions including psoriasis
Other
Arthritis
Peripheral edema

[a]Based on Jefferson et al.[56] and Salzman et al.[57]

In the elderly, the side effect profiles of traditional neuroleptics, including the increased risk for TD, have important implications for maintenance therapy. This consideration has led to the practice of substituting the atypical antipsychotics for traditional neuroleptics in the prophylactic therapy of patients with bipolar disorder. None of the atypical antipsychotics can be given intramuscularly, so they may be difficult to use in an acutely agitated patient. However, they are generally safe in patients who need maintenance therapy with antipsychotic medications and who do not require parenteral administration.

Four atypical antipsychotic medications are currently available: clozapine, risperidone, olanzapine, and quetiapine. All of these medications have unique pharmacologic profiles but are "atypical" because they exert their antipsychotic effect as mixed dopamine-serotonin antagonists. The primary advantage of these atypical antipsychotics is a marked reduction or elimination of extrapyramidal symptoms (EPS), TD, and dystonic reactions. Risperidone and clozapine are effective in the treatment of mania, and both are safe and effective in treating elderly patients.[44–46] There are no published studies of olanzapine and quetiapine in the elderly.[47] Despite the efficacy of clozapine and the other atypical antipsychotics in treating the negative or deficit symptoms in schizophrenia (e.g., withdrawal, poor hygiene, apathy), these agents generally have not demonstrated effectiveness in treating the depressed phase of bipolar patients. However, the efficacy of adjunctive risperidone in depressive symptoms, as noted by improvements in Hamilton Rating Scale for Depression (HAM-D) scores, has been reported recently in an open, multicenter surveillance study.[48]

The most data on the use of atypical antipsychotics in the treatment of mania and schizoaffective disorder are available for clozapine, the oldest of these agents. Clozapine can be difficult for elderly patients to tolerate and is associated with significant orthostatic hypotension, sedation, increased risk of seizures, and agranulocytosis (1% to 3%). Weekly blood monitoring is required to assess the patient's white blood cell count during treatment.

The newer atypical antipsychotics risperidone, olanzapine, and quetiapine are not associated with agranulocytosis and have similar advantages to clozapine, including a decreased incidence of EPS and a much lower risk of dystonia and TD compared with traditional neuroleptics. Risperidone is effective in the treatment of mania in younger patients, but has been associated with a worsening of manic symptoms in a few reports.[48,49] Most patients in these anecdotal reports received high initial doses of risperidone. Lower doses are well tolerated, with a low incidence of TD and anticholinergic effects and minimal weight gain. Risperidone is safe in geriatric populations and effective in decreasing aggression in demented patients and improving both positive and negative symptoms in elderly patients with schizophrenia.[47]

The atypical antipsychotics are excellent adjunctive medications in the treatment of the younger agitated bipolar patient. More clinical experience and controlled studies of these medications in older bipolar patients are needed, particularly with regard to their efficacy in the depressed phase and dysphoric manic states.

Lithium and the Anticonvulsants

Lithium is the first-line treatment for younger patients with mania. Patients older than 70 years, however, have difficulty tolerating lithium side effects. The neurologic side effects of lithium overlap with many of the neurologic findings in elderly patients with mania (e.g., ataxia, tremor), and these side effects are more pronounced in patients with comorbid neurologic or medical illnesses.[50–53] Maintaining low serum lithium concentrations in elderly patients results in decreased efficacy in the treatment of both manic and depressive symptoms.[54,55] Table 3 lists the common side effects of lithium.[56,57]

Many of the side effects listed in Table 3 are common complaints in the elderly. Elderly patients with benign prostatic hypertrophy or difficulty ambulating at night because they use a walker may not tolerate the nocturia and cerebellar dysfunction that are frequently associated with lithium therapy. They also may complain of increased forgetfulness and subjective mental slowing. Lithium therapy can worsen cognitive problems in an elderly patient with mild dementia or age-associated memory im-

Table 4. Subtypes of Patients With Mania Who Are Responsive to Anticonvulsants[a]

Dysphoric mania and severe psychosis
No family history of affective illness
Older age
Mania associated with neurologic dysfunction
Rapid-cycling mania
Lithium-nonresponsive mania

[a]Based on Prien and Gelenberg,[63] Post et al.,[64] McCoy et al.,[65] McElroy and Keck,[66] Stoll et al.,[67] and Calabrese et al.[68,69]

pairment. Lithium-associated weight gain and increases in fasting blood glucose levels can worsen adult-onset diabetes mellitus. In the elderly, sinus node dysfunction and prolonged cardiac conduction are common problems that can be made clinically significant by the addition of lithium. Other relatively common conditions in the elderly such as chronic psoriasis and peripheral edema can also be exacerbated by lithium therapy. Finally, lithium can worsen arthritis. In addition, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and possibly the new cyclooxygenase-2 (COX-2) inhibitors, to treat arthritis and other chronic pain syndromes in the elderly can cause lithium retention and possible toxicity.

Lithium excretion is dependent on the glomerular filtration rate (GFR), and elderly patients may retain lithium because of the age-associated decreases in GFR.[56] Lithium excretion is also dependent upon the sodium pump, and circumstances that decrease serum sodium can increase serum lithium concentrations, including low-sodium diets for heart disease, excessive sweating from prolonged fever, use of thiazide diuretics, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). SIADH can be caused by numerous medications, including antidepressants and anticonvulsants.

Prior to the initiation of lithium therapy in the elderly, initial laboratory tests should indicate normal renal function, electrolytes, ECG, fasting blood glucose, and thyroid function. Older patients are more tolerant of the slow-release form of lithium carbonate, primarily because peak levels of serum lithium (and therefore side effects) are decreased. Slow-release lithium also may decrease the dyspepsia that frequently occurs with lithium carbonate. Another strategy to decrease the subjective experience of side effects such as dyspepsia is to have patients take the entire lithium dosage at bedtime. However, many of the side effects such as sedation, nocturia, and ataxia increase the risk of falling when patients get up at night to urinate.

In the elderly, lithium therapy should be initiated at 300 mg at bedtime. After 3 to 5 days, a serum drug level should be obtained. The dose is adjusted to achieve serum lithium concentrations of 0.6 to 1.0 mEq/L, depending on side effects and clinical response. Elderly patients usually require 300 to 900 mg/day of lithium carbonate to maintain an adequate clinical response.

Increasingly, anticonvulsant medications are being used to treat mania in the elderly. Carbamazepine and valproic acid are the most widely used anticonvulsants in this population. Both medications are as effective as lithium in the treatment of mania in younger patients, and both are better tolerated than lithium.[58–62] The anticonvulsants have been shown to be more effective in specific subgroups of manic patients (Table 4).[63–69] Patients with dysphoric mania, rapid-cycling mania, lithium nonresponsiveness, and no family history of affective illness have increased response to carbamazepine.[64] Response to valproic acid has been correlated with older age; increased severity of manic symptoms, including psychosis; neurologic dysfunction; dysphoria; and lithium nonresponsiveness.[65–69] Several of these characteristics, such as older age, prominent dysphoria and psychosis, lack of family history of affective illness, and neurologic dysfunction, are characteristics found in populations of elderly patients with mania, particularly late-onset disease.

Valproic acid and, to a lesser extent, carbamazepine have become the first-line treatments for acute mania in our geriatric mood disorders program. The U.S. Food and Drug Administration (FDA) has recently approved valproic acid for use in the acute (but not prophylactic) treatment of mania. Open trials of anticonvulsants in the elderly have shown that they are well tolerated in the treatment of both agitated dementia and mania.[70–74]

Prior to initiating therapy with carbamazepine or valproic acid, baseline ECG, complete blood count with platelets, and a multichemistry blood profile with liver enzymes should be reviewed. Valproic acid is available as capsules as well as sprinkles and syrups for older patients with dysphagia. It is associated with nausea, which can be lessened by taking the medication with meals or using delayed-release divalproex sodium. Hospitalized elderly patients are started on 250 mg/day of valproic acid in the hospital, and the dosage is increased to 250 mg twice daily over 3 to 5 days, as tolerated. Dosages are adjusted (usually between 500 to 1000 mg/day) to obtain a blood drug level between 60 and 100 μg/mL. Aspirin,[75] erythromycin,[76] and fluoxetine[77] can increase blood levels of valproic acid, and concomitant administration should be monitored.

Carbamazepine therapy is initiated at 100 mg twice daily and increased to 200 mg twice daily over 3 to 5 days, as tolerated. Dosages are adjusted (usually 400 to 800 mg/day) to obtain a blood level of 6 to 12 μg/mL. Because carbamazepine induces liver enzymes that increase its metabolism (i.e., autoinduction), further increases in carbamazepine dosages will need to be made over the first 2 to 3 weeks of treatment to maintain a steady serum drug concentration. Medications that increase carbamazepine levels include erythromycin,[78] calcium channel blockers,[79] cimetidine,[80] and terfenadine.[81] If carbamazepine and valproic acid are used together, valproic acid can decrease the

Table 5. Side Effects of Valproic Acid and Carbamazepine[a]

Side Effect	Relationship
Neurologic	
Dose-related drowsiness and ataxia	CBZ > VPA
Fine resting tremor	VPA > CBZ
Horizontal nystagmus, diplopia, blurred vision	CBZ > VPA
Gastrointestinal	
Insignificant and transient elevation in liver transaminases	VPA > CBZ
Hepatotoxicity (rare)	VPA > CBZ
Pancreatitis (rare)	VPA > CBZ
Hematopoietic	
Transient leukopenia	CBZ > VPA
Thrombocytopenia	VPA > CBZ
Agranulocytosis (rare)	CBZ > VPA
Dermatologic	
Benign skin rashes	CBZ > VPA
Exfoliative dermatitis (rare, potentially fatal)	CBZ > VPA
Stevens-Johnson syndrome (rare, potentially fatal)	CBZ > VPA
Lyell's syndrome (rare, potentially fatal)	CBZ > VPA
Other	
Weight gain	VPA
Peripheral edema	VPA
Transient hair loss	VPA
Anticholinergic side effects	CBZ
Endocrine	
Hyponatremia secondary to SIADH	CBZ > VPA
Weight gain due to decreased free thyroid hormone	CBZ

[a]Abbreviations: CBZ = carbamazepine, SIADH = syndrome of inappropriate secretion of antidiuretic hormone, VPA = valproic acid.

elimination of the toxic 10, 11-epoxide metabolite of carbamazepine.[82] Carbamazepine induces cytochrome P450 enzymes in the liver and decreases the serum concentrations of a number of medications, including conjugated estrogen tablets,[83] warfarin,[83] theophylline,[83] vitamin K,[83] quinidine,[83] tricyclic antidepressants,[84] neuroleptics,[85] and benzodiazepines.[86]

The common side effects of valproic acid and carbamazepine are listed in Table 5. Although some of these side effects overlap with those of lithium (e.g., ataxia and tremor), they are in general milder, and the anticonvulsants are better tolerated than lithium. Mild increases in liver enzymes can be seen at the start of therapy. Only rarely has fatal hepatotoxicity been reported, and then never in elderly patients taking valproic acid or carbamazepine alone. However, since hepatotoxicity can occur at any time during therapy, patients should be monitored for signs of liver failure (e.g., anorexia, nausea, jaundice, malaise, abdominal pain, bruising). Mild decreases in white blood cell and platelet counts also are relatively common at the initiation of therapy. However, within a few weeks these levels return to baseline. Rarely, an idiosyncratic aplastic anemia (carbamazepine > valproic acid) or thrombocytopenia with platelets < 50,000/cu mm (valproic acid > carbamazepine) may be observed, and patients taking these medications should be monitored for evidence of bone marrow failure (e.g., infection, easy bruising, or bleeding).

Preliminary evidence shows that 3 other antiepileptic medications, lamotrigine, gabapentin, and topiramate, may also be effective in the treatment of bipolar disorder. Preliminary trials indicate that these novel neuroleptics may be effective in younger patients with treatment-resistant bipolar disorder. These agents have a relative advantage over carbamazepine and valproic acid in that they are not associated with potentially fatal idiosyncratic effects on the liver and bone marrow.

Lamotrigine inhibits the presynaptic release of excitatory amino acids and therefore may be effective in the manic and depressed phases of bipolar illness.[87,88] In general, lamotrigine has a benign side effect profile, including dizziness, headache, and diplopia.[89] However, lamotrigine also is associated with a cutaneous rash (in up to 10% of patients) that may evolve into toxic epidermal necrolysis.[89] Although rare, severe hypersensitivity reactions (e.g., Stevens-Johnson syndrome) can occur with lamotrigine, particularly in the early phase of treatment. The risk of developing a rash is increased in patients younger than 16 years, when the initial dose is too high or titrated too quickly, or when lamotrigine is used with adjunctive enzyme inhibitors such as valproic acid. Increases in the dosages of lamotrigine should therefore be gradual (e.g., a starting dose of 25 mg/day, with dose titrations of no more than 25 mg/week and a maintenance dose of 25 to 250 mg/day). There are no published studies of the use of lamotrigine in elderly bipolar patients, and lamotrigine is not recommended as a first-line treatment in this population.

Gabapentin also exerts its anticonvulsant effects through inhibition of excitatory amino acids, and it is structurally related to the neurotransmitter γ-aminobutyric acid (GABA). Gabapentin has no significant drug interactions and only mild and transient side effects, including somnolence, dizziness, ataxia, and fatigue. Side effects that are rare but may cause the drug to be discontinued include hypertension, arthralgia, rash, and irregular heartbeat. Edema and alopecia can also occur. In preliminary studies, gabapentin was shown to be effective in both manic and depressive phases of treatment-resistant bipolar disorder.[87,90,91] At present, there are inadequate data to support the use of gabapentin as either monotherapy or adjunctive therapy in mania, except as a possible third- or fourth-line treatment. The initial dose is usually 300 mg, with dosage increases every 3 to 7 days as tolerated, up to a maximum of 900 to 2400 mg/day.

Topiramate has several potential mechanisms of action, including sodium channel blockade, enhancement of the activity of the inhibitory neurotransmitter GABA, and antagonism of the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate subtype of glutamate receptor. Initial open trials with topiramate have been encouraging.[92] Topiramate may increase phenytoin levels in some patients. Common side effects are gastrointestinal in nature and include decreased appetite or dyspepsia;

neurologic events include somnolence, fatigue, headache, dizziness, paresthesia, and slowed thinking. The majority of side effects associated with topiramate are mild or transient in nature. Less common side effects include kidney stones and depression. A unique side effect of topiramate, compared with the other anticonvulsants and lithium, is weight loss, an advantage in improving compliance.

These newer anticonvulsants are potential alternatives to lithium, antipsychotics, valproic acid, and carbamazepine in patients who fail initial therapy with the traditional agents. However, there are no clinical trials in the elderly, and it is clearly too early to determine the role of these newer drugs in the treatment of geriatric mania.

Electroconvulsive Therapy

ECT has a number of advantages when used in bipolar patients. These advantages include a high, fast rate of response and efficacy in both the manic and depressed phases of bipolar disorder. Published reports of ECT show these treatments to be approximately 80% effective for manic symptoms,[93–99] which is similar to the response rate in depression. Patients administered ECT also show a faster rate of response compared with patients receiving traditional antimanic treatments such as lithium.[94–99]

There has been some disagreement about the most effective method for administering ECT: right unilateral (UL) or bilateral (BL) electrode placement. BL treatments are associated with increased interictal confusion and long-term memory problems, but some groups have maintained that BL placement is more effective in mania than UL placement.[97,98] Other researchers have argued that right UL treatments using the D'Elia placements are equally effective as BL treatments[93,99] and are associated with fewer cognitive side effects. Our own experience in treating elderly bipolar patients is that suprathreshold stimulus (150% to 400% over the stimulus threshold) using the D'Elia placements is as effective as BL treatments. Maintenance ECT may also provide prophylactic therapy for both the manic and depressed phases of bipolar disorder.[100–102] In elderly patients with recurrent unipolar depression, our group has demonstrated that 6 months of maintenance ECT is more effective than prophylactic medication and is more cost-effective than pharmacotherapy.[103]

FUTURE RESEARCH

Prospective studies of mania in the elderly are needed, with appropriate sampling of institutional settings, including nursing homes, to establish the true incidence and prevalence of geriatric mania. The diagnosis of mania in the elderly is difficult even for the most experienced geriatrician, and comorbid manic symptoms add considerable health care costs to the long-term care of elderly patients. Understanding the true prevalence of geriatric mania and developing clinical tools for diagnosing comorbid manic symptoms in frail or demented elderly patients will have important implications as our population ages. The elderly population would also benefit from additional studies using the atypical antipsychotics and anticonvulsants. These medications have a number of potential advantages and better side effect profiles than lithium and the older antipsychotic medications.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), cimetidine (Tagamet and others), clozapine (Clozaril and others), divalproex sodium (Depakote), enalapril (Vasotec and others), fluoxetine (Prozac), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), olanzapine (Zyprexa), phenytoin (Dilantin and others), quetiapine (Seroquel), risperidone (Risperdal), theophylline (Slo-bid and others), thioridazine (Mellaril and others), topiramate (Topamax), trazodone (Desyrel and others), valproic acid (Depakene and others), warfarin (Coumadin).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Kessler RC, Rubinow DR, Holmes C, et al. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997;27:1079–1089
3. Kramer M, German PS, Anthony JC, et al. Patterns of mental disorders among the elderly residents of eastern Baltimore. J Am Geriatr Soc 1985;33:236–245
4. D'Elia G, Perris C. [Attempted suicide during depressive (unipolar) and manic depressive (bipolar) psychoses]. Arch Psychiatr Nervenkr 1969;212:339–356
5. Loranger AW, Levine PM. Age at onset of bipolar affective illness. Arch Gen Psychiatry 1978;35:1345–1348
6. Mendlewicz J, Fieve RR, Rainer JD, et al. Manic-depressive illness: a comparative study of patients with and without a family history. Br J Psychiatry 1972;120:523–530
7. Taylor M, Abrams R. Manic states: a genetic study of early and late onset affective disorders. Arch Gen Psychiatry 1973;28:656–658
8. Young RC, Klerman GL. Mania in late life: focus on age of onset. Am J Psychiatry 1992;49:867–876
9. Young RC. Geriatric mania. Clin Geriatr Med 1992;8:387–399
10. Mirchandani IC, Young RC. Management of mania in the elderly: an update. Ann Clin Psychiatry 1993;5:67–77
11. Greenwald BS, Kremen N, Aupperle P. Tailoring adult psychiatric practices to the field of geriatrics. Psychiatr Q 1992;63:343–362
12. Angst J, Baastrup P, Grof P, et al. The course of monopolar depression and bipolar psychoses. Psychiatria Neurol Neurochir 1973;76:489–500
13. Goodwin FK, Jamison KR, Post RM, et al, eds. The Natural Course of Manic-Depressive Illness: Neurobiology of Mood Disorders. Baltimore, Md: Williams & Wilkins; 1984:20–37
14. Spicer CC, Hare EH, Slater E. Neurotic and psychotic forms of depressive illness: evidence from age-incidence in a national sample. Br J Psychiatry 1973;123:535–541
15. Sibisi CDT. Sex differences in the age of onset of bipolar affective illness. Br J Psychiatry 1990;156:842–845
16. Gerner RH. Psychiatric disorders of late life: mood disorders. In: Kaplan HI, Sadock S, eds. Comprehensive Textbook of Psychiatry, vol 2. 45th ed. Baltimore, Md: Williams & Wilkins; 1985:2024–2026
17. Stone K. Mania in the elderly. Br J Psychiatry 1989;155:220–224
18. Tohen M, Castillo J, Pope HG Jr, et al. Concomitant use of valproate and carbamazepine in bipolar and schizoaffective disorders. J Clin Psychopharmacol 1994;14:67–70
19. Liptzin B, Salzman C, eds. Treatment of Mania: Clinical Geriatric Psychopharmacology. New York, NY: McGraw-Hill; 1984:116–131
20. Shulman KI, Post F. Bipolar affective disorder in old age. Br J Psychiatry 1980;136:26–32

21. Snowdon J. A retrospective case-note study of bipolar disorder in old age. Br J Psychiatry 1991;158:485–490
22. Shulman KI, Tohen M, Satlin A, et al. Mania compared with unipolar depression in old age. Am J Psychiatry 1992;149:341–345
23. Krauthammer C, Klerman GL. Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry 1978; 35:1333–1339
24. Stasiek C, Zetin M. Organic manic disorders. Psychosomatics 1985;26: 394–402
25. Taylor M, Abrams R. Manic states: a genetic study of early and late onset affective disorders. Arch Gen Psychiatry 1973;28:656–658
26. Stenstedt A. A Study in Manic-Depressive Psychosis. Stockholm, Sweden: Psychiatric Clinic of Karolinska Institute; 1952:78–85
27. Hopkinson G. A genetic study of affective illness in patients over 50. Br J Psychiatry 1969;115:917–922
28. James NM. Early- and late-onset bipolar affective disorder. Arch Gen Psychiatry 1977;34:715–717
29. Kay D. Observations on the natural history and genetics of old age psychoses: a Stockholm material. Proc R Soc Med 1959;52:791–794
30. Post F, Coppen A, Walk A, eds. The Factor of Aging in Affective Illness: Recent Developments in Affective Disorders. Special edition. London, England: Royal Medico-Psychological Association; 1968:105–116
31. Starkstein SE, Mayberg HS, Berthier ML, et al. Mania after brain injury: neuroradiological and metabolic findings. Ann Neurol 1990;27:652–659
32. Starkstein SE, Pearlson GD, Boston J, et al. Mania after brain injury: a controlled study of causative factors. Arch Neurol 1987;44:1069–1073
33. Shukla S, Cook BL, Mukherjee S, et al. Mania following head trauma. Am J Psychiatry 1987;144:93–96
34. Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. Am J Psychiatry 1984;141:1084–1087
35. Wylie ME, Mulsant BH, Pollock BG, et al. Age at onset in geriatric bipolar disorder: effects on clinical presentation and treatment outcomes in an inpatient sample. Am J Geriatr Psychiatry 1999;7:77–83
36. McDonald WM, Krishnan KRR, Doraiswamy PM, et al. The occurrence of subcortical hyperintensities in elderly subjects with mania. Psychiatry Res 1991;40:211–220
37. McDonald WM, Tupler LA, Marsteller FA, et al. Hyperintense lesions on magnetic resonance images in bipolar disorder. Biol Psychiatry 1999;45: 965–971
38. Casey DA, Fitzgerald BA. Mania and pseudodementia. J Clin Psychiatry 1988;49:73–74
39. Koenigsberg HW. Manic pseudodementia: case report. J Clin Psychiatry 1984;45:132–134
40. Cowdry RW, Goodwin FK. Dementia of bipolar illness: diagnosis and response to lithium. Am J Psychiatry 1981;138:1118–1119
41. Van Gerpen MW, Johnson JE, Winstead DK. Mania in the geriatric patient population: a review of the literature. Am J Geriatr Psychiatry 1999;7: 188–202
42. Smith JM, Baldessarini RJ. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. Arch Gen Psychiatry 1980;37:1368–1373
43. Hunt N, Silverstone T. Tardive dyskinesia in bipolar affective disorder: a catchment area study. Int Clin Psychopharmacol 1991;6:45–50
44. Banov MD, Zarate CA Jr, Tohen M, et al. Clozapine therapy in refractory affective disorders: polarity predicts response in long-term follow-up. J Clin Psychiatry 1994;55:295–300
45. Zarate CA Jr, Tohen M, Banov MD, et al. Is clozapine a mood stabilizer? J Clin Psychiatry 1995;56:108–112
46. Tohen M, Zarate CA Jr, Centorrino F, et al. Risperidone in the treatment of mania. J Clin Psychiatry 1996;57:249–253
47. Kumar V, Brecher M. Psychopharmacology of atypical antipsychotics and clinical outcomes in elderly patients. J Clin Psychiatry 1999;60(suppl 13): 5–9
48. Dwight MM, Keck PE Jr, Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. Lancet 1994;344:554–555
49. Sajatovic M, DiGiovanni SK, Bastani B, et al. Risperidone therapy in treatment refractory acute bipolar and schizoaffective mania. Psychopharmacol Bull 1996;32:55–61
50. Himmelhoch JM, Neil JF, May SJ, et al. Age, dementia dyskinesias, and lithium response. Am J Psychiatry 1980;137:941–945
51. Kemperman CJ, Gerdes JH, DeRooij J, et al. Reversible lithium neurotoxicity at normal serum level may refer to intracranial pathology. J Neurol Neurosurg Psychiatry 1989;52:679–680
52. Roose SP, Bone S, Haidorfer C. Lithium treatment in older patients. Am J Psychiatry 1979;136:843–844
53. Smith RE, Helms PM. Adverse effects of lithium therapy in the acutely ill elderly patient. J Clin Psychiatry 1982;43:94–99
54. Gelenberg AJ, Kane JM, Keller MB, et al. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989;321:1489–1493
55. Keller MB, Lavori PM, Kane JM, et al. Subsyndromal symptoms in bipolar disorder: a comparison of standard and low serum levels of lithium. Arch Gen Psychiatry 1992;49:371–376
56. Jefferson JW, Greist JH, Ackerman DL, et al. Lithium Encyclopedia for Clinical Practice. 2nd ed. Washington, DC: American Psychiatric Press; 1987
57. Salzman C, Satlin A, Burrows AB, et al, eds. Geriatric Psychopharmacology: Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1995:803–814
58. Post RM, Roy-Byrne PP, Uhde TW. Graphic representation of the life course of illness in patients with affective disorder. Am J Psychiatry 1988; 145:844–848
59. Freeman TW, Clothie JL, Pazzaglia P, et al. A double-blind comparison of valproate and lithium in the treatment of acute mania. Am J Psychiatry 1992;149:108–111
60. Pope HG Jr, McElroy SL, Keck PE Jr, et al. Valproate in the treatment of acute mania: a placebo-controlled study. Arch Gen Psychiatry 1991;48: 62–68
61. Small JG, Klapper MH, Milstein V, et al. Carbamazepine compared with lithium in the treatment of mania. Arch Gen Psychiatry 1991;48:915–921
62. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania: the Depakote Mania Study Group. JAMA 1994;271:918–924
63. Prien RF, Gelenberg AJ. Alternatives to lithium for preventive treatment of bipolar disorder. Am J Psychiatry 1989;146:840–848
64. Post RM, Uhde TW, Roy-Byrne PP, et al. Correlates of antimanic responses to carbamazepine. Psychiatry Res 1987;21:71–83
65. McCoy L, Votolato NA, Schwarzkopf SB, et al. Clinical correlates of valproate augmentation in refractory bipolar disorder. Ann Clin Psychiatry 1993;5:29–33
66. McElroy SL, Keck PE Jr. Valproate in the treatment of bipolar disorder: literature review and clinical guidelines. J Clin Psychopharmacol 1992;12 (1, suppl):S42–S52
67. Stoll AL, Banov M, Kolbrener M, et al. Neurologic factors predict a favorable valproate response in bipolar and schizoaffective disorders. J Clin Psychopharmacol 1994;14:311–313
68. Calabrese JR, Markovitz PJ, Kimmel SE, et al. Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients. J Clin Psychopharmacol 1992; 12(1, suppl):S53–S56
69. Calabrese JR, Rapport DJ, Kimmel SE, et al. Rapid cycling bipolar disorder and its treatment with valproate. Can J Psychiatry 1993;38(3, suppl 2): S57–S61
70. Tariot PN, Erb R, Leibovici A, et al. Carbamazepine treatment of agitation in nursing home patients with dementia: a preliminary study. J Am Geriatr Soc 1994;42:1160–1166
71. Evans DL, Byerly MJ, Greer RA. Secondary mania: diagnosis and treatment. J Clin Psychiatry 1995;56(suppl 3):31–37
72. McFarland BH, Miller MR, Straumfjord AA. Valproate use in the older manic patient. J Clin Psychiatry 1990;51:479–481
73. Risinger RC, Risby ED, Risch SC. Safety and efficacy of divalproex sodium in elderly bipolar patients [letter]. J Clin Psychiatry 1994;55:215
74. Narayan M, Noaghiul S, Nelson JC. Divalproex treatment of mania in elderly patients. Presented at the 150th annual meeting of the American Psychiatric Association; May 17–22, 1997; San Diego, Calif
75. Eadie MJ, Hopper WD, Dickinson RG. Valproate-associated hepatotoxicity and its biochemical mechanism. Med Toxicol 1988;3:85–106
76. Redington K, Wells C, Petitio F. Erythromycin and valproate interaction. Ann Intern Med 1992;116:877–878
77. Sovner R, Davis JM. A potential drug interaction between fluoxetine and valproic acid [letter]. J Clin Psychopharmacol 1991;11:389
78. Jaster P, Abbas D. Erythromycin-carbamazepine interaction. Neurology 1986;36:594–595
79. Gadde K, Calabrese JR. Diltiazem effect on carbamazepine levels in manic depression. J Clin Psychopharmacol 1990;10:378–379
80. Dalton MJ, Powell JR, Messenheimer JA Jr, et al. Cimetidine and carbamazepine: a complex drug interaction. Epilepsia 1986;27:553–558

81. Hirschfeld A, Jarosinski P. Drug interaction of terfenadine and carbamazepine. Ann Intern Med 1993;188:907–908
82. McDonald WM, Nemeroff CB. The diagnosis and treatment of mania in the elderly. Bull Menninger Clin 1996;60:174–196
83. Wilder BJ, Rangel RJ, Pitlick WH, eds. Antiepileptic Drug Interactions. New York, NY: Demos Publications; 1989:65–72
84. Brosen K, Kragh-Sorensen P. Concomitant intake of nortriptyline and carbamazepine. Ther Drug Monit 1993;15:258–260
85. Fast DK, Jones BD, Kusalic M, et al. Effect of carbamazepine on neuroleptic plasma level and efficacy. Am J Psychiatry 1986;143:117–118
86. Arana GW, Epstein S, Molloy M, et al. Carbamazepine-induced reduction of plasma alprazolam concentrations: a clinical case report. J Clin Psychiatry 1988;49:448–449
87. Sussman N. Gabapentin and lamotrigine: alternative agents for the treatment of bipolar disorder. Primary Psychiatry 1997;4:25–42
88. Sporn J, Sachs G. The anticonvulsant lamotrigine in treatment-resistant manic-depressive illness. J Clin Psychopharmacol 1997;17:185–189
89. Sterker M, Berroushot J, Schneider D. Fatal course of toxic epidermal necrolysis under treatment with lamotrigine. Int J Clin Pharmacol Ther 1995;33:595–597
90. Schaffer C, Schaffer L. Gabapentin in the treatment of bipolar disorder [letter]. Am J Psychiatry 1997;154:297
91. Young LT, Robb J, Patelis-Siotis I, et al. Gabapentin in bipolar depression: a case series. Presented at the 150th annual meeting of the American Psychiatric Association; May 17–22, 1997; San Diego, Calif
92. Marcotte D. Use of topiramate, a new anti-epileptic, as a mood stabilizer. J Affect Disord 1998;50:245–251
93. Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. Am J Psychiatry 1994;151:169–176
94. Small JG, Klapper MH, Kellams JJ. Electroconvulsive treatment compared with lithium in the management of manic states. Arch Gen Psychiatry 1988;45:727–732
95. Small JG, Klapper MH, Milstein V, et al. Comparison of therapeutic modalities for mania. Psychopharmacol Bull 1996;32:623–627
96. Small JG, Milstein V, Small IF. Electroconvulsive therapy for mania. Psychiatr Clin North Am 1991;14:887–903
97. Milstein V, Small JG, Klapper MH. Uni- versus bilateral ECT in the treatment of mania. Convuls Ther 1987;3:1–9
98. Small JG, Small IF, Milstein V. Manic symptoms: an indication for bilateral ECT. Biol Psychiatry 1985;20:125–134
99. Black DW, Winokur G, Nasrallah A. Treatment of mania: a naturalistic study of electroconvulsive therapy versus lithium in 438 patients. J Clin Psychiatry 1987;48:132–139
100. Karliner W, Wehrheim HK. Maintenance convulsive treatments. Am J Psychiatry 1965;121:1113–1115
101. Jaffe RL, Rives W, Dubin WR, et al. Problems in maintenance ECT in bipolar disorder: replacement by lithium. Convuls Ther 1991;7:288–294
102. Vanelle JM, Loo H, Galinowski A, et al. Maintenance ECT in intractable manic-depressive disorders. Convuls Ther 1994;10:195–205
103. McDonald WM, Phillips VL, Figiel GS, et al. Cost-effective maintenance treatment of resistant geriatric depression. Psychiatr Ann 1998;28:47–52