

Drug Interactions of Lithium and Other Antimanic/Mood-Stabilizing Medications

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Treatments for bipolar disorder often consist of a combination of 2 or more medications that have mood-stabilizing properties. Lithium is the only agent that has shown efficacy for the treatment of acute mania and acute depression as well as for the prevention of recurrence of mania and depression in patients with bipolar disorder. Other agents frequently used as mood stabilizers in monotherapy and in combination with lithium are valproate and carbamazepine. Several other drugs that have mood-stabilizing properties are used in many combinations to effectively manage the spectrum of symptoms of bipolar disorder throughout the acute and maintenance phases. However, side effects and drug-interaction precautions accompany all agents used to treat bipolar disorder, and often it can be difficult to determine whether a patient is suffering from side effects of treatment or symptoms of the illness itself. It is important to use the lowest effective dose of any treatment medication, to monitor laboratory values closely, and to be familiar with the side effects and interaction precautions of each medication that a patient is taking. Successful management of medications for the patient with bipolar disorder is a challenge, but increased effort and vigilance by clinicians mean a reduced risk of hospitalization and fewer office visits for patients. *(J Clin Psychiatry 2003;64[suppl 5]:38-43)*

The term *mood stabilizer* is frequently used but not well defined. It can be defined as a treatment for one phase of bipolar disorder, either mania or depression, or the definition can be expanded to a treatment for one phase of bipolar illness that also does not induce a switch to the other phase. The best definition of a mood stabilizer is the most stringent: an agent or therapy that both treats mania and depression acutely and prevents both phases of bipolar disorder during maintenance.

Lithium is the only medication that meets the most stringent definition of a mood stabilizer. Controlled trials and clinical experience have shown that lithium not only treats acute mania and acute bipolar depression but also prevents the recurrence of mania and depression in patients with bipolar disorder. Other agents that have been successfully used as monotherapy for the treatment of bipolar disorder are valproate and carbamazepine. While these medications do not have sufficient data to meet the most stringent definition of a mood stabilizer, they are successfully used as such in clinical practice. However, treatment regimens for bipolar disorder often consist of a combination of 2 or more

medications with mood-stabilizing properties. Lithium, valproate, and carbamazepine are used in combination with each other and other treatments to effectively manage the spectrum of symptoms of bipolar disorder in the acute and maintenance phases.

Because side effects and drug-interaction risks accompany all treatments that are used as mood stabilizers, frequent monitoring of the patient is beneficial; this article describes the side effects and interactions to beware of for commonly used bipolar disorder treatments.

LITHIUM

Lithium is approved by the U.S. Food and Drug Administration (FDA) for the treatment of manic episodes and as a maintenance treatment for the prevention of the recurrence of mania. The most common acute side effects of lithium are gastrointestinal (GI) side effects and tremors.¹ Acute side effects can be avoided by beginning with low doses and titrating slowly upward by about 300 mg/week. If GI problems and tremors arise despite slow titration, switching to a slower-release formulation of lithium may be beneficial. GI side effects are usually nausea, vomiting, and diarrhea. Tremors may occur either early or late in treatment and can cause social embarrassment and reduced productivity at work.

Other late-appearing side effects with lithium include cardiovascular, cognitive, dermatologic, endocrine, teratogenic, neurologic, and renal effects; edema; and weight gain.¹ Cardiovascular side effects occur in 20% to 30% of lithium-treated patients and are usually benign.² Changes in the electrocardiogram include T wave flattening and pos-

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sible T wave inversion. Lithium can be associated with a decrease in heart rate and, in rare cases, arrhythmia and cardiac sinus node dysfunction.

Gitlin et al.³ examined the frequency of reported side effects with lithium and the frequency with which those side effects caused noncompliance, and cognitive side effects and weight gain were the most disturbing to patients. A loss of cognitive executive functioning may occur within the first 6 to 8 months of treatment but usually is not progressive. It can be difficult to determine whether the patient's report of cognitive impairment should be attributed to treatment with lithium or to the absence of hypomania, which could have contributed to the patient's perception of higher cognitive function prior to lithium treatment. Neuropsychological testing in patients who complain of a decline in their ability to think can confirm the presence or absence of a cognitive deficit.

Dermatologic effects of lithium are rare, but the most common complaint is dry skin. Other complaints include exacerbation of psoriasis, acne, folliculitis, and hair loss.⁴⁻⁷

Edema can occur within the first year of lithium treatment in some patients.⁸ A change in sodium intake or use of diuretics may help.

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 the incidence of clinically significant hypothyroidism is more likely to be about 5%.⁹ Patients most likely to experience hypothyroidism are women who have a rapid-cycling history.¹⁰ Thus, thyrotropin levels and a thyroid screen should be obtained before starting lithium, and thyrotropin and thyroxine levels should be monitored 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 developing a rapid-cycling illness pattern as a consequence of suboptimal thyroid functioning.

Teratogenic effects of lithium include Ebstein's anomaly. At one time, Ebstein's anomaly was thought to be a common lithium-associated teratogenic effect for fetuses exposed to lithium in the first trimester.¹¹ However, 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%, compared with 2% to 4% in an untreated comparison cohort.¹² Lithium administration to a mother during delivery of her child has been associated with hypotonia in the infant.¹³

Neurologic side effects of lithium can range from mild to moderate. Mild effects include tremor, fatigue, and muscle weakness. These can be treated with gradual dose changes, changing the dosing schedule from once daily to 2

or 3 times a day, and switching to slow-release preparations. Tremor can be treated with the addition of β -blockers. More serious neurologic side effects can include fasciculations, course hand tremors, ataxia, slurred speech, and the possibility of an extrapyramidal syndrome or seizure.¹⁴ In the presence of moderate neurologic symptoms, lithium toxicity should be ruled out by measuring the serum lithium level and perhaps the erythrocyte:serum lithium ratio.

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 patients have greater than 3 liters of urine output per day. However, it is worth noting that patients with untreated mania can excrete 10 to 12 liters of urine per day. Renal function tests should be monitored and medical consultation is recommended if the creatinine level rises and remains above 1.6 mg/100 mL.¹⁵ Renal failure is rarely caused by lithium; however, in my practice, a few patients have had to discontinue lithium because of progressive renal impairment. Whether lithium was to blame or not is undetermined, but it was enough of a medical concern to discontinue lithium treatment.

Weight gain can be a problem for some patients taking lithium, and about 25% gain enough weight to be considered obese.¹⁶ 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. Weight gain is the second most common reason for noncompliance,¹⁷ is more common among patients who are already overweight, and may be more common in women than men.¹⁶ My colleagues and I¹⁸ attempted to evaluate weight gain in patients admitted to a metabolic ward who had gained weight. Patients were put on a 1000-calorie normal-sodium diet, none of their other medications were changed, and they were not given an exercise program. All patients lost about 5 lb in a week or so. Although the issue of weight gain in patients taking lithium is largely a dietary issue, a variety of reasons can make weight difficult to control.

A study¹⁹ of lithium side effects divided patients into those who were euthymic and those who were depressed. There were twice as many lithium side effects in the depressed group as in the nondepressed group, even though the doses of lithium were the same. So, when a patient complains of mental dulling, weight gain, sedation, or fatigue, it can be difficult to determine whether those symptoms are caused by the illness, whether they are side effects of lithium treatment, or both.

Lithium is eliminated through the kidneys and interacts with several types of drugs and treatments (Table 1).²⁰⁻²² Some drugs can increase lithium levels, which can exaggerate side effects or lead to neurotoxicity.²³ These compounds include angiotensin-converting enzyme inhibitors and some

Table 1. Interactions of Serum Lithium Level With Other Agents or Risk Factors^a

Increased	Not Changed	Decreased
Thiazides	Amiloride (?)	Acetazolamide
NSAIDs	Aspirin	Mannitol
ACE inhibitors		Aminophylline
Furosemide		Theophylline
Low sodium diet		Caffeine
Dehydration		Mania
Elderly		Pregnancy
Renal disease		

^aData from Physicians' Desk Reference.^{20,21} Abbreviations: ACE = angiotensin-converting enzyme, NSAID = nonsteroidal anti-inflammatory drug.

anti-inflammatory compounds. Other drugs can decrease lithium levels, causing efficacy to decline and higher doses to be needed,²⁴ and still other drugs can interact with lithium without changing lithium levels. Lithium can interact with some medications such as antidepressants and antipsychotics that could induce or worsen tremors. The tremor associated with lithium used in combination with one of these drugs is clinically somewhat greater than the tremor associated with these drugs used alone.¹ Of note, lithium levels can decrease in a patient with mania for reasons that are unclear. As mentioned above, a patient with mania will excrete more urine while manic than while euthymic, so the increase in fluid pass-through may simply wash out lithium.

Lithium toxicity is a significant medical condition involving ataxia, blurred vision, and myoclonus.^{20,25} 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 plasma or serum lithium:red blood cell 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.²⁶

There is a general consensus that blood lithium levels should be 0.6 to 0.8 mEq/L for maintenance treatment.^{27,28} Blood lithium levels below 0.4 mEq/L as monotherapy do not seem to be effective.²⁹ A patient who is taking lithium should be observed for new side effects any time a new medication is started. Each time a patient is seen, getting a new list of other medications that the patient is taking is helpful in making sure that nothing different has been prescribed. Also, it is important for all patients taking lithium to have an annual physical examination.

VALPROATE

Anticonvulsants are increasingly used as first-line monotherapy in bipolar disorder, and the most frequently

used are valproate and carbamazepine. Valproate is commercially available in the United States in several oral preparations including valproic acid, valproate sodium, and divalproex sodium. Valproate has been approved by the FDA for the treatment of acute mania and may very likely fit the comprehensive definition of a mood stabilizer, although a clinical trial³⁰ testing its efficacy as a mood stabilizer for maintenance treatment failed. The failure of that trial may have been caused by the sample not including more prototypical patients as well as the changing nature of bipolar illness itself over time. However, valproate is successfully used as a mood stabilizer in patients with bipolar disorder both as monotherapy and in combination with lithium and/or other mood-stabilizing agents.

There are considerable side effects of valproate, and some overlap with the side effects of lithium. Valproate carries a black box warning for hepatotoxicity, teratogenicity, and pancreatitis.³¹⁻³³ Children under the age of 2 years seem to be at a considerably increased risk of developing fatal hepatotoxicity,³⁴ especially those taking multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. Incidents of fatal hepatotoxicity usually have occurred during the first 6 months of treatment with valproate and may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting. Although it is rare for profound liver toxicity to occur in adults taking valproate, liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months.

Because valproate can cause neural tube defects in the fetus of a woman who is taking valproate,³⁵ it is recommended that women of childbearing potential also take a folic acid supplement in case of pregnancy.³¹⁻³³

There have been cases of life-threatening pancreatitis reported in children and adults receiving valproate.³⁶ Some cases have included rapid progression from initial symptoms to death, and cases have been reported shortly after initial use as well as after several years of use. Abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.

Valproate has also been associated with bone demineralization.^{37,38} Caution should be taken when giving valproate to patients who have other risk factors for bone demineralization, such as diet or genetic factors or lack of exercise.

Blood valproate levels should remain between 50 mg/mL and 100 mg/mL during maintenance treatment. It is important to monitor complete blood cell (CBC) counts and platelet counts in patients taking valproate. In my practice, I have seen problems with low platelet counts in patients who are taking valproate monotherapy. Thrombocytic function testing may help identify patients at risk for increased bleeding caused by platelet dysfunction.³⁹

Table 2. Drugs Associated With Interactions With Valproate^a

Aspirin	Amitriptyline
Carbamazepine	Nortriptyline
Lamotrigine	Clonazepam
Rifampin	Diazepam

^aData from Physicians' Desk Reference.³¹⁻³³

There is a question about whether valproate use is associated with polycystic ovary syndrome. Isojarvi et al.⁴⁰ first questioned the relationship between an increased incidence of menstrual disturbances, hyperandrogenism, and polycystic ovaries in women taking valproate therapy for epilepsy. However, because polycystic ovaries are more prevalent in women with epilepsy than in the general population and because there is a lack of large controlled studies in women taking valproate monotherapy, it has not been established whether polycystic ovary syndrome or the presence of polycystic ovaries is caused by valproate use.⁴¹ Nevertheless, some clinicians are hesitant to prescribe valproate to women of childbearing potential.

Valproate interacts with several drugs, including some other anticonvulsants, notably carbamazepine and lamotrigine (Table 2), and the concomitant use of valproic acid and clonazepam may induce absence status in patients with a history of absence seizures.³²

CARBAMAZEPINE

Although carbamazepine has not been approved by the FDA for the treatment of bipolar disorder, patients with bipolar disorder have been successfully treated with carbamazepine monotherapy. There are currently no published placebo-controlled studies of the efficacy of carbamazepine in the manic phase of bipolar disorder. Long-term data on the mood-stabilizing effects of carbamazepine are also lacking.

Carbamazepine carries a black box warning for aplastic anemia and agranulocytosis, which, although infrequent, necessitate blood level monitoring.^{42,43} Reports of decreased platelet and white blood cell counts in patients taking carbamazepine are not uncommon. There is no established target blood level for carbamazepine therapy in bipolar disorder, but 4 mEq/L to 10 mEq/L is the range generally used in practice. A CBC count should be obtained as a baseline, and the patient's white blood cell count should be monitored throughout treatment. Other adverse reactions to carbamazepine include skin rashes, cardiovascular effects, liver function abnormalities, pancreatitis, pulmonary hypersensitivity, and genitourinary effects.

Carbamazepine is metabolized by cytochrome P450 (CYP) 3A4, so drugs that increase plasma levels of carbamazepine include fluoxetine and valproate (Table 3).^{42,43} Drugs that decrease plasma carbamazepine levels include clonazepam, olanzapine, and alprazolam. Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Carbamazepine also reduces

Table 3. Carbamazepine Interactions With Other Agents^a

Serum carbamazepine levels are increased by	Carbamazepine decreases levels of
Cimetidine	Clonazepam
Macrolides	Clozapine
Fluoxetine	Olanzapine
Valproate	Haloperidol
Isoniazid	Alprazolam
Verapamil	Bupropion
Ketoconazole	Oral contraceptives

^aData from Physicians' Desk Reference.^{42,43}

the effectiveness of oral and some subdermal contraceptives, which makes this agent difficult to use in women of childbearing age. It also lowers the plasma levels of valproate. Carbamazepine and valproate used together tend to create widely fluctuating blood drug levels, and while they will eventually stabilize, it can take several weeks.

OTHERS

Oxcarbazepine is an anticonvulsant that is a relative derivative of carbamazepine. It has not been approved for use in bipolar disorder but is used as augmentation with mood stabilizers. While there are no boxed warnings, this agent does carry warnings for hyponatremia, so serum sodium levels may need to be monitored in high-risk populations.⁴⁴ Other warnings include cognitive/neuropsychiatric adverse events such as difficulty with concentration, somnolence, and coordination abnormalities. Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4 and CYP3A5, and it can render oral contraceptives less effective, which limits its use in women of childbearing potential.

Olanzapine has been FDA-approved for the treatment of acute mania. It is common knowledge that antipsychotic drugs can effectively treat acute mania; the older antipsychotic agent chlorpromazine was also approved to treat acute mania. To determine whether atypical antipsychotics can be considered mood stabilizers, it must be demonstrated that they both treat and prevent recurrence of depression and mania. Research on the ability of olanzapine to prevent recurrence is ongoing but not yet reported. Clozapine has not received approval for the treatment of mania, but there are data supporting its use in bipolar disorder. Suppes et al.⁴⁵ conducted a randomized open-label trial comparing clozapine with standard mood-stabilizing treatment in patients with treatment-resistant bipolar disorder. At the end of 1 year, clozapine add-on treatment showed benefits over standard treatment.

Gabapentin has been studied for its possible role in the treatment of bipolar disorder. Studies by Pande et al.⁴⁶ and Frye et al.⁴⁷ indicate that gabapentin lacks utility as monotherapy in the management of patients with acute mania or as a mood stabilizer in the treatment of bipolar disorder. However, gabapentin may be a useful and safe agent as an adjunct to other bipolar treatments in the presence of sig-

nificant anxiety.⁴⁸ Gabapentin has no known clinically significant pharmacokinetic interactions, it is safe to use in combination with other agents, side effects seem to be mild (mainly dizziness), and tolerability has been impressive. Although routine monitoring of laboratory measures is unnecessary with gabapentin,⁴⁹ there is no established dose for its use as an adjunctive agent in bipolar disorder. Doses used in practice can range from 300 mg/day to 3600 mg/day.

Lamotrigine monotherapy has demonstrated efficacy in the depressed phase of bipolar disorder without inducing a switch into mania or hypomania⁵⁰ and in the long-term prophylaxis of bipolar disorder and prevention of bipolar episodes.⁵¹ Lamotrigine monotherapy has also shown efficacy in rapid-cycling bipolar disorder.⁵² However, it has not shown compelling evidence of efficacy in acute mania.⁴⁸ Side effects of lamotrigine are generally mild except for rash, which occurs in 10% of patients.⁵³ For the most part, the rash that occurs with lamotrigine is benign, but the label does contain a black box warning about serious rashes related to the use of lamotrigine. The incidence of serious rashes, which have included Stevens-Johnson syndrome, is approximately 1.0% in children and 0.3% in adults. Generally, the rash will appear early in treatment and occurs particularly on the face. If this type of rash occurs, it is important to stop the drug and quickly refer the patient to a dermatologist. A difficult issue in using lamotrigine is dose titration. Because the incidence of rash increases with higher starting doses and faster titration, the recommendations are to start at 25 mg/day and titrate slowly. However, that means it will take several weeks to months to achieve the target dose of 100 to 400 mg/day, and, therefore, the time until the patient realizes a therapeutic effect is extended as well. Also, if more than 1 dose of medication is missed, the patient must start over at 25 mg/day and slowly titrate up to the target dose again.

Topiramate has shown some efficacy in open studies in mania⁵⁴ and bipolar depression⁵⁵ and in acute mania in one controlled study.⁵⁶ However, a recent multicenter trial in acute mania failed, and no further studies of topiramate in mania are planned. The main advantage of topiramate is that it is associated with weight loss, whereas many of the drugs used in psychiatry cause weight gain. Topiramate can cause memory impairment, even at low doses, and there is a slight risk of kidney stones. This agent can compromise the efficacy of oral contraceptives, and the plasma concentration of topiramate is decreased by carbamazepine and valproic acid.

Electroconvulsive therapy (ECT) is clinically used for the treatment of acute mania, acute bipolar depression, and, increasingly, as maintenance therapy in bipolar disorder. However, there is a lack of data to support ECT maintenance treatment for patients with unstable bipolar mood disorders. ECT given concurrently with lithium adds significant risk of delirium and/or the development of neurotoxicity, and valproate, carbamazepine, lamotrigine, gabapentin, and topiramate may inhibit seizure activity.⁵⁷

Vagus nerve stimulation has been approved in Europe and Canada for the treatment of resistant bipolar depression,⁵⁸ and a double-blind trial⁵⁹ in the United States established the efficacy of vagus nerve stimulation as a treatment for low-to-moderate, but not extreme, antidepressant resistance in patients with bipolar depression.

CONCLUSION

The most problematic side effects in patients taking any of the mood stabilizers for bipolar disorder are sedation, weight gain, and cognitive effects. It can be difficult to determine whether those symptoms are caused by the bipolar disorder, depression, or the medications themselves. In a patient taking lithium, those symptoms may be accounted for by an antithyroid effect, so a thyroid function test can be a useful first step. If the symptoms are side effects of the medication, the risk-benefit ratio of treatment must then be determined.

There are strategies to reduce the incidence of side effects related to mood stabilization treatment. It is always desirable to use the lowest effective dose to minimize side effects. Cognitive side effects, which are often the cause for patients to refuse lithium treatment, can be minimized by starting the patient at a lower dose than usual and titrating at a slower rate than usual. Mood stabilizers given at bedtime can help to normalize sleep, avoid daytime drowsiness, and promote daytime functioning. Although some clinicians recommend the use of topiramate as an adjunctive treatment to counteract the weight gain that most mood stabilizers cause, weight gain should be controlled through diet and exercise if possible.

Many patients with bipolar disorder take combinations of several medications at once. For example, a patient may have been successfully maintained for some time with lithium, an anticonvulsant, a thyroid medication, an antidepressant, an antipsychotic drug, and a benzodiazepine. But if the patient becomes more depressed, the antidepressant dose will need to be raised, or if the patient becomes a bit paranoid, the antipsychotic dose will need to be raised. Continuing a patient on this combination may keep him or her out of the hospital, but it is important to be familiar with every medication the patient is taking at each visit, to monitor laboratory values closely, and to be familiar with the side effects and interaction precautions of the medications used.

Drug names: acetazolamide (Diamox and others), alprazolam (Xanax and others), amiloride (Midamor and others), aminophylline (Truphylline and others), amitriptyline (Enderp, Elavil, and others), bupropion (Wellbutrin and others), carbamazepine (Epilex, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), cimetidine (Tagamet and others), clonazepam (Klonopin and others), clozapine (Clozaril and others), diazepam (Valium and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), furosemide (Lasix and others), gabapentin (Neurontin), haloperidol (Haldol and others), isoniazid (Rifamate, Nydravid, and others), ketoconazole (Nizoral and others), lamotrigine (Lamictal), mannitol (Osmitol, Resectisol, and others), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), rifampin (Rifadin, Rimactane, and others), theophylline (Slo-Bid, Aerolate, and others), topiramate (Topamax), valproate sodium

(Depacon), valproic acid (Depakene and others), verapamil (Isoptin, Covera, and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, carbamazepine, clozapine, gabapentin, lamotrigine, oxcarbazepine, and topiramate are not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorders; valproate sodium is not approved for maintenance therapy in bipolar disorders; and electroconvulsive therapy and vagus nerve stimulation are not approved for use in bipolar disorders.

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