

Optimizing Lithium Treatment

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The purpose of this article is to discuss treatment of side effects that can occur during lithium therapy. Side effects from lithium are common but generally benign. For this article, I have divided the side effects into those that occur early, those that are late appearing, side effects related to drug interactions, and lithium toxicity. Side effects can decrease compliance. Lithium is a very effective drug for the stabilization of mood disorder in bipolar patients. Since side effects can affect compliance, recognition and treatment of early and late-appearing side effects are important aspects of lithium pharmacotherapy.

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The purpose of this article is to discuss side effects of lithium treatment. Lithium treatment was introduced into psychiatry approximately 50 years ago. Since then, lithium has become established for the treatment of acute mania and for maintenance treatment for patients who have bipolar I and bipolar II disorder. Its use in other conditions, such as treatment of acute depression, maintenance therapy for recurrent unipolar depression, augmentation for antidepressant nonresponse in major depression and other clinical conditions such as aggression has also been advocated.^{1–4} In general, lithium is administered to willing patients since it is formulated exclusively for oral delivery. The formulations of lithium currently available include pills and capsules (which are both available as immediate release and sustained release) and liquid preparations.

Adverse events occur in 35% to 93% of lithium-treated patients.⁵ Most of the common side effects, which include excessive thirst, polyuria, memory problems, tremor, weight gain, drowsiness, and diarrhea, are troublesome rather than life-threatening, but some, such as memory problems, tremor, and weight gain, often lead to noncompliance (Table 1). Lithium can also have effects on the endocrine, dermatologic, renal, and cardiovascular (infrequently) systems. Side effects and lithium toxicity usually become more evident and troublesome at doses that result in serum lithium levels above the recommended 1.2 mEq/L ceiling for acute treatment and 0.8 mEq/L for maintenance treatment.

When a lithium-treated patient is assessed for potential side effects, the patient's psychiatric history, medical his-

tory, and general medical health should be taken into account. At the beginning of treatment, patients should receive a physical examination and laboratory analysis to include a complete blood count and thyroid and renal function tests. Patients over 40 years old should have an electrocardiogram. In general, lithium side effects are more frequent in the elderly than in the young and in the depressed as compared with those who are euthymic.^{6–8} Higher lithium levels tend to produce more side effects than lower lithium levels. Thus, lithium serum monitoring is an important aspect of treatment. Clinicians should be aware of the possibility of drug interactions. When in doubt, one may try an on/off strategy and reduce or discontinue lithium to determine if the particular side effect abates and then resumes when lithium is restarted. A general dosing strategy to avoid side effects is to start at a low dose and build the dose up slowly. I tend to start outpatients at 300 mg/day at bedtime and increase the dose by 300 mg/day every week or 2. Giving the dose once daily, for example at bedtime, may be helpful to reduce side effects and enhance compliance.

Clinicians need to have the patient return frequently enough to monitor blood levels as well as to monitor side effects. Until the patient achieves a satisfactory blood level, it would be appropriate to measure serum lithium levels every 1 to 2 weeks; after that, the levels should be measured every 2 to 3 months for the first 6 months of treatment and at least every 6 to 12 months thereafter.^{9,10} More frequent monitoring may be necessary for patients who remain symptomatic. Education of the patient and family concerning why lithium is being prescribed, the nature of the psychiatric disorder, the effects anticipated from lithium and when they are likely to occur, and side effect management should be part of the introduction to this treatment. Several publications have been written for patients and are available through the Web sites of the National Institute of Mental Health (<http://www.nimh.nih.gov/publicat/bipolar-menu.cfm>) and the National Depressive and Manic Depres-

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sive Association (<http://www.ndmda.org>). Support groups, which may also be useful for patients, can be found through the National Alliance for the Mentally Ill (<http://www.nami.org>).

In the hospital, a more rapid increase in lithium dose can be beneficial. However, the use of lithium loading strategies is probably best avoided as these strategies tend to produce a number of early side effects and discourage patients from using lithium as a maintenance drug. Perhaps the greatest advantage of lithium is its long-term maintenance effects against recurrence of affective episodes in bipolar and unipolar mood disorder patients. Thus, if patients have an unfavorable early experience with lithium, this negative experience may dissuade them from ever trying the medication again.

The side effects of lithium can be described as those that occur during acute treatment, those that appear late, side effects that are due to drug interactions, and finally, lithium intoxication. These 4 topics will be discussed in this article.

ACUTE SIDE EFFECTS

The side effects noted early during acute administration of lithium generally are gastrointestinal and largely encompass nausea, vomiting, and diarrhea, but tremor is also a frequent early side effect.

Gastrointestinal

Treatment of the nausea that may be experienced with lithium early in treatment is to give lithium with food, to change the time of day of dosing, to reduce the number of pills in a single dose, and perhaps to change to a different lithium preparation. Vomiting during early administration is rare but again can be managed by the same techniques used for nausea. Antacids may be of some assistance in isolated cases. Diarrhea can be persistent. Antidiarrheal agents, changes in food intake, and changes in lithium preparation can be helpful.

Tremor

Tremor, which can be associated with reduced motor coordination, nystagmus, and muscular weakness, can be problematic for some patients.^{6,11-14} Not all patients who experience tremor have difficulties with this particular side effect. However, in some patients, tremor, particularly fine hand tremor, can be occupationally disabling or socially embarrassing. Tremor can often be alleviated by reducing the dose, reducing caffeine intake, decreasing the dose of or eliminating concomitant medications that can be aggravating the tremor, and adding a β -blocker.^{15,16}

Tremor that is related to peak serum levels, e.g., when tremor peaks within 1 or 2 hours of a dose, may be reduced or eliminated by using a slow-release preparation or changing to a single bedtime dose.⁹ While tremor associ-

Table 1. Incidence of Lithium Side Effects and Effect on Noncompliance^a

Side Effect	Percentage With Subjective Complaint ^b	Relative Importance in Noncompliance ^c
Excessive thirst	35.9	...
Polyuria	30.4	4
Memory problems	28.2	1
Tremor ^d	26.9	3
Weight gain	18.9	2
Drowsiness/tiredness	12.4	5
Diarrhea	8.7	...
Any complaint	73.8	...
No complaint	26.2	...

^aFrom Lenox and Manji⁵ with permission.

^bPooled percentage from 12 studies, including 1094 patients.

^cData from Goodwin and Jamison¹; relative ranking of side effects for lithium noncompliance in 71 patients.

^dIncludes incoordination.

ated with therapeutic amounts of lithium is common, the tremor may worsen or generalize as blood lithium concentration approaches toxic levels. A pronounced tremor that interferes with eating may be a warning that blood and tissue lithium concentration is about to reach toxic levels.

LATE APPEARING SIDE EFFECTS

There are several late appearing side effects of lithium. For this review I will consider cardiovascular effects, cognitive effects, dermatologic effects, edema, endocrine effects, teratogenic effects, neurologic effects, renal effects, and weight gain as the principal late appearing side effects.

Cardiovascular

Cardiovascular side effects, which occur in 20% to 30% of lithium-treated patients, are usually benign.¹⁷ Changes in the electrocardiogram, which are seldom of clinical significance, include T wave flattening and possible T wave inversion. Thus, obtaining an electrocardiograph prior to treatment may be useful, especially for older patients.⁷ Lithium can be associated with a decrease in heart rate and rarely arrhythmia. Isolated cases of cardiac sinus node dysfunction during lithium treatment have been reported.¹⁸ Our experience with this phenomenon indicated that it was more likely to occur in elderly patients who may be prone to develop cardiac sinus node dysfunction spontaneously but developed sinus node dysfunction earlier with lithium treatment (lithium unmasking their latency for sinus node dysfunction). The clinical manifestations of cardiac sinus node dysfunction include syncope. Thus, in a patient who has a syncopal episode, who is on lithium treatment, and who is elderly, obtaining a Holter monitor study to assess for cardiac sinus node dysfunction is certainly worthwhile. One of my patients experienced sinus node dysfunction only during an episode of lithium toxicity and never experienced this phenomenon again over about a 10-year follow up. My colleagues and I¹⁸ reported on a patient who

required a pacemaker to treat the disorder since sinus node dysfunction occurred during therapeutic lithium levels.

Cognitive

Cognitive side effects from lithium are a leading cause of noncompliance with treatment (see Table 1), but they have been little studied. If patients complain of impairment in cognitive functioning during lithium treatment, measurement of cognitive function using psychological tests may be helpful. The cognitive decline usually is not progressive but is experienced as a loss of cognitive executive functioning and usually occurs within the first 6 to 8 months of treatment. There are conflicting reports in the literature regarding cognitive impairment during lithium but the complaint should be taken seriously.¹⁹⁻²⁴ My approach to this problem is to review with the patient the reasons for maintenance treatment, alternatives available, and the side effects of the alternatives. I will try to measure intellectual functioning using neuropsychological testing with the idea of remeasuring it if the complaints worsen.

Many patients attribute noncompliance to impairment in cognitive functioning during lithium treatment that is reported as lack of drive and loss of productivity. Loss of creativity is a complaint sometimes voiced by patients taking lithium.^{25,26} This may reflect an absence of the creative energy during hypomania (which has been blocked by lithium treatment) and is often balanced by the lack of depressive episodes, which indeed impair creative efforts. It has been difficult to find convincing evidence for cognitive effects of lithium in clinical studies, and one study²⁵ found that more than 75% of a group of writers, artists, and business executives believed that lithium treatment either enhanced or had no effect on their creativity. There is no measured consistent effect of lithium on creative abilities. Perhaps using a lower dose but keeping the dose within the therapeutic range may be of benefit.

Dermatologic

Dermatologic effects of lithium are usually rare.^{27,28} Perhaps the most common is a complaint of dry skin, which can be alleviated by topical lotions. Exacerbation of psoriasis has been a serious problem in some patients and may require an alternative treatment.²⁹ Acne can also be exacerbated during lithium treatment. Antiacne treatments will usually suffice to treat this difficulty. Sometimes, usually in the spring, there is a folliculitis that can be related to lithium. This is an interesting phenomenon and appears to be an erythematous rash associated with considerable itching. Patients may complain of "lithium allergy," but it is unlikely that a true allergy to a normal salt can occur. What is probably more likely is that lithium excretion in the sweat produces a local irritation of hair follicles. Usually symptomatic treatment and antihistamines (if necessary for the itching) can be useful. Hair loss can be related to lithium treatment.³⁰ However, the hypothyroid effects of

lithium (see below) may be a more important cause, and thus in a patient complaining of hair loss who is taking lithium, the clinician should first monitor thyroid function.

Edema

Edema can occur within the first year of lithium treatment in some patients.³¹ A repeat medical examination may be necessary if edema develops. Treatment for edema can involve changing the sodium intake or use of diuretics. Spironolactone may be preferred over other diuretics. However, the clinician needs to carefully observe the patient for the development of lithium toxicity should diuretics be used as they often increase lithium concentration.

Endocrine

The major endocrine effects of lithium include thyroid and parathyroid effects, which occur in 5% to 35% of patients.⁹ Lithium can induce hypothyroidism, which tends to appear after 6 to 18 months of treatment. Approximately 30% of lithium-treated patients have elevated levels of thyrotropin, but significant decreases in levels of circulating thyroid hormones are less common, and the incidence of clinically significant hypothyroidism is more likely to be about 5%.⁶ The subjects most likely to experience hypothyroidism are women who have a rapid cycling history.³²⁻³⁴ Thus, thyrotropin and thyroid screen should be obtained before starting lithium (hypothyroidism can be associated with the presenting mood disorder), and one should monitor thyrotropin and thyroxine during lithium treatment. While lithium-induced hypothyroidism is generally reversible when lithium is discontinued, hypothyroidism is not a contraindication for continued lithium treatment. However, in addition to the normal symptoms of hypothyroidism, patients with bipolar disorder are at risk of experiencing depressive episodes or becoming rapid cyclers as a consequence of suboptimal thyroid functioning. Thyroid supplementation and/or discontinuation of lithium may be necessary if these symptoms occur and laboratory tests continue to reveal suboptimal thyroid function. Perhaps treatment of hypothyroidism with thyroxine rather than triiodothyronine may be preferable since it has been suggested that this thyroid hormone may have greater benefits in bipolar patients than triiodothyronine.^{35,36} Hyperthyroidism during lithium treatment is rare. At one point, lithium salts were used in some medical situations to treat hyperthyroidism. I have seen a patient present with hyperthyroidism during lithium treatment. This patient had a typical history of psychomotor retarded depressions but during this particular episode was quite agitated.

Lithium can increase serum calcium levels, and the association of parathyroid abnormalities with lithium use is possible,³⁷ but is much less common than hypothyroidism. However, it is more likely that the availability of calcium testing has increased the ability to diagnose parathyroid abnormalities and that lithium's role in the development

of parathyroid adenomas is probably low and is unsubstantiated.

Teratogenic

Teratogenic effects of lithium include the presence of Ebstein's abnormality.^{38,39} Although this was thought to be a lithium-associated teratogenic effect for fetuses exposed to lithium in the first trimester, more recent research has cast doubt on this relationship.⁴⁰ In the children of women treated with lithium during the first trimester of pregnancy, the risk of a major congenital malformation is currently estimated to be in the range of 4% to 12% as opposed to 2% to 4% in an untreated comparison cohort.⁴¹ Lithium is indicated as a category D drug, indicating there is evidence of risk to a human fetus, but benefits from use in pregnant women may be acceptable despite the risk. Cohen et al.⁴¹ recommended that, for the purpose of prenatal diagnosis, patients who continue to take lithium throughout pregnancy be administered a fetal echocardiogram and high-resolution ultrasound examination at 16 to 18 weeks of gestation. Furthermore, lithium administration to a mother during delivery of her child has been associated with "floppy" infant syndrome (an infant with hypotonia).⁴² Therefore it is recommended that the lithium dose be reduced prior to delivery.

Neurologic

Neurologic side effects from lithium are on a continuum with lithium neurotoxicity.⁴³ Mild lithium side effects include tremor, fatigue, and muscle weakness. These effects can be treated with gradual dose changes, changing the dosing schedule from once daily to 2 or 3 times a day, and, in more severe cases, switching to slow-release preparations. Tremor can be treated with the addition of β -blockers. Moderate neurologic side effects can include fasciculations, coarse hand tremors, ataxia, slurred speech, and the possibility of an extrapyramidal syndrome.⁴⁴ Lithium has also been reported to lower the seizure threshold. In the presence of moderate neurologic symptoms, one should rule out lithium toxicity by measuring the serum lithium level and perhaps the erythrocyte:serum lithium ratio. A review for other medical causes of the neurologic status is certainly in order, and one may lower or discontinue the lithium dose temporarily to determine if these symptoms and signs are lithium related. Lithium is actively excluded from erythrocytes and is less concentrated in brain cells than body cells. The lithium red blood cell:serum or plasma ratio gives some idea of intracellular lithium concentrations. Generally, this ratio is about 0.5. However, during cases of lithium toxicity, higher lithium ratios may be observed.

Renal

Renal side effects include initial diuresis, which is present in most patients and is usually mild and of no clinical

consequence. Decreased renal concentration ability also results in a polyuria, which in most cases is mild. Nephrogenic diabetes insipidus can be a more significant problem related to lithium treatment. Diabetes insipidus is generally diagnosed if subjects have greater than 3 liters output of urine per day. Nocturia associated with this disorder can induce sleep disturbance resulting in mood disruption. Furthermore, the use of high caloric beverages to treat polydipsia can cause weight gain. The first step when a subject complains of nocturia, an increase in frequency of urination, thirst, and increased fluid intake is to measure the 24-hour urine volume. Secondly, the lowest effective lithium dose should be applied. Lithium has been reported to cause an interstitial nephritis that is usually of no clinical significance, but the effects of lithium on the kidney may be lessened with single daily dosing.^{45,46} A change in lithium preparation may be useful if the polyuria persists. Renal function tests such as blood urea nitrogen (BUN), creatinine, and 24-hour urine volume should be monitored,⁴⁷ and medical consultation is recommended if the creatinine level rises and remains above 1.6 mg/100 mL.⁴⁸ The use of thiazide diuretics is the equivalent of lowering the lithium dose.⁴⁹ On the other hand, amiloride has been reported to be useful for the treatment of lithium-induced nephrogenic diabetes insipidus.⁵⁰ Renal failure is rarely caused by lithium.⁵¹⁻⁵⁴

Weight Gain

Weight gain can be a problem in approximately one third of patients who are treated with lithium,⁵⁵ and about 25% of lithium-treated patients gain enough weight to be considered obese.⁵⁶ Lithium-induced weight gain is often related to dose, and weight increases are less likely when the plasma lithium concentration is less than 0.8 mmol/L, which, however, may be subtherapeutic. Weight gain, which is the second most common reason for noncompliance (see Table 1), is more common among patients who are already overweight, and may be more common in women than men.⁵⁶

It is important to review dietary intake and especially to consider if the subject is consuming high caloric beverages as a result of polydipsia. Thyroid status should be assessed since hypothyroidism that might be induced by lithium can be a cause of the weight gain. Lithium-induced edema may also be a cause of weight gain. Concomitant medications that may be associated with weight gain should be reviewed. Our recommended treatment is to increase exercise and to provide a normal sodium low-calorie diet. Keeping sodium intake normal should help to prevent lithium toxicity.

DRUG INTERACTIONS

Lithium is eliminated through the kidney and interacts with several types of drugs and treatments.⁵⁷ A series of

drugs can increase lithium levels and exaggerate side effects, or, perhaps, lead to neurotoxicity. These compounds include carbamazepine, thiazide diuretics, and some anti-inflammatory compounds such as ibuprofen.⁵⁸⁻⁶⁰ On the other hand, some compounds decrease lithium levels. Theophylline and verapamil are reported to increase lithium clearance and decrease lithium levels.^{61,62}

Lithium can also have drug interactions with some medications such as antidepressants and antipsychotic drugs that could induce or worsen tremors. The tremor associated with lithium used concomitantly with these drugs is clinically somewhat greater than the tremor associated with these drugs used alone.

Lithium should be avoided during treatment with electroconvulsive therapy.⁶³ There have been reports of persistent neurotoxicity occurring if electroconvulsive therapy is given to subjects who are taking lithium.

LITHIUM NEUROTOXICITY

Lithium toxicity or lithium intoxication is a significant medical condition involving an impairment of consciousness, increased deep tendon reflexes, and other neurologic side effects such as ataxia, choreiform movements, and the possibility of seizures.^{64,65} It is more common at higher serum concentrations or in patients with risk factors such as reduced renal clearance due to age or renal disease, organic brain disorder, physical illness with vomiting and/or diarrhea, diuretic and/or other concomitant pharmacotherapy, low sodium intake and/or high sodium excretion, and pregnancy. Severe toxicity can result in coma and death. Lithium toxicity is diagnosed by measuring the plasma lithium level and perhaps a lithium:red blood cell plasma or serum ratio. Most patients will experience some toxic effects when serum lithium levels are above 1.5 mEq/L, and levels higher than 2.0 mEq/L can be associated with life-threatening effects.⁹ Acute overdoses may be treated with the use of gastric lavage. If the levels are above 2.5 mEq/L, lithium should be discontinued.

In general, there should be fluid replacement with both water and electrolytes. Lithium has natriuresis and kaluresis effects, and, in my experience, both potassium and sodium should be administered along with water. Hemodialysis may be necessary in more extreme cases. There have been reports of some individuals who experience lithium toxicity and have persistent neurologic sequelae (even after recovery) accompanied by ataxia and scanning speech (cerebellar signs).⁶⁶

LITHIUM MONITORING

Lithium monitoring should take place in the context of a history of the patient's medical and psychiatric conditions, a physical examination, baseline laboratory studies including complete blood count (lithium increases the

white blood count), BUN and creatinine (to assess renal effects), thyroid studies including thyrotropin and thyroid screen, and an electrocardiogram for older individuals. Periodic monitoring with laboratory tests during lithium treatment is highly recommended.

I generally see outpatients about once a month during the first 6 months of lithium treatment. This is the time of highest probability of relapse and a likely time for the development of early side effects, which can lead to noncompliance. Once the patient has been stabilized for that period I generally evaluate patients every 2 to 3 months for the next few years. Only after they have been stabilized and are compliant for several years do I decrease the frequency of visits to every 6 months and in isolated situations every year. I also recommend that our patients be under the care of a general physician and have an annual physical examination to include tests of renal and thyroid function. Patients are generally advised not to start new medications prior to reviewing whether there are potential effects of this medication on mood or potential side effects with lithium.

CONCLUSIONS

Lithium treatment, in use in psychiatry for over 50 years, has been proved to be of considerable benefit to mood disorder patients. To enhance long-term compliance, the clinician must adjust the treatment in order to minimize side effects.

Drug names: amiloride (Midamor), carbamazepine (Tegretol and others), ibuprofen (Motrin and others), spironolactone (Aldactone and others), theophylline (Pemophylline), verapamil (Calan and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration-approved labeling.

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