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Dr. McInnis: Practical recommendations for prescribing lithium

LITHIUM FOR BIPOLAR DISORDER: A re-emerging treatment for mood instability

Low dosage, slow titration might mitigate side effects

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Disclosure
Dr. McInnis reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Lithium is among the most effective therapies for bipolar disorder (BD), and enthusiasm for this simple molecule is waxing. The history of lithium is fascinating,[1] and recent considerations include that this element, the third on the periodic table, has few, if any, industry champions. The recent renaissance is caused by a groundswell of appreciation for the clinical efficacy of lithium and an increasing number of providers who are willing to manage patients with lithium.

Target: Bipolar disorder

The target illness for lithium is BD, a spectrum of mood disorders with characteristic features of unstable mood and affect. Shifts in mood include recurrent episodes of mania, which are pathologically energized states with misguided volition and behavior with intoxicating euphoria (or irritability).[2] Psychomotor activity is elevated and out of character; speech and body movements are revved up, with a diminished need for sleep. The social, personal, and vocational consequences often are disastrous.

The most common mood state of BD is depression. Depressive episodes consist of pathologically compromised energy and volition with a slowing of bodily functions, most prominently cognition and concentration; a pervasive depressed or sad mood is common but not always present. Presence of mixed states, when features of depression and mania are present simultaneously, is one of the many challenges of treating BD; an elevated volitional or energized state may occur with a depressed, dysphoric mood.

continued

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Lithium for bipolar disorder

Clinical Point

The primary evidence for lithium is for maintenance treatment of BD and for preventing manic and depressive episodes

Table 1

Strategies for using lithium

Pre-treatment	Lab tests: CBC, comprehensive biochemistry panel, TSH, free T3, magnesium, phosphorus, urine pregnancy test for women of reproductive age Clinical: vital signs, height, weight, and waist circumference In a medically complex patient, consider the underlying disorder and investigate system accordingly
Treatment	Low dosage: begin at 150 mg/d, increase as tolerated every 2 to 3 days to 600 mg/d, observe for 1 week and request a serum lithium level Target lithium level is 0.6 mEq/L
Post-treatment	Monitor lithium level monthly for first 3 months; if stable, monitor every 6 months Comprehensive biochemistry panel and TSH every 6 months Repeat pre-treatment lab tests annually
Managing side effects	Increasing dosage slowly minimizes emerging side effects Obtain lithium and electrolyte levels when the side-effect profile changes When mental confusion occurs, assess lithium and electrolyte levels urgently Symptomatic strategies can be used in stable patients Before discontinuing lithium, consult a medical specialist who is familiar with lithium

CBC: complete blood count: TSH: thyroid-stimulating hormone

Evidence for lithium

Efficacy studies of lithium have focused on managing mood disorders, treating mania and depression, and prevention or maintenance care.[3] Most were performed during the 1970s and 1980s,[3] but recent studies have been comparing lithium with other mood stabilizers[4-7] and searching for a genetic basis for lithium response.[8-10] Other researchers have examined the use of lithium to prevent suicide.[11] Some have suggested a neuroprotective effect of lithium, which may have profound implications for neuropsychiatry if valid.[12-14] Results of additional studies, which are at different stages of completion, will clarify lithium use,[15,16] and characterize the genetic makeup of individuals who respond to lithium.[17] The primary evidence for lithium, however, is for maintenance treatment of BD and for preventing manic and depressive episodes.

Biochemistry and physiology of lithium. The biochemical and physiological effects of lithium are complex, wide-ranging, and likely to affect hundreds, if not thousands, of genes and gene products. The mechanisms of action remain a focus of academic pursuit (for a review of hypotheses related to these mechanisms see Goodwin and Jamison[2] and Can et al[18]) Lithium is involved in cell signaling pathways that involve complex molecular mechanisms of inter- and intracellular communication[19]; some neural receptors are down-regulated[20] and others show inhibition,[21] which is thought to be a mechanism of lithium. The hypothesized neuroprotective effect of lithium[22] may be mediated through an increased level of brain-derived neurotrophic factor in brain tissue.[14] Recently, investigators using induced pluripotent stem cell derived neurons have shown that patterns of calcium-related cell signaling in bipolar neurons are affected specifically by lithium in the culture media.[23] There likely are many mechanisms through which lithium's effects are mediated, including a series of dynamic pathways that vary over time and in reaction to the internal and external environments of the cell and person.

The lithium renaissance

In the past decade, there has been an increase in interest and use of lithium because clinicians recognize its efficacy and advantages and can monitor serum levels and gauge the patient's response and side effects[24] against the lithium level. This is important because balancing effi-

continued on page 41

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continued from page 40

cacy and side effects depends on the serum level. Efficacy often is not immediate, although side effects may emerge early. All systems of the body may show effects that could be related to lithium use. It is helpful to be aware of the side effects in chronological order, because some immediate effects may be associated with starting at higher dosages (***Table 1, page 40***). Common side effects in the short term include:

- GI distress, such as nausea, vomiting, diarrhea, and abdominal discomfort
- a fine neurologic tremor, which may be seen with accentuation upon deliberate movement
- prominent thirst with polyuria
- drowsiness and clouded thinking, which can be upsetting to the patient and family.

In the longer term, adverse effects on kidney and thyroid function are common. Management must include monitoring of the serum level.

Lithium is FDA-approved for acute and maintenance treatment of mania in BD. There are reports that discuss most variants of mood disorders, including BD I, BD II, unipolar depression, rapid cycling, and even alcohol abuse.[25-29] Lithium could help manage mood dysregulation in the context of temperament and personality.[30] There is evidence that lithium has an antidepressant effect[31-33] and has shown efficacy as an adjunctive treatment for depression.[31-33] There are data that suggest that lithium, with its neuroprotective mechanisms, may prevent progression of mild cognitive impairment.[34]

Is there an ideal lithium candidate?

Mood instability is the characteristic feature of a lithium responder. The instability may be over the course of the day, such as a dysregulated temperament that often is associated with DSM-IV personality categories, shorter-term fluctuations (within days with BD II), or in the context of episodic shifts of mood states over weeks and months, which are characteristic of BD I. The hallmark of mood instability is fluctuation from depression to elevated mood states and charged emotions with increased energy.

The patient considered ideal for lithium treatment has BD I with recurrent severe euphoric manic episodes, absence of significant comorbid disorders such as substance abuse, and a family history of lithium response. However, any patient with a clinically significant and unstable mood disorder, regardless of the DSM diagnosis, should be considered for lithium treatment.

When considering a lithium trial for a patient with significant mood instability, it is critical to establish the target symptoms and behavior that will help you gauge the efficacy of the intervention. Measurement-based care utilizes clinician and self-report instruments to provide data on the illness course and response to intervention. Commonly used clinician driven assessments include the Young Mania Rating Scale[35] and the Quick Inventory of Depressive Symptoms,[36] while the self-report assessments are the Patient Health Questionnaire[37] and the Altman Self-Rating Mania Scale.[38]

During acute mania or depression, lithium often is used in combination with another medications such as an antipsychotic or antidepressant. Used in the outpatient and non-acute setting, lithium may be an "add-on" or monotherapy for preventing recurrence of episodes. Response in early acute manic symptoms are predictive of later response and remission.[39]

Dosing strategies

An initial problem with lithium is side effects that emerge when beginning treatment, which may discourage the patient and family from using this agent. Starting with 150 mg/d for the first 2 or 3 doses is unlikely to produce any adverse effects and can show the patient that there is a high likelihood that he will be able to tolerate the medication. Gradual titration over several days—or even weeks—to the target dosage and serum levels will enhance patient compliance. Rate of dosage increase is best guided by tolerance to the medication. The general consensus

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Clinical Point

Mood instability is the characteristic feature of a lithium responder

Clinical Point

Many patients will benefit with low-level lithium use; yet some require a higher dosage for effective maintenance

Table 2

Side effects of lithium

Short term (days or weeks)	Diarrhea, abdominal discomfort
	Dysgeusia, nausea
	Tremor, ataxia
	Polydipsia, polyuria
	Dry mouth, dysarthria
	Drowsiness, slowed mentality
Intermediate to long term (weeks or months)	Nausea, diarrhea
	Tremor, ataxia
	Polydipsia, polyuria
	Diabetes insipidus
	Myeloproliferation
Long term (months or years)	Decreased renal function
	Hypothyroidism
	Tremor, ataxia
	Acne, alopecia

is that lithium is most effective at levels of 0.6 to 0.8 mEq/L,[40] although a lower level (0.5 mEq/L) over a 2-year period also can be effective.[41] Lithium may be used in to treat acute mania at higher serum levels (0.8 to 1.2 mEq/L), however, the acute phase often requires urgent management, usually with an antipsychotic.

Emerging consensus

Although there is a need to gather and analyze longer observational periods to clarify the clinical and biological characteristics of persons who respond to lithium, there are several points of consensus. Management will be guided by patient characteristics such as age, comorbidities, and other therapies. Most studies that address the effect of lithium level focus on high vs low serum levels. There are 3 categories of lithium serum levels, low (<0.6 mEq/L), mid-range (0.6 to 0.8 mEq/L), and high (>0.8 mEq/L), each has risk-benefit considerations.

The LiTMUS study[42] compared low-level lithium augmentation with optimized personal treatment without lithium. Both groups had similar outcomes but the lithium-treated group had significantly lower use of atypical antipsychotics. This may be important when considering the long-term risk of the metabolic syndrome because the tolerability and side-effect profile of lithium at lower levels is more favorable than that of atypical antipsychotics. As lithium levels increase, there seems to be concomitant increase in efficacy and side effects. Many patients will benefit with low-level lithium use; yet clearly some individuals require higher dosages for effective maintenance therapy.

Dosing and monitoring. In patients age >50 or those with comorbid medical conditions, use a lower level of lithium (<0.6 mEq/L). Most individuals with BD likely will benefit from the mid-range level strategy (0.6 to 0.8 mEq/L); however, there will be those who require a higher level. When beginning lithium, start at a low dosage (150 mg/d) and increase as tolerated to the desired serum level. With acute mania, temporary use of an antipsychotic will be required.

There are no tests available to determine whether a patient will do well at any of these lithium serum levels. Breakthrough mania in an adherent patient with a serum lithium level of 0.7 mEq/L indicates the need to obtain a higher lithium level. A major deficit in lithium research is the lack of long-term data (>5 years) on outcomes, clinical and biological features with lithium levels because of a lack of pharmaceutical company support.[3,17] Monitoring mood symptoms using detailed mood charts, whether clinician-administered or self-reported, is an effective way to monitor outcomes, provided the clinician uses the same scales or methods to record a patient's moods. If a patient wants to discontinue lithium, taper the drug over an extended period (months) to minimize the likelihood of emerging manic or depressive episodes related to drug discontinuation.

Managing side effects

Consider lithium's side effects in the context of their short-, intermediate-, and long-term presence (***Table 2***). Gradually increasing the lithium dosage often will prevent side effects that manifest in the

short term. If side effects emerge at low dosages, proceed slowly with lithium and manage symptoms with other medications. When a patient shows a change in side effects, obtain lithium and electrolytes levels; a change in mental status with confusion will require an acute lithium level.

A diary of symptoms or clinically relevant matters such as fluid intake or frequency of GI- or neurological-related events will help the clinician monitor the frequency and severity of side effects. The patient and clinician should not be discouraged by emerging side effects in the short term, because they may dissipate or become minimally intrusive.

Several strategies can alleviate immediate GI effects, such as dosing with meals, enteric-coated formulations, multiple dose strategies, and short-term use of antidiarrheal medicine as needed. Side effects that disrupt a patient's fluid and electrolyte balance (diabetes insipidus) to the point of clouding mental status will require discontinuing the medication until mental status improves, then reconsideration of the treatment regime, which will include managing diabetes insipidus with amiloride. Managing side effects may require consultation with specialty services. Likewise, some patients might experience neurologic side effects, such as profound tremor, that interferes with their ability to function. However, many side effects can be managed symptomatically with practical strategies (eg, a sugar-free lozenge for dry mouth or dysgeusia). Consider lower lithium dosages and serum levels because patients may experience benefits with lower therapeutic levels.

Long-term side effects include decreased renal function, hypothyroidism, persistent tremor, and dermatologic effects of acne and alopecia. Monitor renal and thyroid function annually in stable patients and more frequently when making changes in the treatment plan.

Before discontinuing lithium, consider discussing the medical issues with a specialist who has experience with complications of lithium.

Related Resources

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Drug Brand Names

Amiloride • Midamor
Lithium • Eskalith, Lithobid

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Bottom Line

Lithium is an effective and under used medication for managing bipolar disorder. Initial prejudices and side effects often deter patients and prescribers from proceeding with a therapeutic trial of lithium. Although the mid-range lithium level of 0.6 to 0.8 mEq/L is desirable, many patients will experience significant benefits with lower levels. Initial strategies include the use of low-dose preparations that are unlikely to have uncomfortable side effects.

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Clinical Point

Do not be discouraged by emerging side effects in the short term, because they may dissipate or become minimally intrusive

Lithium for bipolar disorder

Clinical Point

Long-term side effects include decreased renal function, hypothyroidism, persistent tremor, and dermatologic effects

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