MAMTA BHATNAGAR, MD
Section of Geriatric Medicine, Department of Internal Medicine, Cleveland Clinic

ROBERT PALMER, MD, MPH
Head, Section of Geriatric Medicine, Department of General Internal Medicine, Cleveland Clinic

A 61-year-old with bipolar disorder and cognitive impairment: Dementia or polypharmacy?

He reports poor concentration, using wrong words, forgetting names, and sleepiness. The cause?

A 61-YEAR-OLD MAN PRESENTS for evaluation of new-onset cognitive impairment, which has developed over the past 6 to 8 months. He has bipolar disorder, for which he has been taking lithium carbonate (Eskalith) for the past 15 years. This therapy kept his mood stable until a relapse of depression and mania 1 year ago required hospitalization and an increase in the lithium dose, which was then lowered somewhat after he improved (see below). His cognitive symptoms appeared gradually within 2 months after his release from the hospital.

He now has difficulty concentrating, a tendency to substitute words incorrectly during conversation, and difficulty recalling names and "retrieving memories." He also reports a worsening tremor in his dominant hand that compromises his ability to eat with a spoon or a fork. He complains of increasing daytime somnolence, which began when his lithium dose was increased and improved when the dose was decreased.

The patient is a mathematician and recently finished revising the curriculum for an undergraduate course in advanced mathematics that he teaches. He does not smoke cigarettes, and he drinks alcohol only socially. He has no other medical conditions and no known cardiovascular risk factors.

Current and recent medications

- Lithium carbonate 600 mg twice daily (before his hospitalization he had been taking 600 mg twice daily; this was increased to 1,500 mg/day during the hospitalization and then decreased to the current dose as maintenance therapy)
- Divalproex (Depakote) 250 mg every night
- Gabapentin (Neurontin) 400 mg every night (the dosages of divalproex and gabapentin have remained unchanged since before his hospitalization)
- A multivitamin daily
- Naproxen (Naprosyn, Aleve) 250 mg up to two times a week for arthritic knee pain
- Aripiprazole (Abilify). This antipsychotic drug was recently discontinued because of parkinsonian symptoms, which then gradually improved.
- Memantine (Namenda), which is indicated for the treatment of moderate to severe Alzheimer disease. The patient reports that he stopped taking it after 3 weeks because he did not perceive it to be helping.

THE INITIAL EVALUATION

Physical examination

Temperature 98.3°F (36.8°C), pulse 60 beats per minute, respirations 16 per minute, blood pressure 126/64 mm Hg sitting and 118/71 mm Hg standing.

The patient is well groomed, alert, and cooperative. His head, eyes, ears, nose, and throat are normal. His teeth are in good condition. His skin is normal. We note no thyromegaly, carotid bruits, or palpable lymphadenopathy. His lungs are clear to auscultation. Results of cardiac, abdominal, and musculoskeletal examinations are all normal.

His deep tendon reflexes, sensory and motor testing, and gait are normal. The cerebellar examination is normal, aside from a mild tremor in his right hand when it is outstretched, with no resting tremor or cogwheel rigidity.

On the Mini-Mental State Examination (MMSE) he scores a perfect 30/30 (normal 24–30). He can draw a clock normally. His score on the short-form Geriatric Depression Scale is 4/15 (a score of 6 or higher indicates depression).

Laboratory tests

- Serum lithium level 0.8 mmol/L (therapeutic range 0.5–1.5 mmol/L) (his previous values are not available)
- Thyroid-stimulating hormone level 1.61 µU/mL (normal 0.40–5.50)
- Complete blood cell count and comprehensive metabolic panel values are within normal limits.

Magnetic resonance imaging

Noncontrast magnetic resonance imaging of the head reveals two nonspecific punctate foci of high signal intensity on T2-weighted images in the left frontal white matter, but the results are otherwise normal.

DIFFERENTIAL DIAGNOSIS

1 On the basis of this information, which is the most likely cause of this patient's cognitive impairment?

- ❑ Dementia with Lewy bodies
- ❑ Early-onset Alzheimer disease
- ❑ Stroke with vascular cognitive impairment
- ❑ Lithium neurotoxicity

Lithium neurotoxicity is the most likely cause of this patient's symptoms, given the temporal relationship between the adjusting of his lithium dose and the onset of his symptoms. Lithium therapy causes subtle cognitive deficits. Its dosing in older patients requires careful monitoring because of age-related alterations in its pharmacology and its various drug interactions; both mechanisms played a role in precipitating lithium toxicity in this patient.

Although his lithium levels are in the broadly accepted therapeutic range, there is much debate about the best maintenance level for patients with bipolar disorder. A level in the range of 1 to 1.2 mmol/L may be best in acute mania, while a lower level of around 0.8 mmol/L is preferred in the depressive phase. Once the patient's mood has stabilized, the best maintenance level may be in the range of 0.2 to 0.6 mmol/L.

Dementia with Lewy bodies, although suggested by the patient's cognitive impairment, history of parkinsonian symptoms, and somnolence, is an unlikely cause because his motor symptoms resolved after the aripiprazole was discontinued, his somnolence improved after the dose of lithium was reduced, and his alertness did not fluctuate thereafter as would be expected in dementia with Lewy bodies.

Alzheimer disease usually manifests as gradually progressive cognitive deficits involving memory impairment with one or more of the following: aphasia, apraxia, agnosia, and disturbance in executive functioning. In contrast, this patient's memory loss was fairly abrupt and not slowly progressive.

Stroke is also unlikely, as he has no history of stroke or focal neurologic deficits. Although a magnetic resonance scan of the brain showed some evidence of small-vessel ischemic changes, it showed no cortical infarcts.

Be vigilant in monitoring older patients taking lithium

MECHANISMS OF LITHIUM NEUROTOXICITY

2 What are the possible mechanisms of lithium neurotoxicity in this patient?

- ❑ The increased dose of lithium
- ❑ The interaction of nonsteroidal anti-inflammatory drugs (NSAIDs) and lithium
- ❑ The interaction of the other psychotropic medications with lithium
- ❑ All of the above
- ❑ None of the above

All of the above could be contributing.

Although lithium is thought to cause side effects in as many as 60% of patients of any age who take it, the rate of serious adverse effects is reportedly higher in older patients than in younger patients.[1]

Several plausible explanations for this age-related risk of lithium neurotoxicity can be

TABLE 1

Drug-related adverse cognitive effects of lithium with aging

CAUSE	MECHANISM	CLINICAL EXAMPLE	LABORATORY OR CLINICAL FINDING
Decreased renal clearance or altered volume of distribution	Age-related decline in glomerular filtration rate	A frail woman taking lithium	Higher serum lithium concentrations at any given dose of lithium
	Loss of lean body mass	A patient receiving rapid lithium dose adjustments develops tremor, ataxia, confusion	
Drug-patient interaction	Lithium-mediated inhibition of release of thyroid hormones	A patient with new onset of apathy and listlessness with cognitive deficits	Hypothyroidism
Drug-disease interaction	Parathyroid adenoma	A patient with bipolar disorder on lithium develops acute cognitive symptoms	Hypercalcemia
		An asymptomatic bipolar patient on lithium has an abnormal laboratory finding	
Drug-drug interaction	Concomitant use of psychotropics, selective serotonin reuptake inhibitor, carbamazepine (Tegretol)	A patient with a long psychiatric history taking lithium for bipolar disorder starts taking an antipsychotic drug	No alteration in serum lithium levels
	Drugs causing reduced lithium clearance, leading to increased renal sodium loss or polyuria, or leading to decreased renal prostaglandin activity	1 or 2 months after starting concomitant therapy with a diuretic (thiazide or loop), an angiotensin-converting enzyme inhibitor or angiotensin reuptake inhibitor, any drug that inhibits antidiuretic hormone,* or a nonsteroidal anti-inflammatory drug that inhibits renal prostaglandins	Hyponatremia, acute exacerbations of chronic kidney disease, exacerbation of congestive heart failure

*Acetaminophen, amitriptyline, aspirin, barbiturates, carbamazepine, clofibrate, cyclophosphamide, fluphenazine, haloperidol, oxytocin, thiothixene, vasopressin, vincristine

offered. Lithium's pharmacokinetics (drug distribution) and pharmacodynamics (the patient's sensitivity to it) are affected by the physiologic changes of aging, comorbidities, and the simultaneous use of other drugs, including psychotropic agents.[2] TABLE 1 summarizes the potential mechanisms of adverse drug effects and interactions leading to lithium neurotoxicity.

That said, cognitive deficits are common in bipolar disorder irrespective of lithium use.

COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER

3 If cognitive impairment in bipolar disorder is common, when does it occur?

- ❑ Only in the remission phase
- ❑ Only in the manic phase
- ❑ Only in the depression phase
- ❑ In all phases of the disease

Cognitive impairment occurs in all phases of

bipolar disorder. Neuropsychological testing of bipolar patients in remission uncovers subtle, persistent cognitive impairment in executive function and in visuospatial memory without mood symptoms.[3–5] Impaired executive functioning, predominantly frontal lobe dysfunction, interferes with one's ability to initiate, plan, perform, and successfully complete a task and challenges one's ability to function effectively in society and to comply with medical advice and instructions on taking medications.

RECOMMENDATIONS

4 What should we recommend to this patient?

- ❑ Decrease the current dose of lithium
- ❑ Stop all medications
- ❑ Undergo detailed neuropsychological testing
- ❑ Follow up with a psychiatrist, if needed

The patient's lithium level was within the therapeutic range and his bipolar symptoms were well controlled. In older patients, however, the optimal serum level of lithium is often unclear, making it advisable to reduce the dose when an adverse effect is suspected.

His other medications should be reviewed. Gabapentin is not indicated for use as a mood stabilizer, and his divalproex dose (250 mg) is well below the usual therapeutic dose of 1,000 to 2,000 mg/day.[6] The gabapentin could be discontinued, and the divalproex could be increased to a therapeutic dose.

NSAIDs can increase serum lithium levels, diminish renal lithium clearance, and possibly induce lithium toxicity, but the effect varies considerably among drugs and individuals.[7] We would advise this patient to stop taking naproxen and switch to acetaminophen (Tylenol) for his arthritis pain, and we would inform him of the risk of lithium toxicity with continuous use of NSAIDs.

We would also recommend additional neuropsychological testing. The patient noticed subtle difficulties in his cognitive abilities that were not apparent on the MMSE. While the MMSE is an acceptable cognitive test, it is often not sensitive enough to detect milder forms of cognitive impairment, especially in well-educated patients at the usual cut-point of 24. A comprehensive neuropsychological examination is a more sensitive measure of cognition, involving the detailed testing of various cognitive domains. It can reveal a pattern of cognitive impairment that helps to differentiate between normal and mood disorders and also can detect subtle executive dysfunction.

However, detailed neuropsychological testing is time-consuming and may not be obtained rapidly enough to help in making clinical decisions quickly. In this patient's case, immediate collaboration and follow-up with the patient's psychiatrist would be the most expeditious way to reassess the patient's medication regimen.

FOLLOW-UP COURSE

We informed the patient's psychiatrist that we thought the patient had increased sensitivity to lithium (even at "therapeutic" levels), possibly related to a drug-drug interaction.

His dose of lithium was kept at 600 mg twice daily, as the lithium toxicity was most likely due to a drug-drug interaction.

We discontinued his memantine, since he did not have Alzheimer disease and since he wasn't taking it anyway. He continued taking gabapentin and divalproex at the same doses, and he stopped taking naproxyn and substituted acetaminophen for his arthritis pain. We advised him about about health maintenance, including proper nutrition, mineral and vitamin supplements, and exercise.

Lithium interacts with many other drugs, diseases, and age-related changes

The patient underwent neuropsychological testing to better characterize his cognitive impairment. The findings did not suggest dementia, but were consistent with minor cognitive deficits caused by lithium.

When seen at a follow-up visit 6 weeks later the patient was free of symptoms except for the tremor in his dominant hand. His mood was stable and his cognition was better. No further changes were required in his psychotropic drug regimen.

TAKE-HOME POINTS

When a bipolar patient develops acute changes in cognition, we should suspect adverse effects of lithium as the cause, because

of its narrow therapeutic window and interactions with other prescribed drugs. The case presented here reminds us to consider adverse drug effects any time an older patient develops acute changes in cognition. One should also consider the potential for a drug-drug interaction when reviewing the patient's medication list and be especially vigilant in monitoring patients taking lithium, since its safety and effectiveness are affected by aging and by the co-administration of drugs that influence its clearance.

Despite these caveats, lithium remains an effective treatment in elderly patients, provided we are aware of the risks and benefits of its use.

REFERENCES

1. **Juurlink DN, Mamdani MM, Kopp A, Rochon PA, Shulman KI, Redelmeier DA.** Drug-induced lithium toxicity in the elderly: a population-based study. J Am Geriatr Soc 2004; 52:794–798.
2. **Sproule BA, Hardy BG, Shulman KI.** Differential pharmacokinetics of lithium in elderly patients. Drugs Aging 2000; 16:165–177.
3. **Martinez-Aran A, Vieta E, Colom F, et al.** Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 2004; 6:224–232.
4. **Martinez-Aran A, Vieta E, Reinares M, et al.** Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry 2004; 161:262–270.
5. **Rubinsztein JS, Michael A, Paykel ES, Sahakian BJ.** Cognitive impairment in remission in bipolar affective disorder. Psychol Med 2000; 30:1025–1036.
6. **Sajatovic M, Madhusoodanan S, Coconcea N.** Managing bipolar disorder in the elderly: defining the role of the newer agents. Drugs Aging 2005; 22:39–54.
7. **Ragheb M.** The clinical significance of lithium-non-steroidal anti-inflammatory drug interactions. J Clin Psychopharmacol 1990; 10:350–354.

ADDRESS: *Robert Palmer, MD, MPH, Section of Geriatric Medicine, Department of General Internal Medicine, A91, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail palmerr@ccf.org.*