Rediscovering the art

Current PSYCHIATRY

# of lithium therapy

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Lithium is not a fad whose time came and went. It is a valuable medication that belongs in our arsenal for bipolar disorder.

As a mood stabilizer for patients with bipolar disorder, lithium was the darling of U.S. psychiatry from the 1970s to well into the 1990s. It then began an ill-deserved, gradual fall from grace and today could be considered a pharmaceutical endangered species. But why?

Did lithium lose effectiveness? Is it too toxic? Is its side effect burden too heavy? Does it interact adversely with too many medicines? Is it too cumbersome to use? Was it just a fad whose time came and went—a psychiatric pet rock? Did it fall prey to the marketing might behind patent-protected drugs? Was it replaced by more effective and safer drugs?

You are partially correct if you checked "all of the above," because all contain a kernel of truth. At the same time, each is an exaggeration that does grave injustice to a remarkable medication. In addition, psychiatry appears to pay only lip service to convincing evidence that lithium is the only mood stabilizer that reduces the risk of suicide during long-term treatment.[1]

Some psychiatrists rationalize that "lithium is too difficult to use, so I never prescribe it."[2,3] My response is simply, "try it, and I think you'll like it." Measuring serum lithium concentrations is simple, accurate, and inexpensive. And we know quite a bit about how lithium dosage and blood level relate to response and tolerability.

Where does lithium stand?

Lithium is the first solid element in the periodic table (atomic number 3, atomic weight 6.94) (*Box 1*). As a treatment for

Box 1

HOW LITHIUM IS METABOLIZED

Lithium has no meaningful protein binding and no metabolites, being excreted almost entirely by the kidneys. Its elimination half-life of 18 to 24 hours may be longer in the elderly and shorter in youth because of age-dependent variations in glomerular filtration rate. For unclear reasons, renal lithium clearance appears to be more rapid in obese persons.

Lithium preparations available in the United States include standard-release (150, 300, 600 mg), slow-release (Lithobid and generic 300 mg), and controlled-release (Eskalith CR 450 mg) forms of lithium carbonate and a lithium citrate liquid. Lithium carbonate, 300 mg, and lithium citrate, 5 cc, each contain about 8 mmols of lithium. Lithium and lithium carbonate are **not** the same—there are 56.36 mg of lithium in 300 mg of lithium carbonate. The correct formula for lithium carbonate is Li_2CO_3, not $LiCO_3$ as is commonly and erroneously written.

With the standard-release preparation, peak serum levels are reached in about 1 1/2 hours and with the slow- and controlled-release forms in about 4 to 4 1/2 hours. At times, the slower-release forms may be better tolerated, but they are also a bit more costly (although all forms of lithium are inexpensive, compared with other mood stabilizers).

bipolar disorder, lithium's rise to prominence in the United States was far from rapid. Its antimanic properties were described by John Cade in Australia in 1949 in an open-label case series, but it was not FDA-approved for 20 years—for acute manic episodes in 1970 and for maintenance therapy "in those manic depressive patients with a history of mania" in 1974. Today, lithium shares FDA-approved manic episode billing with chlorpromazine (1973), divalproex (1995), and olanzapine (2000), but it remains the only FDA-approved drug for maintenance (although the FDA is considering a bipolar depression maintenance indication for lamotrigine).

If you examine lithium's status relative to other bipolar medications, you'll find some inconsistencies. For example:

- Clinical practice guidelines from the Department of Veterans Affairs (January 1999) recommended lithium as the first-line agent for acute and prophylactic treatment of manic and mixed states, bipolar depression, and rapid cycling.[4]
- The Expert Consensus Guidelines (April 2000) gave at least equal billing—if not preferred status—to divalproex for those indications.[5]
- The American Psychiatric Association's (APA) revised guidelines (April 2002) gave the nod to lithium for classic elated mania and bipolar depression but to divalproex for mixed mania and rapid cycling.[6] Divalproex was rated comparable to lithium for maintenance therapy, despite the lack of convincing data.
- The European perspective (January 2002) is most similar to that of the Department of Veterans Affairs, favoring lithium for acute mania, bipolar depression, and long-term treatment.[7]

There is no clear winner (or loser) in the battle for bipolar marketplace supremacy. The belief that one drug does everything is a fantasy for all but a small minority of patients with bipolar disorder. Polypharmacy is the rule, and rational polypharmacy the goal. To exclude lithium from the arsenal of bipolar drugs would be folly, yet lithium prescribing seems to have become a vanishing art. One of my psychopharmacologist colleagues recently expressed bewilderment at the number of "treatment-resistant" bipolar patients referred to him who had never been treated with lithium.

Diagnosis matters

Lithium is most effective in patients with euphoric mania, full remission between episodes, and normal interepisode functioning. Its potential benefits, however, clearly extend to all other aspects of bipolar disorder, to augmentation for treatment-resistant major depressive disorder, to schizoaffective disorder, and—at times—to aggressive states. As the bipolar spectrum expands, it is hardly surprising that the effectiveness of lithium (or any other drug) lessens as we approach the periphery of the spectrum.

Blood levels and dosing

Recommended lithium serum concentrations are given as ranges, realizing that individual variability makes exact numbers impractical. Package inserts for lithium products list serum concentrations between 1.0 and 1.5 mEq/L for acute mania and 0.6 and 1.2 mEq/L for maintenance therapy. The APA's revised guidelines are a bit more conservative, recom-

mending 0.5 to 1.2 mEq/L for acute mania and waffling somewhat on maintenance.[4] Many patients on maintenance therapy do well at levels between 0.6 and 0.8 mEq/L, and some prosper at even lower levels.

To avoid obtaining a misleading blood level:

- Samples should be drawn in the morning as close as possible to 12 hours after the last dose.
- Steady state conditions should exist, usually meaning 4 or 5 days on the same dosage without any missed or extra doses (*Box 2*).

Start treatment using divided dosages, but—following stabilization—once-daily dosing is possible for many patients. If lithium is taken as a single daily dose, 12-hour blood levels will be somewhat higher than with multiple daily dosing. Single and multiple daily dosing are similarly effective, but once-daily dosing may have a compliance and tolerability edge in some patients.

Considering individual patient variability, a lithium carbonate dosage of 1,200 to 1,800 mg/d is likely to be therapeutic for mania and 900 to 1,200 mg/d for maintenance in otherwise healthy, nongeriatric adults.

Box 2

TWO KEYS TO OBTAINING A MEANINGFUL LITHIUM SERUM LEVEL

- Draw samples in the morning, as close as possible to 12 hours after the last dose.
- Measure serum levels at steady state, at least 4 or 5 days on the same dosage without any missed or extra doses.

Lithium's potential to cause birth defects is less than that of carbamazepine or valproate

Starting and maintaining lithium

Medical history. Assuming that lithium theapy is indicated, obtain a detailed medical history. Focus on findings that increase the risk of lithium toxicity, such as renal impairment, drug interactions, and unstable fluid-electrolyte balance.

Although lithium is not contraindicated in patients with renal disease, using an alternate drug is probably preferable. On the other hand, because lithium does not adversely affect the liver or pancreas, it may be preferred to some other mood stabilizers if these organs are diseased.

A thorough diet and drug history is also important. Because low-sodium diets reduce renal lithium clearance, lower doses may be required to reach a given serum concentration. Some drugs alter lithium excretion and can increase or decrease blood levels (see "Drug combinations," page 23).

Advise women of childbearing age about lithium's teratogenic potential (which is considerably less than that of carbamazepine or valproate). The risk of cardiovascular malformation of the fetus has been estimated at 1/1,000 to 1/2,000 births among women who took lithium during the first trimester of pregnancy.[8]

Baseline lab tests. Assessing renal function is essential. A serum creatinine level will usually suffice, unless a history of renal disease suggests the need for a more extensive evaluation, such as creatinine clearance, renal ultrasound, or nephrology consultation.

A urinalysis is often part of the package. Because thyroid dysfunction can alter mood and lithium can disrupt thyroid function, baseline TSH and T4 tests are recommended. CBC is optional (lithium can cause leukocytosis). The medical history should determine whether additional blood work is necessary. An ECG is sometimes advised in older patients, especially if the history suggests cardiovascular disease. Finally, don't forget a pregnancy test in women of childbearing potential (*Box 3*).

Monitoring. Early in the course of therapy, lithium blood levels are usually obtained at 5- to 7-day intervals until the patient is stabilized. After that, assuming all is well, routine monitoring can occur every 3, 4, or even 6 months, depending on the individual's reliability and stability. Because ongoing assessment of renal and thyroid function is also important, it makes sense to obtain:

- a serum creatinine measurement linked to each lithium level
- and a serum TSH yearly or at the slightest indication of thyroid dysfunction, such as fatigue, weight gain, cognitive impairment, cold intolerance, or depression.

Stopping lithium. Lithium can be discontinued abruptly without side effects if it is ineffective or not tolerated. Stopping lithium after successful long-term use is another story. There is a high likelihood of illness recurrence and a small but real possibility that lithium will be ineffective when

restarted. Also, abrupt or rapid discontinuation (within 1 to 14 days) is believed to increase the likelihood of earlier recurrence, compared with more gradual discontinuation.[9]

Side effects and toxicity

One reason for lithium's slide in popularity is its perceived side-effect profile. Toxic amounts can be lethal, and therapeutic amounts can be bothersome. Yet concerns are often exaggerated because of lack of familiarity with the drug.[10,11]

Intoxication. Lithium does have a narrow therapeutic index, with toxicity related to serum concentration and duration of exposure. Acute overdoses, while not benign, are often better tolerated than gradual, more tissue-saturating exposures. Idiosyncratic factors are also involved, as evidenced by documented toxicity at "therapeutic" levels and tolerability despite very high levels.

Early warnings of impending toxicity include:

- neurologic findings such as dysarthria, new or worsening tremor, and ataxia
- gastrointestinal symptoms such as anorexia, nausea, vomiting, and diarrhea.

Severe toxicity can be fatal or cause permanent neurologic (often cerebellar) damage. Causes of intoxication range from deliberate overdose to renal impairment, low-sodium diets, drug interactions, and dehydration. At particular risk are patients with lithium-induced polyuria whose access to fluid replacement is compromised.

Treatment involves reducing absorption, increasing excretion, and restoring fluid-electrolyte balance. Severe intoxication, especially if renal function is impaired, is best treated with hemodialysis.

Neurologic. Mild neurologic complaints such as memory impairment, slow reaction time, lack of spontaneity, and lost creativity have been ascribed to lithium and may lead to noncompliance. Under such circumstances, other diagnostic considerations include breakthrough depression, hypothyroidism, other illness, hypercalcemia, other medications, and absence of hypomania.

Like valproate, lithium can cause a benign postural tremor that is usually tolerable and often transient. Should the tremor be problematic, treatment considerations include dosage reduction, switching to a slow-release preparation, reducing caffeine intake, avoiding other tremor-causing drugs such as theophylline or stimulants, and treating associated anxiety. If an anti-tremor drug is needed, a beta-blocker such as propranolol is used most commonly; other options to consider are primidone and gabapentin. Don't forget that a worsening tremor may indicate impending toxicity.

Very rarely, lithium has been associated with pseudotumor cerebri (benign intracranial hypertension), peripheral neuropathy, and a myasthenia gravis-like syndrome.

Cardiovascular. Like many drugs, lithium can cause benign ST-T wave changes on ECG.

More serious, but fortunately quite uncommon, is lithium-induced sinus node dysfunction manifesting as a variety of bradyarrhythmias and, at times, syncopal episodes. Since normal aging is associated with a gradual loss of sinus node pacemaker cells, the elderly may be especially sensitive to this problem. Unless a pacemaker is implanted, sinus node dysfunction usually requires lithium discontinuation.

Endocrine. The association between lithium and goiter and hypothyroidism is well-recognized, with elevated risk in women and in patients with pre-existing thyroid disease. Both clinical and symptomatic subclinical hypothyroidism will improve with supplemental thyroid hormone. Less well appreciated are reports of hyperthyroidism occurring during lithium therapy or shortly after its discontinuation. Because subclinical hyperthyroidism may not be benign, careful attention must be paid to main-

Box 3

RECOMMENDED TESTS BEFORE PRESCRIBING LITHIUM

Test	Indication
Serum creatinine, urinalysis	To screen for renal function
TSH and T4	To establish baseline thyroid function
CBC (optional)	If indicated by patient's overall medical condition or because some doctors prefer to do more general screening
ECG (optional)	For patients with risk factors for heart disease
Pregnancy test	For at-risk women because of lithium's teratogenic potential

taining thyroid function well within the normal range.

Reports continue to accrue of lithium-related hypercalcemia and increased parathyroid hormone levels, with an occasional patient developing parathyroid hyperplasia or adenoma requiring surgical intervention.[12] No specific guidelines have been established for monitoring serum calcium, but some authors have recommended periodic testing.

Weight. At least one-third of patients on lithium gain weight for a variety of reasons, such as altered lipid and carbohydrate metabolism, use of high-calorie fluids to combat polydipsia and polyuria, hypothyroidism, and the use of other drugs associated with weight gain. If weight gain occurs, recognize it early (weigh your patients) and institute appropriate dietary and exercise measures.

Hematologic. A mild, benign leukocytosis is seen sometimes during treatment with lithium. This effect has been harnessed to treat some neutropenic conditions. Lithium does not increase the risk of blood dyscrasias.

Dermatologic. Acne, psoriasis, and follicular keratosis may first appear or worsen during lithium therapy. Occasionally, otherwise successful lithium therapy has been rendered impossible by a dramatic dermatologic flare-up. Hair loss has also been associated with lithium use for unclear reasons, although hypothyroidism is occasionally a factor.

Renal. Impaired urinary concentrating ability and polyuria are common adverse effects. Both may be reversed with timely treatment discontinuation, but they may persist even after discontinuation in patients on long-term lithium treatment.[12]

Polyuria is largely nephrogenic in origin and, at times, can be voluminous, cause great inconvenience, and pose a risk of dehydration and lithium intoxication. Patients sometimes believe that thirst drives the polyuria and attempt to deal with it by restricting fluid intake, which can be quite dangerous. More appropriate interventions include dosage reduction (if possible) and the use of a thiazide and/or potassium-sparing diuretic. If diuretics are used, serum lithium concentrations may rise. Debate remains as to whether slow- or controlled-release preparations or single daily dosing are "kinder to the kidney."

Box 4

FACTS ABOUT PRESCRIBING LITHIUM

- Lithium is most effective in patients with euphoric mania, full remission between episodes, and normal interepisode functioning.
- Lithium is the only mood stabilizer that has been shown to reduce the risk of suicide during long-term treatment.
- Renal impairment, drug interactions, and unstable fluid-electrolyte balance increase the risk of lithium toxicity.
- Lithium does not adversely affect the liver or pancreas and may be the preferred mood stabilizer if these organs are diseased.
- Lithium has teratogenic potential but less than that of carbamazepine or valproate.
- Because lithium can disrupt thyroid function, baseline and ongoing thyroid function tests are recommended.

In recent years, there has been a disturbing increase in reports of elevated serum creatinine and reduced creatinine clearance associated with long-term lithium use.[13] Because renal impairment has many causes, evaluation by a nephrologist is strongly advised. Then if the finger of causation points strongly at lithium, a careful risk/benefit analysis is in order. Even if lithium is discontinued—and especially if it is continued—regular renal function assessment is essential.

Rarely, lithium can cause a nephrotic syndrome (proteinuria, edema, decreased serum albumin, and increased serum lipids) that tends to be reversible with drug discontinuation.

Drug combinations

First the good news. Lithium tends to combine well with all the anticonvulsant mood stabilizers, making it the favored drug for combination therapies. Lithium/antidepressant combinations can be useful for treatment-resistant depression, although serotonin syndrome occasionally has been reported when lithium is combined with selective serotonin reuptake inhibitors.[10,11] Using lithium with atypical antipsychotics is common, often effective, and usually well-tolerated.

Drug-drug interactions. Some nonpsychiatric drugs are associated with reduced renal lithium clearance and potential lithium toxicity. Because nonpsychiatrists usually prescribe these drugs, encourage patients taking lithium to ask their doctors about the possibility of interactions whenever a new

drug is prescribed. Pharmacists can be particularly helpful in avoiding drug-drug interactions.

In patients taking diuretics, serum lithium concentrations are definitely increased by thiazides, possibly by potassium-sparing types, and occasionally by loop types. Osmotic and xanthine diuretics do just the opposite. Because diuretics are often used in medically unstable patients, assume that all can disrupt lithium balance.

Most nonsteroidal anti-inflammatory drugs can increase serum lithium levels, although dose and treatment duration are important variables. Aspirin and acetaminophen should not cause problems. The effect of COX-2 inhibitors on lithium levels has not been studied adequately, so these drugs should remain under suspicion.[14]

Lithium toxicity has been reported with angiotensin-converting enzyme (ACE) inhibitors, and their package inserts caution about this possibility. More recently, a few cases of lithium toxicity have been reported in patients taking angiotensin II receptor type-1 (AT-1) antagonists (e.g., candesartan, losartan, valsartan).[15]

Other, less well-substantiated pharmacokinetic and pharmacodynamic interactions that have been reported with lithium and other drugs can be researched, by using a computer-based drug interaction program or consulting with a drug information center.

Patient and clinician education

Both patients and clinicians have an obligation to ensure that lithium (or any other drug) is used safely and effectively (*Box 4*). Excellent sources of continuing education are listed below in "Related resources." Rather than fall prey to the illusion that lithium therapy is a "vanishing art," it would be better for clinicians to heed these words from the APA's 2002 practice guidelines for bipolar disorder:

"No other treatment has performed as well as lithium in as many aspects of long-term care of bipolar disorder patients, and despite some risks and limitations lithium remains the standard against which all proposed alternatives are compared."[6]

Related resources

- Depression and Bipolar Support Alliance. www.dbsalliance.org
- Lithium Information Center. www.miminc.org

DRUG BRAND NAMES

Chlorpromazine • Thorazine
Divalproex • Depakote
Gabapentin • Neurontin
Lamotrigine • Lamictal
Olanzapine • Zyprexa
Primidone • Mysoline
Propranolol • Inderal

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Bottom Line

Lithium is a valuable medication with potential benefits that extend to all aspects of bipolar disorder. Measuring serum levels is simple, accurate, and inexpensive. Concerns about side effects and toxicity are often exaggerated. Lithium combines effectively and safely with anticonvulsants, antipsychotics, and many antidepressants.

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