Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

After controlling his bipolar disorder for 20 years, Mr. B suffers mania, paranoia, and depression late in life. What's causing these episodes? Which treatments can he tolerate?

'Killer trolls': One older man's battle

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Neil A. Smith, DO
Third-year resident in psychiatry
University of California San Francisco-Fresno
Medical Education Program

Robert Hierholzer, MD
Associate chief of staff, research, and education
VA Central California Health Care System, Fresno
Clinical professor, University of California, San Francisco

HISTORY BIPOLAR FOR 30 YEARS

Mr. B, age 66, was diagnosed 30 years ago with type I bipolar disorder and has type 2 diabetes, hypertension, alcohol abuse disorder, and cardiac disease. After repeated suicide attempts and hospitalizations in the past, he has been stable for 20 years on lithium, 600 mg bid, and nortriptyline, 50 mg at bedtime. He has had intermittent mania with little evidence of depression.

Two years ago, Mr. B called a local clinic to report that an intruder had him "holed up." His speech was pressured and garbled, and his thoughts were tangential, irrational, and markedly paranoid. A clinic psychiatrist called Mr. B's son, who said his father "built a bomb shelter" because "trolls and little people" were out to kill him. A family member called police, and Mr. B was brought to the ER and admitted for treatment.

A hospital psychiatrist stopped lithium in light of Mr. B's history of cardiac problems and because the psychiatrist considered the medication ineffective, even though serum lithium was only 0.03 mEq/L. The psychiatrist then started:

- divalproex at 500 mg bid, titrated over 1 week to 500 mg each morning and 1,000 mg at bedtime to reach serum valproate of 80 mEq/L
- quetiapine at 200 mg at bedtime, titrated over 1 week to 400 mg at bedtime.

Mr. B was still manic, paranoid, and hallucinating 1 week later, yet was discharged after he convinced the county hearing officer that he had recovered.

Two weeks later, Mr. B is brought to another psychiatric hospital, where a psychiatrist restarts unknown dosages of lithium, risperidone, and nortriptyline. From there, he is transferred to our inpatient unit. At presentation, he claims he has been drinking and that members of a drug cartel have recruited him. He says he has been skipping medications because he is "unclear which drugs to take."

We stop lithium and restart divalproex, 500 mg each morning and 1,500 mg at bedtime, to try to treat his mania without causing cognitive problems.

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We stop risperidone because of his hypotension and nortriptyline because it was not working, and restart quetiapine, 600 mg at bedtime, for his paranoia. He remains paranoid 1 week later but his mania improves, so we discharge him on the above regimen. We urge him to take his medications and follow up with his outpatient psychiatrist 1 week later.

Divorced, Mr. B lives alone with no family nearby. His son comes in from out of town to help him resettle after discharge, then leaves the next day.

Several months later, Mr. B's paranoia returns. He is not taking his medications because "the doctors took away my lithium and these new drugs don't work." He tells staff he is a martial arts expert and has purchased 7 cars in recent weeks. We restart lithium at 600 mg bid; serum lithium reaches 1.1 mEq/L, but his mania persists. After 5 days, we add aripiprazole, 15 mg/d.

Nearly 2 weeks after admission, a county hearing officer recommends discharging Mr. B despite his severe mania and paranoia. We release him on the above regimen, arrange appointments with his outpatient psychiatrist and primary care physician, and urge medication adherence. We schedule a blood test 3 days after discharge to check serum lithium, but Mr. B does not keep the appointment.

Mr. B's mania and paranoia suggest:

a) late-life bipolar disorder
b) a secondary cause
c) cognitive effects of bipolar disorder
d) delirium and/or dementia
e) frontal lobe lesions

The authors' observations

Suspect delirium after rapid onset of mania or paranoia in any patient. Also consider dementia and cognitive deficits in older adults, although Mr. B's symptoms resembled those of previous manic episodes. Although Mr. B's psychosis was more severe than before, his case underscores the importance of a thorough patient history.

Late-life bipolar disorder. Little is known about diagnosing and treating bipolar disorder (BPD) in older patients. Gaps in empiric knowledge can confound diagnosis, treatment, and outcome. Also, patients age ≥65 with BPD often have severe medical illness and are difficult to treat.[1]

Keys to detecting late-life BPD include:

- recognizing clinical features of BPD unique to older persons
- differentiating the disorder from late-life schizophrenia (*Table, page 97*).[1,2]

Older patients' symptoms usually match DSM-IV-TR criteria for BPD; their response to treatment mirrors that of younger adults.[3]

Secondary cause. When an older patient's mania has atypical features or doesn't respond to conventional treatment, look for a nonpsychiatric process such as a general medical condition or substance abuse (see possible medical causes with this article at www.currentpsychiatry.com). Order laboratory and other tests as clinical suspicion warrants.

Cognitive deficits secondary to BPD can occur at any age and be persistent or progressive,[4] although Depp et al[1] found more-severe impairment in older patients. Cognitive impairment can endure after successful BPD treatment, although acute treatment might improve cognition in older patients.[5]

Lithium can cause dull affect, cognitive slowing, and depersonalization. Titrating to the lowest effective dosage might minimize these effects.

Dementia. Cognitive deficits that accompany mania in older adults could suggest dementia, which usually develops over years and is preceded by cognitive changes without manic-type symptoms. By contrast, bipolar mania emerges more abruptly and is accompanied by affective symptoms. Agitation and psychosis—both symptoms of late-stage dementia—can be early signs of geriatric BPD.[2]

Delirium. Restlessness, irritability, aggression, and changes in affect can accompany delirium, espe-

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cially the hyperactive or hyperalert types. Symptoms of anxiety, depression, fear, and loose or tangential thinking also are common.

Mania shares some of these features but typically presents with an abnormally and persistently elevated or irritable mood lasting ≥1 week, usually without prominent cognitive impairment.[6] Mania can also include:

- grandiosity
- decreased need for sleep
- flight of ideas
- distractibility
- pressured or increased rate of speech
- psychomotor agitation
- potentially harmful activities
- increased goal-directed activities.[6]

By contrast, delirium is marked by waxing and waning consciousness and changes in cognition, such as disorientation and confusion.[6]

Frontal lobe lesions. Decreased prefrontal executive control could underlie mania's cognitive and emotional symptoms. Decreased right rostral and orbital prefrontal cortex activation has been associated with impaired planning, judgment, and insight, as well as inappropriate conduct.[7]

Table

Clinical features of geriatric bipolar disorder (BPD)

Psychotic features (delusions, hallucinations)

- Mean prevalence of 64% (range 20% to 85%) is similar to that of mixed-age groups; paranoia might be more prevalent

Family history

- High rates of psychiatric disorders ("affective disorder" in most studies) reported in 10 studies

Compared with younger adults with BPD, older patients:

- show longer latency from first depression to mania onset
- might be more likely to relapse into depression after mania
- might have less-intense mania
- are hospitalized longer, possibly because of greater medical comorbidity
- have less comorbid substance abuse and more-prominent age-associated morphologic abnormalities on neuroimaging[2]

Compared with late-life schizophrenia, late-life BPD patients show:

- more depressive symptoms
- fewer positive and negative symptoms
- greater community living and relationship skills, with similar activities of daily living

Source: References 1,2

CONTINUED TREATMENT DEPRESSION EMERGES

Several months later, Mr. B presents with severe depression and continued medication nonadherence. He complains of hypersomnia, poor appetite, anhedonia, amotivation, and a leaden-like paresis in his hands and feet.

We readmit Mr. B to the psychiatric unit. He avoids contact with others, has lost 18 lbs over 6 weeks, and suffers hypotension caused by poor hydration before admission. Three weeks later, he complains that ants are crawling around his room and into his mouth.

Noncontrast brain CT shows no abnormalities. Laboratory tests performed at admission show a subtherapeutic lithium level (0.03 mEq/L), unremarkable thyroid panel, and normal B_{12} and folate, so we begin to rule out a medical cause for his psychiatric symptoms.

continued

What caused Mr. B's depression?
a) bipolar disorder
b) medication side effects
c) medical disease
d) vascular disease

The authors' observations

Check for these and other possible causes of depressive symptoms in older patients with a history of BPD. Mr. B's depression likely resulted from multiple causes, including medical disease, functional impairment, loss of social and family contacts, and substance abuse—all late-life predictors of depression. BPD also predisposed him to depression.

Bipolar depression. Despite its profound morbidity and mortality, bipolar depression remains a mystery, especially in the elderly. Mr. B's depression emerged after he was free of depressive symptoms for more than 20 years.

Some researchers believe that compared with other depressions, bipolar depression has a more acute onset, marked psychomotor retardation, and lessened response to antidepressants.[6,8] Kraepelin associated bipolar depression with lethargy, mental slowing, and hypersomnia, whereas agitation and insomnia signal unipolar depression.[9]

To differentiate bipolar from unipolar or secondary depression in older patients, watch for:

- suicide risk, which is heightened during BPD's depressive phase[9]
- secondary manias, for which underlying causes must be determined and treated if possible.

Medication-induced depression. Medications can cause depressive symptoms *(see Related resources, page 105)*, but identifying an offending agent without an obvious chronologic relationship can be difficult, especially in older patients who are taking numerous medications.[9]

Depression caused by medication might be limited to somatic complaints such as fatigue or tiredness,[9] and often lacks features seen with mood disorders such as depressed mood, anhedonia, guilt, and diminished interest in activities. Mr. B's anhedonia and amotivation suggest his depression was not medication-induced.[10]

Disease-induced depression. Medical comorbidities are common among older persons with mood disorders and can complicate treatment response and outcome. Physical disease can cause or worsen depression:[11]

- Endocrine and immunologic diseases might cause depression or mania.
- Cardiovascular and cerebrovascular diseases; CNS disorders such as dementia, Parkinson's disease, and multiple sclerosis; cancer; and connective tissue disease increase risk for comorbid depression.

Mr. B's hypertension, diabetes, or coronary artery disease could have contributed to his depression or complicated the course.[11]

Vascular depression. Comorbid depressive symptoms and vascular disease—or "vascular depression"—can cause ischemic brain lesions, cognitive impairment, increased apathy and retardation, and impaired fluency and naming.[12]

What defines vascular depression has been debated. Watch for clinical or laboratory evidence of vascular disease, depression, and neuropsychological impairment.[13]

How would you handle this case?

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TREATMENT SEARCHING FOR EVIDENCE

Two days after admission, Mr. B is transferred to the ICU after suffering severe hypoglycemia and showing signs of medically induced delirium. Elevated creatinine (1.7 mg/dL) indicates acute renal failure, which could be related to his elevated serum lithium (1.7 mEq/L). Acting on the internist's advice, the consulting psychiatrist stops lithium and restarts valproate, 500 mg bid.

Mr. B becomes medically stable after 3 days, mostly through acute IV hydration and by withholding oral diabetes medications, which normalizes his blood sugar. He is transferred back to the psychiatry unit. We try lithium again at 300 mg bid, but creatinine and serum lithium quickly rise.

Mr. B remains hospitalized for 3 months with severe, treatment-resistant depression. Trials of nearly every second-generation antipsychotic (SGA) cause symptomatic orthostatic hypotension, leading to several falls. He does not respond to divalproex, up to 2,000 mg/d; citalopram, 60 mg/d; mirtazapine, 30 mg at bedtime; venlafaxine, 100 mg tid; or bupropion, 100 mg tid.

We suggest electroconvulsive therapy (ECT) but Mr. B declines, saying this treatment caused his mother to decompensate. We try lamotrigine, 25 mg/d, and titrate it over 6 weeks to 200 mg bid. After we add haloperidol, 5 mg at bedtime, and bupropion, 300 mg/d, Mr. B becomes mentally stable.

The authors' observations

Numerous clinical challenges—such as managing complicated/refractory BPD, medical comorbidity, and medication adherence (*Box*)[14,15]—complicate treatment of late-life BPD.[16] Regular communication with providers and integrating health care services can minimize complication risk.[16]

Pharmacotherapy, a core element of BPD treatment, is challenging in older patients because of their:

- heightened threat of complications and sensitivity to side effects because of age-related pharmacokinetic changes
- increased risk of drug-drug interactions
- increased potential for age-related psychosocial problems (increased social isolation, financial difficulties, demoralization, increased stress, inability to work).

Initial clinical and laboratory evaluations can rule out aggravating or causative factors and identify conditions that can cause drug intolerability.[5] Check orthostatic vital signs and perform a detailed medical and psychosocial history, neurologic examination, ECG, and cognitive evaluation.

Consider side effects, medical and neurologic comorbidities, and treatment history before prescribing a mood stabilizer, antipsychotic, or anti-

Box

Medication adherence a problem? Try educational/cognitive approach

Between 40% and 60% of patients do not take medications as prescribed.[14] That percentage probably is higher among cognitively impaired older adults because cognitive problems can compound other causes of nonadherence.

Few published controlled clinical trials have addressed adherence interventions for older adults. Educational approaches combined with cognitive supports are most likely to succeed. Ownby et al[15] hypothesized that effective approaches usually employ multiple components including counseling, information reminders, and family therapy.

Techniques for improving adherence include:

- addressing the patient's beliefs about his or her illness
- exploring how patient characteristics affect medication adherence
- use of memory aids, such as 7-day pill boxes
- working with caregivers
- prescribing lower-than-normal dosages to minimize side effects.

depressant to an older patient. Avoid unwarranted discontinuation of a previously effective agent, such as when drug concentrations are elevated or inadequate—as happened with Mr. B.[5] Also investigate the patient's side-effect history before stopping a medication.[5]

Medications. Mr. B's inability to tolerate lithium posed a treatment challenge. Adjusting lithium dosages to compensate for age-related pharmacokinetic, pharmacodynamic, and renal clearance changes can prevent toxicity.[5] Avoid stopping lithium abruptly, as this can trigger recurrence of manic or depressive episodes.[17]

Lamotrigine, indicated for BPD maintenance therapy, appears to prevent depressive/mood relapse. Compared with other anticonvulsants, lamotrigine might cause fewer negative effects on cognition and less induction of hepatic enzymes. It is well tolerated by older patients but has not been studied adequately in this age group.[16]

Antipsychotics are widely used in BPD,[16] especially when psychosis is present with mania or depression or the patient is agitated. Most studies of antipsychotics in BPD have followed younger adults, however, and most studies in older patients have followed those with dementia or schizophrenia.

Use of first-generation antipsychotics such as haloperidol is especially challenging in the elderly because these drugs increase risk of cardiovascular effects, extrapyramidal symptoms, and tardive dyskinesia and can cause depression in BPD.[16] By comparison, SGAs carry a lower risk of involuntary motion[18] but can increase risk of obesity, diabetes, and dyslipidemia. However:

- The need to manage psychosis usually overrides concerns about metabolic sequelae.
- Older patients might be less susceptible to metabolic effects,[16] though this has not been confirmed.

SGAs can be used safely in patients with a history of diabetes. Start at lower-than-normal dosages and titrate slowly. Perform baseline and regular checks—including weight, blood glucose, lipid levels, and blood pressure—following American Psychiatric Association and American Diabetes Association consensus guidelines.[19] Also check glycosylated hemoglobin every 3 to 6 months in patients with diabetes, and follow up with other providers to ensure proper diabetes management.

As with most aspects of late-life BPD, scant evidence guides SGA use. Avoid low-potency neuroleptics such as chlorpromazine, which can cause severe sedation and orthostatic hypotension. For Mr. B, a more-tolerable SGA such as aripiprazole or ziprasidone might be prudent, given his propensity for orthostatic hypotension and history of diabetes. Olanzapine or clozapine can cause anticholinergic effects and—in Mr. B's case—lead to weight gain and worsen diabetes.

Antidepressant use in BPD usually is reserved for depressive symptoms that impair occupational or social functioning and exceed DSM-IV-TR diagnostic criteria.[8,9] Consider later-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs), because tricyclics pose a greater risk of triggering a switch into hypomania or mania and can cause sedation and orthostatic, cardiac, anticholinergic, and anti-alpha 1 effects.

Bottom Line

Suspect a range of psychiatric or medical causes when older patients present with abrupt-onset mania or paranoia. Consider increased risk of drug-drug interactions, age-related pharmacokinetic changes, and higher sensitivity to side effects before choosing a medication. Watch for medical comorbidities, and consult regularly with other providers to minimize complication risk.

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Among SSRIs, consider citalopram, escitalopram, or sertraline for older patients taking one or more other medications, as these antidepressants have less potential for drug-drug interactions than fluoxetine and paroxetine.[11] In a recent comparison of newer antidepressants,[20] venlafaxine showed the highest relative risk of mood polarity switching and bupropion the lowest.

Consider ECT for older patients with refractory mania or depression or who show evidence of suicidality or inadequate nutrition.[5]

FOLLOW-UP ONGOING ISSUES

Three months after his admission, we discharge Mr. B to a board-and-care facility because family members will not take him in. Several weeks later, he again ignores his prescriptions and decompensates with worsening depression.

Family members have Mr. B admitted to an inpatient psychiatric facility closer to their home. He remains depressed, stays at the facility on and off for almost 1 year, and is eventually conserved by the county. Adverse side effects—mostly constipation and orthostatic hypotension—continue to complicate treatment.

Before Mr. B's most recent discharge, another psychiatrist restarts lithium, 300 mg bid, and nortriptyline, 100 mg at bedtime—the combination that kept Mr. B relatively stable for more than 2 decades.

Related resources

- National Institute of Mental Health—depression information. www.nimh.nih.gov/healthinformation/depressionmenu.cfm.
- Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). www.stepbd.org.
- Medicinenet.com. Medicines that cause depression. www.medicinenet.com/depression/index.htm. Click on "Medicines that cause depression."

DRUG BRAND NAME

Aripiprazole • Abilify
Bupropion • Wellbutrin
Chlorpromazine • Thorazine
Citalopram • Celexa
Clozapine • Clozaril
Divalproex • Depakote
Escitalopram • Lexapro
Fluoxetine • Prozac
Haloperidol • Haldol
Lamotrigine • Lamictal
Lithium • Various
Mirtazapine • Remeron
Nortriptyline • Pamelor
Olanzapine • Zyprexa
Paroxetine • Paxil
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Venlafaxine • Effexor
Ziprasidone • Geodon

DISCLOSURES

The authors report no financial relationship with any company whose products are mentioned in this article, or with manufacturers of competing products.

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