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

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).

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