Bipolar Disorder in the Elderly: Differential Diagnosis and Treatment

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Bipolar disorder (BD) in later life is a complex and confounding neuropsychiatric syndrome with diagnostic and therapeutic challenges. Complicating the clinician's approach to treatment of older patients with BD is the paucity of controlled pharmacological studies in this age group. In this article, we use a case vignette to illustrate some of the diagnostic and therapeutic difficulties presented by BD in geriatric patients. We discuss the epidemiological data, differential diagnosis, evidence-based pharmacotherapy, and psychosocial interventions available for treatment of BD in older adults.

Case Vignette
Mrs Smith, a 74-year-old widow with a 30-year history of BD, was referred because of concerns about increasing depression. She had remained stable on lithium since 1979; her current dosage was 900 mg/d. Over the past few months, her family had noted increasing apathy, lack of motivation, and a decline in her functional capacity, although she had denied feeling depressed. The dosage of furosemide, a diuretic, was recently increased for hypertension.

On examination, Mrs Smith had a notable intention tremor of the hands, a Mini-Mental State Examination (MMSE) score of 28 of 30, and a lithium level of 0.9 mmol/L. Because lithium neurotoxicity was suspected, her lithium dosage was decreased to 450 mg/d; on follow-up her serum lithium level was 0.5 mmol/L. Within 2 weeks, Mrs Smith's daughter called to report that her mom was "no longer depressed," and had improved motivation, energy, and concentration, as well as a return to independent functioning.

Two years later, a routine check of renal function demonstrated renal insufficiency with a creatinine level of 1.4 mg/dL. Consultation with a urologist led Mrs Smith and her family to discuss gradually tapering off lithium. This possibility caused her severe anxiety and sleeplessness, leading to a brief hospitalization for a mixed episode with racing thoughts, irritable mood, and pressured speech.

Mrs Smith was discharged with the addition of olanzapine 5 mg/d at bedtime to her drug regimen. As an outpatient, lamotrigine was prescribed, which was titrated to 100 mg/d over 2 months. Lithium was then tapered and discontinued, and olanzapine was maintained at 2.5 mg/d at bedtime. In the past 6 months, Mrs Smith's condition has been stable with no further mood episodes. Recent follow-up neuropsychological testing after 2 years indicated a stable impairment in memory retrieval and executive functioning. This case highlights a number of important clinical issues when treating older adults with BD, including the importance of maintaining these patients at lower serum levels of medications, the development of cognitive impairment, the challenges in switching from lithium to alternative mood-stabilizing therapies, and the use of combination pharmacotherapy.

EPIDEMIOLOGY
Much of what we know about the epidemiology of geriatric BD derives from data on mixed adult populations, geriatric and nongeriatric. Lifetime prevalence of BD appears uniform across cultures and similar between men and women. The 1-year prevalence of BD among adults aged 65 and older is 0.4%, significantly lower than in younger adults (1.4%). BD is highly recurrent, with 85% to 100% of patients experiencing a recurrence after the initial episode. In as many as 10% of patients with BD, the illness develops after the age of 50. Later-onset BD is associated with a lower rate of familial illness than early-onset cases, a higher rate of medical and neurological comorbidity, and an increased vulnerability to relapse. In patients with a history of unipolar depression, mania may not develop until later life, and misdiagnosis is common, especially...
in type II BD.

DIFFERENTIAL DIAGNOSIS
The evaluation of manic symptoms or episodes in an older adult requires a thorough differential diagnosis to accurately determine the cause and to guide appropriate treatment (Table 1). Mania or major depression with anxious features should be considered when a patient is known to have had prior mood disorders. The new onset of bipolar symptoms in later years may represent secondary mania attributable to medical, pharmacological, or other organic dysfunction. Early stages of dementia may include manic symptoms such as irritable mood, emotional lability, sleep disturbance, and impaired social judgment. The co-occurrence of significant signs of confusion, fluctuation of alertness, or evidence of autonomic dysfunction may indicate the presence of delirium. In a patient with a history of BD, any change in baseline mood or functioning suggests a decompensation, warranting a workup for a concurrent medical condition.

In patients with MMSE scores of less than 15, the diagnosis of mania is especially problematic, particularly in distinguishing mania from dementia, delirium, or agitated depression. The following pearls may help with the differential diagnosis for patients who present with a combination of manic and cognitive symptoms.7

- The onset of a manic episode may be indicated by a rapid decline in cognitive functioning in a patient who has dementia, along with fluctuations in mood, energy, and sleep.
- Mixed manic and depressive symptoms are common in older patients who are manic.
- Dementia is typically associated with focal neurological findings, such as aphasia, apraxia, or impaired visuospatial functioning.
- It is typical for dementia or delirium to be associated with nighttime agitation and confusion in patients (“sundowning”).
- A negative family history of BD may be unreliable, as family members may have received a diagnosis (or misdiagnosis) before the modern diagnostic classification.8

Unfortunately, the literature is lacking regarding the clinical presentation of geriatric bipolar depression and how or whether it may be distinguished from bipolar depression in a younger population.5

PHARMACOTHERAPY
Most of what we know about the treatment of BD comes from randomized, controlled clinical trials in adult or mixed-age populations. There are no double-blind, placebo-controlled studies of geriatric BD. Our current guidelines for treating BD in the elderly are derived from uncontrolled studies and findings reported in younger and mixed-age populations (Table 2).

Treatment of geriatric mania
**Antipsychotic medications.** In treating older adults with mania, conventional antipsychotic medications have been used during the acute phase of the disorder.6 Atypical agents have supplanted conventional antipsychotic medications as first-line treatments in geriatric clinical practice largely because of the adverse effects associated with conventional antipsychotics, including a heightened risk of tardive dyskinesia with long-term use in older adults.9 In controlled and uncontrolled trials, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole have each been shown to be beneficial in younger patients who are manic.10 All atypical antipsychotic medications, except clozapine and paliperidone, have been FDA-approved for the treatment of acute mania, both as monotherapy and in combination with lithium or divalproex sodium (DVP), and may be used in the elderly as well.11

Dosing of atypical antipsychotics in the elderly is generally one half to one third the dose recommended for younger patients, although it varies with factors such as comorbid medical illness and age.12 Studies of mixed-age patients have shown benefit from adjunctive risperidone with DVP or lithium.13,14 Olanzapine monotherapy has demonstrated superior effectiveness compared with placebo for the treatment of mania in mixed-age patients, and a preliminary analysis of manic patients aged 50 years and older also suggests effectiveness.15 Preliminary open-label experience with quetiapine in older adults suggests that it may also have a role in treatment.16

Lithium remains a first-line treatment for acute mania in younger adults.17 It has not been studied in the elderly under double-blind conditions but has been reported to be as effective as acute or prophylactic treatments in several open trials.10 Because lithium pharmacokinetics are altered in the elderly—resulting in increased serum levels and elimination half-life—lithium can be associated with adverse effects even at lower serum levels.18 The presence of cognitive impairment or preexisting
tremor increases the likelihood of adverse effects. Finally, recovery from lithium-induced delirium can be prolonged in older patients. Lithium's serum level can be raised by many NSAIDs, angiotensin-converting enzyme inhibitors, and even more strongly by thiazide diuretics. Thus, pretreatment workup should include a thorough list of current medications, as well as ECG and assessment of electrolytes, blood urea nitrogen, creatinine, and thyroid-stimulating hormone levels.

**Mood stabilizing anticonvulsants.** DVP is effective for the acute treatment of mania in younger adults and appears to be at least modestly effective and well-tolerated in elderly patients who are manic. A mixed-age population of lithium-refractory patients and those who have neurological abnormalities appear particularly responsive to DVP. Some older patients with mania may require higher doses, and measurement of serum levels of DVP during acute illness and after stabilization is recommended. Toxic adverse effects, including sedation and gait instability, may develop during an acute phase and during maintenance therapy. Although hepatic and pancreatic toxicity are infrequent in the elderly, baseline liver functions should be obtained. DVP interacts with other highly protein-bound medications such as warfarin, is a modest cytochrome P450 enzyme inhibitor, and also strongly inhibits certain glucuronidation enzymes, thus increasing levels of lamotrigine. Other anticonvulsants have been used in elderly patients who have BD, with limited support from controlled studies. DVP and oxcarbazepine have replaced carbamazepine because of fewer adverse effects and better tolerability, although there is far less efficacy data for treatment of mania with oxcarbazepine. Serum sodium levels should be monitored for patients taking oxcarbazepine because it can cause hyponatremia. Several newer anticonvulsants may have more tolerable adverse-effect profiles, including gabapentin, topiramate, tiagabine, zonisamide, lamotrigine, and levetiracetam. However, as with gabapentin, topiramate and levetiracetam have failed in industry-supported studies of acute mania. Zonisamide still appears to hold some promise of efficacy in studies of adults with BD. Overall, these newer anticonvulsants have yet to be studied sufficiently in elderly patients with BD and mania to justify an authoritative recommendation for use.

**Electroconvulsive therapy.** Electroconvulsive therapy (ECT) remains an important intervention in the treatment of acute mania in later life and is often reserved for patients whose illness is resistant to medication or who require a rapid symptomatic resolution because of risks of dangerousness or malnutrition. Most responders can then be switched to pharmacotherapeutic maintenance, with or without continued ECT maintenance. Bilateral treatments may be more effective in mania, while unilateral placement may be associated with reduced cognitive disturbance. The co-administration of ECT and lithium has been associated with increased confusion and should generally be avoided.

**Geriatric bipolar depression**
Bipolar depression is a complex and difficult-to-treat condition that remains seriously understudied. Antidepressants can provide short-term benefit but may increase the risk of mania and rapid cycling over the long-term. Minimizing the use of antidepressants in bipolar depression may be possible since some newer mood stabilizers appear to have stronger antidepressant properties than conventional mood stabilizers. The combination of olanzapine and fluoxetine was the first FDA-approved medication for the treatment of bipolar depression, although research and clinical experience for its use in geriatric BD is limited. Quetiapine was recently approved for bipolar depression in adults. The combination of a standard mood stabilizer, such as lithium or DVP, with an antidepressant is a common and accepted form of treatment.

"Switching" to mania while receiving tricyclic antidepressants (TCAs) and other antidepressant agents can occur in older adults. SSRIs and bupropion are favored in younger patients who have bipolar depression to reduce rates of switching. Monoamine oxidase inhibitors (MAOIs) can benefit younger patients with bipolar depression and are effective in older patients with unipolar depression. In general, TCAs and MAOIs have higher rates of switching than SSRIs and bupropion, but they have not been studied in geriatric bipolar depression. For a moderate to severe or treatment-refractory episode of major depression, more aggressive pharmacotherapy or ECT is indicated. Highly refractory and protracted depressive episodes in BD have not been studied systematically in adult populations or in the elderly. Because of the risk of death and continued morbidity, the physician must make decisions based on clinical judgment or consensus guidelines. Some of these measures include lowering the dosage or even discontinuing a mood stabilizer; sleep deprivation; ECT; or combination therapies, including tranylcypromine plus risperidone or venlafaxine plus mirtazapine.

**Maintenance treatment**
Little information is available regarding maintenance treatment and prevention of subsequent episodes of late-life mania. Lithium has demonstrated efficacy as maintenance therapy in younger...
adults, and, although often used for maintenance, DVP has not received an FDA indication for that use.

Lamotrigine, olanzapine, and aripiprazole have been FDA-approved for the prevention of recurrent episodes of bipolar mania and depression. Lamotrigine has been shown to have acute and prophylactic antidepressant effects in patients with acute bipolar depression and in delaying relapse of bipolar depression. Among the major mood stabilizers, lamotrigine stands out as the best-tolerated medication; the only serious adverse effect is risk of Stevens-Johnson syndrome. It is attractive for treatment in older adults. Maintenance ECT is an option for patients who show poor response to maintenance medication regimens.

**Psychosocial interventions**

A number of studies have demonstrated the efficacy of psychotherapy in improving medication adherence in adult bipolar patients, although it has not been addressed in the geriatric population. In some promising preliminary studies, interventions in which bipolar patients are taught to monitor and manage stress have been effective in reducing rates of recurrence. Recent studies have demonstrated the efficacy of family interventions focused on reducing "expressed emotion," or negative familial attitudes of criticism, hostility, and emotional overinvolvement. Studies of group interventions over the past 3 decades for patients with BD have yielded positive results, including reduced re-admissions and improved medication adherence. Pollack conducted a study of inpatient group treatment for BD with 3 therapeutic goals: sharing information, learning strategies of coping, and improving interpersonal relationships. Other researchers have reported effective group treatments that include psycho-education on triggers, confrontation of denial about the illness, and restoration of patients’ identity and capacity for intimacy. In addition, interpersonal psychotherapy, social rhythm therapy, and cognitive-behavioral therapy have demonstrated promising results.

Researchers stress the relative power of combined psychosocial and pharmacological treatments in older adults with depression compared with either form of treatment alone. Gerocognitive behavior therapy combines a developmental perspective with cognitive interventions modified for older adults. This integrative model offers preventive strategies, including management of stress, attention to biological rhythms, and improved medication compliance, as well as reparative measures to deal with the interpersonal, social, and practical aftermath of the manic or depressive episode.

**CONCLUSIONS**

BD presents complex diagnostic and treatment challenges in later life. Confounding syndromes of delirium and dementia often present difficulties in accurate diagnosis. The occurrence of manic symptoms in the older adult must prompt careful evaluation to identify treatable medical conditions. Pharmacological approaches and ECT can be helpful in acute and maintenance treatment of late life mania and bipolar depression, although prospective, randomized, controlled trials in geriatric BD of all phases are currently lacking. Psychotherapy has much to offer in enhancing treatment compliance, addressing relapse risks, and helping patients cope with the implications of a chronic mental disorder. Controlled clinical research, in partnership with the technologies of genetics, molecular biology, and functional neuroimaging, will provide a better understanding of the neurobiological causes of geriatric BD and will promote more specific and effective treatment strategies.

**References**


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