

19 - 29.19 Lithium

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29.19 Lithium

The effectiveness of lithium for mania and for the prophylactic treatment of manic-depressive disorder was established in the early 1950s as a result of research done by John F.J. Cade, an Australian psychiatrist. Concerns about toxicity limited initial acceptance of lithium use in the United States, but its use increased gradually in the late 1960s. It was not until 1970 that the Food and Drug Administration (FDA) approved its labeling for the treatment of mania. The only other approved FDA indication came in 1974, when it was accepted as maintenance therapy in patients with a history of mania. For several decades, lithium was the only drug approved for both acute and maintenance treatment. It is also used as an adjunctive medication in the treatment of major depressive disorder. Lithium (Li), a monovalent ion, is a member of the group IA alkali metals on the periodic table, a group that also includes sodium, potassium, rubidium, cesium, and francium. Lithium exists in nature as both ^6Li (7.42%) and ^7Li (92.58%). The latter isotope allows the imaging of lithium by magnetic resonance spectroscopy. Some 300 mg of lithium is contained in 1,597 mg of lithium carbonate (Li_2CO_3). Most lithium used in the United States is obtained from dry lake mining in Chile and Argentina.

PHARMACOLOGICAL ACTIONS Lithium is rapidly and completely absorbed after oral administration, with peak serum concentrations occurring in 1 to 1.5 hours with standard preparations and in 4 to 4.5 hours with slow-release and controlled-release preparations. Lithium does not bind to plasma proteins, is not metabolized, and is excreted through the kidneys. The plasma half-life is initially 1.3 days, and is 2.4 days after administration for more than 1 year. The blood-brain barrier permits only slow passage of lithium, which is why a single overdose does not necessarily cause toxicity and why long-term lithium intoxication is slow to resolve. The elimination half-life of lithium is 18 to 24 hours in young adults, but is shorter in children and longer in elderly persons. Renal clearance of lithium is decreased with renal insufficiency. Equilibrium is reached after 5 to 7 days of regular intake. Obesity is associated with higher rates of lithium clearance. The excretion of lithium is complex during pregnancy; excretion increases during pregnancy but decreases after delivery. Lithium is excreted in breast milk and in insignificant amounts in the feces and sweat. Thyroid and renal concentrations of lithium are higher than serum levels. An explanation for the mood-stabilizing effects of lithium remains elusive. Theories include alterations of ion transport and effects on neurotransmitters and neuropeptides,

signal transduction pathways, and second messenger systems. THERAPEUTIC INDICATIONS Bipolar I Disorder Manic Episodes. Lithium controls acute mania and prevents relapse in about 80 percent of persons with bipolar I disorder and in a somewhat smaller percentage of persons with mixed (mania and depression) episodes, rapid-cycling bipolar disorder, or mood changes in encephalopathy. Lithium has a relatively slow onset of action when used and exerts its antimanic effects over 1 to 3 weeks. Thus, a benzodiazepine, dopamine receptor antagonist (DRA), serotonin-dopamine antagonist (SDA), or valproic acid is usually administered for the first few weeks. Patients with mixed or dysphoric mania, rapid cycling, comorbid substance abuse, or organicity respond less well to lithium than those with classic mania. Bipolar Depression. Lithium has been shown to be effective in the treatment of depression associated with bipolar I disorder, as well as in the role of add-on therapy for patients with severe major depressive disorder. Augmentation of lithium therapy with valproic acid (Depakene) or carbamazepine (Tegretol) is usually well tolerated, with little risk of precipitation of mania. When a depressive episode occurs in a person taking maintenance lithium, the differential diagnosis should include lithium-induced hypothyroidism, substance abuse, and lack of compliance with the lithium therapy. Possible treatment approaches include increasing the lithium concentration (up to 1 to 1.2 mEq/L); adding supplemental thyroid hormone (e.g., 25 µg a day of liothyronine [Cytomel]), even in the presence of normal findings on thyroid function tests; augmentation with valproate or carbamazepine; the judicious use of antidepressants; or electroconvulsive therapy (ECT). After the acute depressive episode resolves, other therapies should be tapered in favor of lithium monotherapy, if clinically tolerated. Maintenance. Maintenance treatment with lithium markedly decreases the frequency, severity, and duration of manic and depressive episodes in persons with bipolar I disorder. Lithium provides relatively more effective prophylaxis for mania than for depression, and supplemental antidepressant strategies may be necessary either intermittently or continuously. Lithium maintenance is almost always indicated after the first episode of bipolar I disorder, depression or mania, and should be considered after the first episode for adolescents or for persons who have a family history of bipolar I disorder. Others who benefit from lithium maintenance are those who have poor support systems, had no precipitating factors for the first episode, have a high suicide risk, had a sudden onset of the first episode, or had a first episode of mania. Clinical studies have shown that lithium reduces the incidence of suicide in bipolar I disorder patients sixfold or sevenfold. Lithium is also an effective treatment for persons with severe cyclothymic

disorder. Initiating maintenance therapy after the first manic episode is considered a wise approach based on several observations. First, each episode of mania increases the risk of subsequent episodes. Second, among people responsive to lithium, relapses are 28 times more likely after lithium use is discontinued. Third, case reports describe persons who initially responded to lithium, discontinued taking it, and then had a relapse but no longer responded to lithium in subsequent episodes. Continued maintenance treatment with lithium is often associated with increasing efficacy and reduced mortality. Therefore, an episode of depression or mania that occurs after a relatively short time of lithium maintenance does not necessarily represent treatment failure. However, lithium treatment alone may begin to lose its effectiveness after several years of successful use. If this occurs, then supplemental treatment with carbamazepine or valproate may be useful. Maintenance lithium dosages can often be adjusted to achieve plasma concentration somewhat lower than that needed for treatment of acute mania. If lithium use is to be discontinued, then the dosage should be slowly tapered. Abrupt discontinuation of lithium therapy is associated with an increased risk of recurrence of manic and depressive episodes. Major

Depressive Disorder Lithium is effective in the long-term treatment of major depression, but it is not more effective than antidepressant drugs. The most common role for lithium in major depressive disorder is as an adjuvant to antidepressant use in persons who have failed to respond to the antidepressants alone. About 50 to 60 percent of antidepressant nonresponders do respond when lithium, 300 mg three times daily, is added to the antidepressant regimen. In some cases, a response may be seen within days, but most often, several weeks are required to see the efficacy of the regimen. Lithium alone may effectively treat depressed persons who have bipolar I disorder but have not yet had their first manic episode. Lithium has been reported to be effective in persons with major depressive disorder whose disorder has a particularly marked cyclicity. Schizoaffective Disorder and Schizophrenia Persons with prominent mood symptoms—either bipolar type or depressive type—with schizoaffective disorder are more likely to respond to lithium than those with predominant psychotic symptoms. Although SDAs and DRAs are the treatments of choice for persons with schizoaffective disorder, lithium is a useful augmentation agent. This is particularly true for persons whose symptoms are resistant to treatment with SDAs and DRAs. Lithium augmentation of an SDA or DRA treatment may be an effective treatment for persons with schizoaffective disorder even in the absence of a prominent mood disorder component. Some persons with schizophrenia who cannot take antipsychotic drugs may benefit from lithium treatment alone.

Other Indications Over the years, reports have appeared about the use of lithium to treat a wide range of other psychiatric and nonpsychiatric conditions (Tables 29.19-1 and 29.19-2). The effectiveness and safety of lithium for most of these disorders have not been confirmed. Lithium has antiaggressive activity that is separate from its effects on mood. Aggressive outbursts in persons with schizophrenia, violent prison inmates, and children with conduct disorder and aggression, or self-mutilation in persons with mental retardation can sometimes be controlled with lithium. Table 29.19-1 Psychiatric Uses of Lithium

Table 29.19-2 Nonpsychiatric Uses of Lithiuma

PRECAUTIONS AND ADVERSE EFFECTS More than 80 percent of patients taking lithium experience side effects. It is important to minimize the risk of adverse events through monitoring of lithium blood levels and to use appropriate pharmacological interventions to counteract unwanted effects when

they occur. The most common adverse effects are summarized in Table 29.19-3. Patient education can play an important role in reducing the incidence and severity of side effects. Patients taking lithium should be advised that changes in the body's water and salt content can affect the amount of lithium excreted, resulting in either increases or decreases in lithium concentrations. Excessive sodium intake (e.g., a dramatic dietary change) lowers lithium concentrations. Conversely, too little sodium (e.g., fad diets) can lead to potentially toxic concentrations of lithium. Decreases in body fluid (e.g., excessive perspiration) can lead to dehydration and lithium intoxication. Patients should report whenever medications are prescribed by another clinician because many commonly used agents can affect lithium concentrations. Table 29.19-3 Adverse Effects of Lithium Cardiac Effects Lithium can cause diffuse slowing, widening of frequency spectrum, and potentiation and disorganization of background rhythm on electrocardiography (ECG). Bradycardia and cardiac arrhythmias may occur, especially in people with cardiovascular disease. Lithium infrequently

reveals Brugada syndrome, an inherited, life-threatening heart problem that some people may have without knowing it. It can cause a serious abnormal heartbeat and other symptoms (such as severe dizziness, fainting, shortness of breath) that need medical attention right away. Before starting lithium treatment, clinicians should ask about known heart conditions, unexplained fainting, and family history of problems or sudden unexplained death before age 45.

Gastrointestinal Effects

Gastrointestinal (GI) symptoms—which include nausea, decreased appetite, vomiting, and diarrhea—can be diminished by dividing the dosage, administering the lithium with food, or switching to another lithium preparation. The lithium preparation least likely to cause diarrhea is lithium citrate. Some lithium preparations contain lactose, which can cause diarrhea in lactose-intolerant persons. Persons taking slow-release formulations of lithium who experience diarrhea caused by unabsorbed medication in the lower part of the GI tract may experience less diarrhea than with standard-release preparations. Diarrhea may also respond to antidiarrheal preparations such as loperamide (Imodium, Kaopectate), bismuth subsalicylate (Pepto-Bismol), or diphenoxylate with atropine (Lomotil). Weight Gain Weight gain results from a poorly understood effect of lithium on carbohydrate metabolism. Weight gain can also result from lithium-induced hypothyroidism, lithium-induced edema, or excessive consumption of soft drinks and juices to quench lithium-induced thirst. Neurological Effects Tremor. A lithium-induced postural tremor may occur that is usually 8 to 12 Hz and is most notable in outstretched hands, especially in the fingers, and during tasks involving fine manipulations. The tremor can be reduced by dividing the daily dosage, using a sustained-release formulation, reducing caffeine intake, reassessing the concomitant use of other medicines, and treating comorbid anxiety. β -Adrenergic receptor antagonists, such as propranolol, 30 to 120 mg a day in divided doses, and primidone (Mysoline), 50 to 250 mg a day, are usually effective in reducing the tremor. In persons with hypokalemia, potassium supplementation may improve the tremor. When a person taking lithium has a severe tremor, the possibility of lithium toxicity should be suspected and evaluated. Cognitive Effects. Lithium use has been associated with dysphoria, lack of spontaneity, slowed reaction times, and impaired memory. The presence of these symptoms should be noted carefully because they are a frequent cause of noncompliance. The differential diagnosis for such symptoms should include depressive disorders, hypothyroidism, hypercalcemia, other illnesses, and other drugs. Some, but not all, persons have reported that fatigue and mild cognitive impairment decrease with time. Other Neurological Effects. Uncommon neurological adverse effects include symptoms of mild parkinsonism, ataxia, and dysarthria, although the last two symptoms may also be attributable to lithium intoxication. Lithium is rarely associated with the development of peripheral neuropathy, benign intracranial hypertension (pseudotumor cerebri), findings resembling myasthenia gravis, and increased risk of seizures.

Renal Effect The most common adverse renal effect of lithium is polyuria with secondary polydipsia. The symptom is particularly a problem in 25 to 35 percent of persons taking lithium who may have a urine output of more than 3 L a day (reference range: 1 to 2 L a day). The polyuria primarily results from lithium antagonism to the effects of antidiuretic hormone, which thus causes diuresis. When polyuria is a significant problem, the person's renal function should be evaluated and followed up with 24-hour urine collections for creatinine clearance determinations. Treatment consists of fluid replacement, the use of the lowest effective dosage of lithium, and single daily dosing of lithium. Treatment can also involve the use of a thiazide or potassium-sparing diuretic—

for example, amiloride (Midamor), spironolactone (Aldactone), triamterene (Dyrenium), or amiloride–hydrochlorothiazide (Moduretic). If treatment with a diuretic is initiated, the lithium dosage should be halved, and the diuretic should not be started for 5 days, because the diuretic is likely to increase lithium retention. The most serious renal adverse effects, which are rare and associated with continuous lithium administration for 10 years or more, involve appearance of nonspecific interstitial fibrosis, associated with gradual decreases in glomerular filtration rate and increases in serum creatinine concentrations, and rarely with renal failure. Lithium is occasionally associated with nephrotic syndrome and features of distal renal tubular acidosis. Another pathological finding in patients with lithium nephropathy is the presence of microcysts. Magnetic resonance imaging (MRI) can be used to demonstrate renal microcysts secondary to chronic lithium nephropathy and therefore avoid renal biopsy. It is prudent for persons taking lithium to check their serum creatinine concentration, urine chemistries, and 24-hour urine volume at 6-month intervals. If creatinine levels do rise, then more frequent monitoring and MRI might be considered.

Thyroid Effects Lithium causes a generally benign and often transient diminution in the concentrations of circulating thyroid hormones. Reports have attributed goiter (5 percent of persons), benign reversible exophthalmos, hyperthyroidism, and hypothyroidism (7 to 10 percent of persons) to lithium treatment. Lithium-induced hypothyroidism is more common in women (14 percent) than in men (4.5 percent). Women are at highest risk during the first 2 years of treatment. Persons taking lithium to treat bipolar disorder are twice as likely to develop hypothyroidism if they develop rapid cycling. About 50 percent of persons receiving long-term lithium treatment have laboratory abnormalities, such as an abnormal thyrotropin-releasing hormone response, and about 30 percent have elevated concentrations of thyroid-stimulating hormone (TSH). If symptoms of hypothyroidism are present, replacement with levothyroxine (Synthroid) is indicated. Even in the absence of hypothyroid symptoms, some clinicians treat persons with significantly elevated TSH concentrations with levothyroxine. In lithium-treated persons, TSH concentrations should be measured every 6 to 12 months. Lithium-induced

hypothyroidism should be considered when evaluating depressive episodes that emerge during lithium therapy.

Cardiac Effects The cardiac effects of lithium resemble those of hypokalemia on ECG. They are caused by the displacement of intracellular potassium by the lithium ion. The most common changes on the ECG are T-wave flattening or inversion. The changes are benign and disappear after lithium is excreted from the body. Lithium depresses the pacemaking activity of the sinus node, sometimes resulting in sinus dysrhythmias, heart block, and episodes of syncope. Lithium treatment, therefore, is contraindicated in persons with sick sinus syndrome. In rare cases, ventricular arrhythmias and congestive heart failure have been associated with lithium therapy. Lithium cardiotoxicity is more prevalent in persons on a low-salt diet, those taking certain diuretics or angiotensin-converting enzyme inhibitors (ACEIs), and those with fluid-electrolyte imbalances or any renal insufficiency.

Dermatological Effects Dermatological effects may be dose dependent. They include acneiform, follicular, and maculopapular eruptions; pretibial ulcerations; and worsening of psoriasis. Occasionally, aggravated psoriasis or acneiform eruptions may force the discontinuation of lithium treatment. Alopecia has also been reported. Persons with many of those conditions respond favorably to changing to another lithium preparation and the usual dermatological measures. Lithium concentrations should be monitored if tetracycline is used for the treatment of acne because it can increase the retention of lithium.

Lithium Toxicity and Overdoses The early signs and symptoms of lithium toxicity include neurological symptoms, such as coarse tremor, dysarthria, and ataxia; GI symptoms; cardiovascular changes; and renal

dysfunction. The later signs and symptoms include impaired consciousness, muscular fasciculations, myoclonus, seizures, and coma. Signs and symptoms of lithium toxicity are outlined in Table 29.19-4. Risk factors include exceeding the recommended dosage, renal impairment, low-sodium diet, drug interaction, and dehydration. Elderly persons are more vulnerable to the effects of increased serum lithium concentrations. The greater the degree and duration of elevated lithium concentrations, the worse the symptoms of lithium toxicity. Table 29.19-4 Signs and Symptoms of Lithium Toxicity

Lithium toxicity is a medical emergency, potentially causing permanent neuronal damage and death. In cases of toxicity (Table 29.19-5), lithium should be stopped and dehydration treated. Unabsorbed lithium can be removed from the GI tract by ingestion of sodium polystyrene sulfonate (Kayexalate) or polyethylene glycol solution (GoLYTELY), but not activated charcoal. Ingestion of a single large dose may create clumps of medication in the stomach, which can be removed by gastric lavage with a wide-bore tube. The value of forced diuresis is still debated. In severe cases, hemodialysis rapidly removes excessive amounts of serum lithium. Postdialysis serum lithium concentrations may increase as lithium is redistributed from tissues to blood, so repeat dialysis may be needed. Neurological improvement may lag behind clearance of serum lithium by several days because lithium crosses the blood-brain barrier slowly. Table 29.19-5 Management of Lithium Toxicity

Adolescents The serum lithium concentrations for adolescents are similar to those for adults. Weight gain and acne associated with lithium use can be particularly troublesome to adolescents.

Elderly Persons Lithium is a safe and effective drug for elderly persons. However, the treatment of elderly persons taking lithium may be complicated by the presence of other medical illnesses, decreased renal function, special diets that affect lithium clearance, and generally increased sensitivity to lithium. Elderly persons should initially be given low dosages, their dosages should be switched less frequently than those of younger persons, and a longer time must be allowed for renal excretion to equilibrate with absorption before lithium can be assumed to have reached its steady-state concentrations.

Pregnant Women Lithium should not be administered to pregnant women in the first trimester because of the risk of birth defects. The most common malformations involve the cardiovascular system, most commonly Ebstein's anomaly of the tricuspid valves. The risk of Ebstein's malformation in lithium-exposed fetuses is one in 1,000, which is 20 times the risk in the general population. The possibility of fetal cardiac anomalies can be evaluated with fetal echocardiography. The teratogenic risk of lithium (4 to 12 percent) is higher than that for the general population (2 to 3 percent) but appears to be lower than that associated with the use of valproate or carbamazepine. A woman who continues to take lithium during pregnancy should use the lowest effective dosage. The maternal lithium concentration must be monitored closely during pregnancy, and especially after pregnancy, because of the significant decrease in renal lithium excretion as renal function returns to normal in the first few days after delivery. Adequate hydration can reduce the risk of lithium toxicity during labor. Lithium prophylaxis is recommended for all women with bipolar disorder as they enter the postpartum period. Lithium is excreted into breast milk and should be taken by a nursing mother only after careful evaluation of potential risks and benefits. Signs of lithium toxicity in infants include lethargy, cyanosis, abnormal reflexes, and sometimes hepatomegaly.

Miscellaneous Effects Lithium should be used with caution in diabetic persons, who should monitor their blood glucose concentrations carefully to avoid diabetic ketoacidosis. Benign, reversible leukocytosis is commonly associated with lithium treatment.

Dehydrated, debilitated, and medically ill persons are most susceptible to adverse effects and toxicity. DRUG INTERACTIONS

Lithium drug interactions are summarized in Table 29.19-6. Table 29.19-6 Drug Interactions with Lithium Lithium is commonly used in conjunction with DRAs. This combination is typically effective and safe. However, coadministration of higher dosages of a DRA and lithium may result in a synergistic increase in the symptoms of lithium-induced neurological side effects and neuroleptic extrapyramidal symptoms. In rare instances, encephalopathy has been reported with this combination. The coadministration of lithium and carbamazepine, lamotrigine, valproate, and clonazepam may increase lithium concentrations and aggravate lithium-induced neurological adverse effects. Treatment with the combination should be initiated at slightly lower dosages than usual, and the dosages should be increased gradually. Changes from one to another treatment for mania should be made carefully, with as little temporal overlap between the drugs as possible. Most diuretics (e.g., thiazide and potassium sparing) can increase lithium concentrations; when treatment with such a diuretic is stopped, the clinician may need to increase the person's daily lithium dosage. Osmotic and loop diuretics, carbonic anhydrase inhibitors, and xanthines (including caffeine) may reduce lithium concentrations to below therapeutic concentrations. Whereas ACEIs may cause an increase in lithium concentrations, the AT1 angiotensin II receptor inhibitors losartan

(Cozaar) and irbesartan (Avapro) do not alter lithium concentrations. A wide range of nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease lithium clearance, thereby increasing lithium concentrations. These drugs include indomethacin (Indocin), phenylbutazone (Azolid), diclofenac (Voltaren), ketoprofen (Orudis), oxyphenbutazone (Oxalid), ibuprofen (Motrin, Advil), piroxicam (Feldene), and naproxen (Naprosyn). Aspirin and sulindac (Clinoril) do not affect lithium concentrations. The coadministration of lithium and quetiapine (Seroquel) may cause somnolence but is otherwise well tolerated. The coadministration of lithium and ziprasidone (Geodon) may modestly increase the incidence of tremor. The coadministration of lithium and calcium channel inhibitors should be avoided because of potentially fatal neurotoxicity. A person taking lithium who is about to undergo ECT should discontinue taking lithium 2 days before beginning ECT to reduce the risk of delirium. LABORATORY INTERFERENCES Lithium does not interfere with any laboratory tests, but lithium-induced alterations include an increased white blood cell count, decreased serum thyroxine, and increased serum calcium. Blood collected in a lithium-heparin anticoagulant tube will produce falsely elevated lithium concentrations. DOSAGE AND CLINICAL GUIDELINES Initial Medical Workup All patients should have a routine laboratory workup and physical examination before being started on lithium. The laboratory tests should include serum creatinine concentration (or a 24-hour urine creatinine if the clinician has any reason to be concerned about renal function), electrolytes, thyroid function (TSH, T3 [triiodothyronine], and T4 [thyroxine]), a complete blood count (CBC), ECG, and a pregnancy test in women of childbearing age. Dosage Recommendations Lithium formulations include immediate-release 150, 300, and 600 mg lithium carbonate capsules (Eskalith and generic), 300 mg lithium carbonate tablets (Lithotabs), 450 mg controlled-release lithium carbonate capsules (Eskalith CR and Lithonate), and 8 mEq/5 mL of lithium citrate syrup. The starting dosage for most adults is 300 mg of the regular-release formulation three times daily. The starting dosage for elderly persons or persons with renal impairment should be 300 mg once or twice daily. After stabilization, dosages between 900 and 1,200 mg a day usually produce a therapeutic plasma concentration of 0.6 to 1 mEq/L, and a daily dose of 1,200 to 1,800 mg usually produces a therapeutic concentration of 0.8 to 1.2 mEq/L. Maintenance dosing can be given either

in two or three divided doses of the regular-release formulation or in a single dosage of the sustained-release

formulation equivalent to the combined daily dosage of the regular-release formulation. The use of divided doses reduces gastric upset and avoids single high-peak lithium concentrations.

Discontinuation of lithium should be gradual to minimize the risk of early recurrence of mania and to permit recognition of early signs of recurrence. Laboratory Monitoring The periodic measurement of serum lithium concentration is an essential aspect of patient care, but it should always be combined with sound clinical judgment. A laboratory report listing the therapeutic range as 0.5 to 1.5 mEq/L may lull a clinician into disregarding early signs of lithium intoxication in patients whose levels are less than 1.5 mEq/L. Clinical toxicity, especially in elderly persons, has been well documented within this so-called therapeutic range. Regular monitoring of serum lithium concentrations is essential. Lithium levels should be obtained every 2 to 6 months except when there are signs of toxicity, during dosage adjustments, and in persons suspected to be noncompliant with the prescribed dosages. Under these circumstances, levels may be done weekly. Baseline ECG studies are essential, and should be repeated annually. When obtaining blood for lithium levels, patients should be at steady-state lithium dosing (usually after 5 days of constant dosing), preferably using a twice-daily or thrice-daily dosing regimen, and the blood sample must be drawn 12 hours (± 30 minutes) after a given dose. Lithium concentrations 12 hours postdose in persons treated with sustained-release preparations are generally about 30% higher than the corresponding concentrations obtained from those taking the regular-release preparations. Because available data are based on a sample population following a multiple-dosage regimen, regular-release formulations given at least twice daily should be used for initial determination of the appropriate dosages. Factors that may cause fluctuations in lithium measurements include dietary sodium intake, mood state, activity level, body position, and use of an improper blood sample tube. Laboratory values that do not seem to correspond to clinical status may result from the collection of blood in a tube with a lithium-heparin anticoagulant (which can give results falsely elevated by as much as 1 mEq/L) or aging of the lithium ion-selective electrode (which can cause inaccuracies of up to 0.5 mEq/L). After the daily dose has been set, it is reasonable to change to the sustained-release formulation given once daily. Effective serum concentrations for mania are 1.0 to 1.5 mEq/L, a level associated with 1,800 mg a day. The recommended range for maintenance treatment is 0.4 to 0.8 mEq/L, which is usually achieved with a daily dose of 900 to 1,200 mg. A small number of persons will not achieve therapeutic benefit with a lithium concentration of 1.5 mEq/L, yet will have no signs of toxicity. For such persons, titration of the lithium dosage to achieve a concentration above 1.5 mEq/L may be warranted. Some patients can be maintained at concentrations below 0.4 mEq/L. There may be considerable variation from patient to patient, so it is best to follow the maxim "treat the patient, not

the laboratory results." The only way to establish an optimal dose for a patient may be through trial and error. Package inserts (U.S.) for lithium products list effective serum concentrations for mania between 1.0 and 1.5 mEq/L (usually achieved with 1,800 mg of lithium carbonate daily) and for long-term maintenance between 0.6 and 1.2 mEq/L (usually achieved with 900 to 1,200 mg of lithium carbonate daily). The dose-blood level relationship may vary considerably from patient to patient. The likelihood of achieving a response at levels above 1.5 mEq/L is usually outweighed greatly by the increased risk of toxicity, although rarely a patient may both require and tolerate a higher-than-usual blood concentration. What constitutes the lower end of the therapeutic range

remains a matter of debate. A prospective 3-year study found patients who maintained a concentration between 0.4 and 0.6 mEq/L (mean 0.54) were 2.6 times more likely to relapse than those who maintained between 0.8 and 1.0 mEq/L (mean 0.83). However, the higher blood concentrations produced more adverse effects and were less well tolerated. If there is no response after 2 weeks at a concentration that is beginning to cause adverse effects, then the person should taper off lithium over 1 to 2 weeks and other mood-stabilizing drugs should be tried. Patient Education Lithium has a narrow therapeutic index, and many factors can upset the balance between lithium concentrations that are well tolerated and therapeutic, and those that produce side effects or toxicity. It is thus imperative that persons taking lithium be educated about signs and symptoms of toxicity, factors that affect lithium levels, how and when to obtain laboratory testing, and the importance of regular communication with the prescribing physician. Lithium concentrations can be disrupted by common factors such as excessive sweating from ambient heat or exercise or use of widely prescribed agents such as ACEIs or nonsteroidal anti-inflammatory drugs (NSAIDs). Patients may stop taking their lithium because they are feeling well or because they are experiencing side effects. They should be advised against discontinuing or modifying their lithium regimen. Table 29.19-7 lists some important instructions for patients. Table 29.19-7 Instructions to Patients Taking Lithium

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Revision #1

Created 2026-01-04 19:51:47 UTC by Omar Ayman

Updated 2026-01-04 19:51:47 UTC by Omar Ayman