INTRODUCTION

Lithium is one of the most effective medications for the continuous treatment of bipolar disorder. It is particularly useful for the treatment of acute manic episodes and reduces rates of suicide associated with affective disorders.\textsuperscript{1,2,3} Off-label uses for lithium include augmentation of the action of other antidepressant drugs and treatment of aggression, posttraumatic stress disorder, and pediatric conduct disorders. Lithium for the treatment of Alzheimer's disease is under investigation.\textsuperscript{4} Lithium toxicity most often results from accidental or intentional overdose, increased dose, or reduction in renal clearance of lithium.

PHARMACOLOGY

The specific pharmacologic effect responsible for the therapeutic benefit in bipolar disorder and mania is unknown.\textsuperscript{5} Lithium competes with other similar cations, including sodium, potassium, magnesium, and calcium, and displaces them from intracellular and extracellular sites. Interference with sodium ions at the sodium channel and the sodium-potassium pump on the cell membrane is responsible for lithium's adverse effect on myocardial electrical activity. Lithium inhibits arginine vasopressin, an effect that is responsible for polyuria and nephrogenic diabetes insipidus seen during lithium therapy. Some toxic effects of lithium may be due to inhibition of 3-glycogen synthase kinase, which is present in high quantities in the brain.\textsuperscript{5} Other pharmacologic effects include inhibition of inositol monophosphatase and reduction of the concentration of inositol in the cytoplasm, inhibition of adenylate cyclase and reduction of intracellular cyclic adenosine monophosphate and possibly cyclic guanosine monophosphate, and interference with the release and reuptake of norepinephrine at the nerve terminal site. Lithium may enhance serotonin release, particularly from the hippocampus, and has been implicated in serotonin syndrome when combined with other medications that alter serotonin metabolism.

Lithium is excreted by the kidneys, so medications that reduce glomerular function have the potential to contribute to lithium toxicity, particularly thiazide diuretics.\textsuperscript{6} Neuromuscular blocking agents such as succinylcholine, vecuronium, and pancuronium may result in a prolonged neuromuscular blockade when given to patients receiving long-term lithium therapy.

PHARMACOKINETICS
After oral ingestion of therapeutic doses, lithium is rapidly and almost completely absorbed, although delayed absorption may occur with sustained-release products and after ingestion of a large number of tablets. Lithium is not bound to plasma proteins and has an initial volume of distribution of 0.6 L/kg, which is similar to that of body water, but over time this can increase to 0.9 L/kg as the ion distributes throughout the body. Ingestion of a single tablet of lithium carbonate 300 milligrams containing 8.12 mEq of lithium ion will acutely raise serum lithium levels by about 0.2 mEq/L (0.2 mmol/L) in a 70-kg adult.

Lithium distribution into and out of the brain is slower, resulting in neurologic effects that do not correlate with serum levels. The lithium concentrations in the brain and in the serum may differ by twofold to threefold. Continuation of toxic effects, even after hemodialysis, can be due to the drug’s slow movement out of the CNS. Therefore, serum levels do not predict CNS levels and only roughly correlate with clinical symptoms.

The elimination half-life after a single dose of lithium is about 18 to 24 hours in young adults and almost twice that in the elderly. After continued therapy of longer than a year, the lithium elimination half-life increases, up to almost 60 hours in all ages. Lithium is not metabolized and is excreted unchanged, primarily in the urine. Like other cations of similar size, lithium is reabsorbed in the proximal tubule.

Renal insufficiency is a critical factor in the development of lithium toxicity. Changes in fluid and electrolyte status can impact lithium clearance; sodium and water loss due to heat or exercise may lead to lithium retention. The elderly are particularly prone to toxicity because of their decreased volume of distribution and reduced renal clearance. Elderly patients are at risk for lithium toxicity when concomitantly treated with either loop diuretics or angiotensin-converting enzyme inhibitors.

### CLINICAL FEATURES

#### ADVERSE EFFECTS OF CHRONIC LITHIUM THERAPY

Adverse effects during therapeutic lithium use are common, occurring in up to 90% of treated patients. The most frequent adverse effects include fine postural hand tremor, fatigue, polyuria due to loss of urinary concentration ability, hypothyroidism, and hyperparathyroidism with hypercalcemia. Worsening of a baseline tremor and development of ataxia or dysarthria are important signals of developing toxicity and may signal a need to decrease the dose of lithium. Long-term lithium treatment can lead to electroencephalographic changes, including diffuse slowing, an increase in theta and delta waves, and a decrease in alpha activity.

Lithium is a common cause of drug-induced nephrogenic diabetes insipidus, which is prevalent in up to 40% of patients receiving long-term lithium treatment and occurs through decreased expression of aquaporin-2 in the distal tubule of the nephron. This leads to decreased urinary concentrating ability, which is usually compensated in patients by increased thirst. The defect in the distal nephron can also result in an inability to acidify the urine, causing an incomplete distal renal tubular acidosis without acidemia. Long-term lithium
Treatment can lead to a progressive nephropathy, with a mild reduction in glomerular filtration\textsuperscript{12,15} and about a 1\% absolute risk of requiring renal replacement therapy.\textsuperscript{15,16} Maintaining serum lithium levels below 0.8 mEq/L (0.8 mmol/L) may reduce long-term renal damage.\textsuperscript{17}

GI side effects, including nausea, vomiting, and diarrhea, are common at initiation of treatment, are generally transient, and can be decreased by giving the lithium dose with food or dividing the dose over the day. Development of these symptoms during the course of treatment, on the other hand, may signal toxicity or may cause volume depletion and induce toxicity.

ECG abnormalities commonly reported with lithium use include QT interval prolongation, T-wave flattening or inversion, and significant bradycardia.\textsuperscript{18}

Hypothyroidism is the most prevalent endocrine dysfunction, occurring at a rate almost six times that in the general populace.\textsuperscript{12,19} Hyperparathyroidism and hypercalcemia are frequently reported and can be associated with stimulation of hyperplasia or adenomas.\textsuperscript{20}

**TOXIC EFFECTS**

Lithium toxicity can be divided into three main categories: acute toxicity in naïve patients, acute-on-chronic toxicity in those who take lithium long term and take an acute intentional overdose, and chronic toxicity developing in patients receiving long-term lithium therapy who experience a change in lithium dosage or decreased renal clearance.\textsuperscript{21,22,23,24} Decreases in glomerular filtration or intravascular volume depletion are a precipitating cause in nearly all cases of chronic toxicity. Other factors may also contribute to the development of lithium toxicity (**Table 181–1**).\textsuperscript{25}

**Table 181–1**

**Factors Precipitating the Development of Lithium Toxicity**

- Decreased glomerular filtration: renal injury or failure, heart failure, sepsis
- Volume depletion: diuretic use, vomiting, diarrhea, diaphoresis, decreased oral intake
- Drug–drug interaction, including polypharmacy

Recognizing lithium toxicity may be challenging, particularly in patients with chronic toxicity.\textsuperscript{26,27} There is only an approximate correlation between serum levels and clinical symptoms.\textsuperscript{24} Common symptoms are increased tremor, muscle fasciculations, clonus, choreoathetosis, ataxia, muscle weakness, dysarthria, agitation, and lethargy (**Table 181–2**).\textsuperscript{25,27,28} It may be difficult to distinguish between lithium toxicity and organic delirium.\textsuperscript{29} Although most patients present with a slowing of cognitive function, cases of lithium
Lithium levels have only an approximate correlation with severity. As toxicity worsens, confusion, lethargy, stupor, seizures, and finally coma develop.

Table 181–2

**Lithium Toxicity**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Clinical Features</th>
<th>Typical Lithium Level (mEq/L or mmol/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Nausea, vomiting, fatigue, lethargy, fine tremor</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>Confusion, agitation, dysarthria, ataxia, hypertonia, hyperreflexia, nystagmus, muscular weakness</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Severe</td>
<td>Coma, seizures, myoclonus, hyperthermia, cardiovascular collapse</td>
<td>&gt;3.5</td>
</tr>
</tbody>
</table>

*Lithium levels have only an approximate correlation with severity.

Lithium toxicity commonly produces distal renal tubule dysfunction, with decreased response to arginine vasopressin, so that patients may develop significant polyuria compensated by polydipsia. Alteration of this balance can lead to electrolyte disturbances such as hypernatremia, volume depletion, and renal insufficiency.

GI symptoms such as nausea, vomiting, diarrhea, bloating, or generalized abdominal pain are common in both acute and chronic toxicity. Cardiac abnormalities are more common in acute toxicity and can cause hypotension, bradycardia, and ventricular dysrhythmias, presenting as syncope. Chronic lithium toxicity may be associated with rare cases of ventricular tachycardia. ECG changes with a prolonged QT interval, transient ST-segment depression, or T-wave inversion are seen in some patients. Less common toxic effects include hyperthermia, hypothermia, peripheral neuropathy, and severe leukopenia. Rare cases of adult respiratory distress syndrome have been associated with acute lithium toxicity.

Up to 10% of patients with severe lithium toxicity die, generally of respiratory failure or cardiovascular collapse. Most patients recover, with toxic effects resolving as the body burden of lithium decreases. Permanent cerebellar and basal ganglia damage may develop. A syndrome of irreversible lithium-effectuated neurotoxicity has been described after lithium toxicity and involves various degrees of neurologic dysfunction after cessation of lithium use for at least 2 months. These patients have truncal ataxia, ataxic gait, scanning speech, and diffuse incoordination. Short-term memory loss, dementia, and a tremor of the hands and head accompany the cerebellar signs.
DIAGNOSIS

Acute lithium overdoses present with more GI toxicity and less neurologic toxicity because of the slower accumulation into the brain after ingestion and distribution in body water. With time, as CNS lithium levels rise, neurologic findings increase after GI symptoms abate. Patients with acute overdose may have markedly elevated serum concentrations that do not correlate well with either symptom severity or prognosis.

Patients with chronic toxicity display earlier and more prominent neurologic effects in association with lower serum concentrations. Serum lithium levels in such patients correlate better with degree of toxicity, but the clinical condition of the patient is the most important factor. Lithium toxicity has even been reported at therapeutic levels.

Acute-on-chronic ingestions occur in patients who are undergoing treatment with lithium and ingest an additional amount. These patients can have both GI and neurologic symptoms and signs.

Monitor lithium serum concentrations and obtain serial serum measurements during observation and treatment. Collect blood samples for measurement of serum lithium concentration in the appropriate tube to avoid falsely increased levels; collection in tubes containing lithium-heparin may cause false elevation in lithium level. Therapeutic lithium levels are considered to be 0.6 to 1.2 mEq/L (0.6 to 1.2 mmol/L). The toxic range varies according to the clinical circumstance, with most patients manifesting toxic effects at levels >2 mEq/L (>2 mmol/L).

A 12-lead ECG may be helpful in identifying a level >1.2 mEq/L (>1.2 mmol/L); QTc interval >440 milliseconds and diffuse T-wave inversions have positive likelihood ratios of 7 and 4, respectively.

Lithium-induced hypothyroidism can be severe, precipitating myxedema crisis, so check thyroid-stimulating hormone and thyroid hormone levels in patients with altered level of consciousness.

TREATMENT

Initial stabilization of the patient's condition includes protection of the airway and provision of ventilatory and hemodynamic support. Establish IV access, initiate cardiac rhythm monitoring, obtain an ECG, and order renal function tests, fluid and electrolyte levels, calcium levels, magnesium levels, CBC, thyroid-stimulating hormone and thyroid hormone levels if altered level of consciousness, pregnancy test where applicable, and serum levels of lithium and other possible co-ingestions. Subsequent treatment depends on clinical severity (Table 181–3).
Table 181–3

Management of Lithium Toxicity

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV saline infusion</td>
<td>Used in essentially all patients with toxicity</td>
</tr>
<tr>
<td></td>
<td>Reestablishes euvolesia and normal lithium renal elimination</td>
</tr>
<tr>
<td>Whole-bowel irrigation</td>
<td>Used in awake patients who ingest sustained-release lithium preparations</td>
</tr>
<tr>
<td>Sodium polystyrene sulfonate</td>
<td>Consider in awake patients with mild to moderate toxicity</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Used for patients with severe toxicity</td>
</tr>
<tr>
<td></td>
<td>Also used for patients with renal failure, patients who cannot tolerate IV saline infusion, and patients with high elevated serum lithium levels (&gt;4.0 mEq/L in any type of overdose and &gt;2.5 mEq/L in chronic toxicity)</td>
</tr>
<tr>
<td>IV benzodiazepines</td>
<td>Used for seizures seen in severe toxicity</td>
</tr>
</tbody>
</table>

Treat seizures with IV benzodiazepines, such as lorazepam. Obtain toxicology and neurology consultation for refractory seizures. Phenytoin is ineffective in controlling drug-induced seizures.

Gastric lavage has no role in most cases of lithium overdose because the sustained-release preparations are often too large and the immediate-release preparations are too rapidly absorbed. Ipecac syrup is no longer recommended. Whole-bowel irrigation with polyethylene glycol solution at 2 L/h is effective in removing lithium from the body after an acute ingestion of sustained-release preparations, as long as there is no alteration of mental status. GI decontamination is useless in patients with chronic toxicity.

IV administration of normal saline is critical, because nearly all patients with significant toxicity have some sodium and volume deficit. Typical adult dosing is an IV bolus of normal saline, 20 mL/kg, followed by continuous infusion at 1.5 to 2 times the maintenance rate. Volume repletion reestablishes normal renal elimination kinetics of lithium. Diuretic-induced diuresis does not enhance lithium elimination, and in fact, loop and thiazide diuretics promote water loss, which is followed by lithium retention.

**Sodium polystyrene sulfonate (Kayexalate®)**, an exchange resin, binds lithium, relieves a modest amount of the body burden of lithium, and shortens elimination half-life. Doses used in observational studies, mostly in patients with chronic toxicity, are 30 grams dissolved in 120 mL of water, orally, every 4 to 6 hours.
This approach is not widely used because oral drugs are to be avoided in patients with impaired mental status due to the risk of aspiration, the potential for hypokalemia and constipation, and the effectiveness of other therapies.

Anecdotal treatment with sodium bicarbonate and acetazolamide (both for urinary alkalinization) and aminophylline has no proven benefit.

Lithium can be removed by hemodialysis, but there is much debate over the threshold for initiating this treatment. Hemodialysis is indicated in patients with symptoms of severe toxicity, those who cannot tolerate treatment with IV fluids, or those whose renal function is impaired and who lack the ability to eliminate lithium. Extracorporeal treatment is recommended for severe toxicity (coma, seizures, life-threatening dysrhythmias) or a serum lithium level > 4.0 mEq/L (> 4 mmol/L) in the presence of renal insufficiency. Consult with a medical toxicologist or nephrologist for patients who have little decrease or increase in serum lithium level after 6 hours of IV saline administration or for patients who have ingested sustained-release preparations.

The goal of hemodialysis is to reduce the body burden of lithium. Because of the intracellular concentration of lithium, redistribution after hemodialysis is expected and an increase in serum levels after hemodialysis is common. Therefore, monitor serum lithium levels for up to 8 hours after hemodialysis. If symptoms of toxicity recur or worsen or if the levels rise significantly, consider repeat hemodialysis. Peritoneal dialysis has been used for treatment of lithium toxicity in the past, but the clearance rates are approximately the same as through normal renal clearance (Table 181–4).

Table 181–4

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Elimination Half-Life (h)</th>
<th>Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>18–42*</td>
<td>10–40*</td>
</tr>
<tr>
<td>IV saline</td>
<td>13–20</td>
<td>–</td>
</tr>
<tr>
<td>Sodium polystyrene sulfonate</td>
<td>12–20</td>
<td>–</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>12–16</td>
<td>10–15</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>4–6</td>
<td>70–170</td>
</tr>
</tbody>
</table>

* Longer elimination half-lives and reduced clearance rates are seen in older adults and in patients with acute-on-chronic toxicity.
DISPOSITION

Admission decisions are made by considering such issues as the presence and persistence of factors predisposing the patient to toxicity, the acuity of the toxicity, and the circumstances that led to the toxicity. Asymptomatic patients with acute ingestions should be monitored for 4 to 6 hours, with serial serum lithium levels measured. Admit patients with serum lithium levels of >1.5 mEq/L (>1.5 mmol/L) after an acute ingestion. Any patient with an acute ingestion of a sustained-release preparation should be admitted regardless of serum lithium level.

Patients with mild toxicity who have no additional risk factors may be managed with IV saline treatment for 6 to 12 hours, often in an observation unit. Once repeated serum lithium levels decrease to <1.5 mEq (<1.5 mmol/L), such patients can be discharged after psychiatric evaluation, if needed. Patients with moderate toxicity require admission, and patients with severe toxicity require intensive care.

Patients taking lithium may seek care in the ED for conditions not related to mental health or lithium toxicity. Take care to avoid prescribing any drugs that negatively impact glomerular filtration and renal function. Thiazide diuretics, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are some common agents that have the potential for lithium interaction promoting toxicity.

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[PubMed: 25583292]

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[PubMed: 14658947]

USEFUL WEB RESOURCES
47. American Association of Poison Control Centers — http://www.aapcc.org/DNN/


49. European Association of Poisons Centres and Clinical Toxicologists — http://www.eapcct.org/

50. Lithium overdose, United Kingdom Medicines and Healthcare Products Regulatory Agency (information can be located through these links: How We Regulate, Medicines, Licensing of Medicines, Information for Licence Holders, Guidance, Overdose sections of Summary of Product Characteristics, generic overdose sections, Lithium) — http://www.mhra.gov.uk/index.htm

51. TOXBASE: The primary clinical toxicology database of the National Poisons Information Service (free access for U.K. National Health Service hospital departments and general practices, and National Health Service departments of public health and health protection agency units; available to hospital EDs in Ireland by contract; available to European poison centers whose staff are members of the European Association of Poisons Centres and Clinical Toxicologists; overseas users may be allowed access on payment of a yearly subscription, subject to the approval of the Health Protection Agency) — http://www.toxbase.org/