LITHIUM

THERAPEUTICS

Brands • Eskalith
• Eskalith CR
• Lithobid slow-release tablets
• Lithostat tablets
• Lithium carbonate tablets
• Lithium citrate syrup

see index for additional brand names

Generic? Yes

Class • Mood stabilizer

Commonly Prescribed For (bold for FDA approved)
• Manic episodes of manic-depressive illness
• Maintenance treatment for manic-depressive patients with a history of mania
• Bipolar depression
• Major depressive disorder (adjunctive)
• Vascular headache
• Neutropenia

How The Drug Works
• Unknown and complex
• Alters sodium transport across cell membranes in nerve and muscle cells
• Alters metabolism of neurotransmitters including catecholamines and serotonin
• May alter intracellular signaling through actions on second messenger systems
• Specifically, inhibits inositol monophosphatase, possibly affecting neurotransmission via phosphatidyl inositol second messenger system
• Also reduces protein kinase C activity, possibly affecting genomic expression associated with neurotransmission
• Increases cytoprotective proteins, activates signaling cascade utilized by endogenous growth factors, and increases gray matter content, possibly by activating neurogenesis and enhancing trophic actions that maintain synapses

How Long Until It Works
• 1–3 weeks

If It Works
• The goal of treatment is complete remission of symptoms (i.e., mania and/or depression)
• Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists
• Continue treatment indefinitely to avoid recurrence of mania or depression

If It Doesn’t Work
• Many patients only have a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of mood
• Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
• Consider checking plasma drug level, increasing dose, switching to another agent or adding an appropriate augmenting agent
• Consider adding psychotherapy
• Consider the presence of noncompliance and counsel patient
• Switch to another mood stabilizer with fewer side effects
• Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

Best Augmenting Combos for Partial Response or Treatment Resistance
• Valproate
• Atypical antipsychotics (especially risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole)
• Lamotrigine
• Antidepressants (with caution because antidepressants can destabilize mood in some patients, including induction of rapid cycling or suicidal ideation; in particular consider bupropion; also SSRIs, SNRIs, others; generally avoid TCAs, MAOIs)

Tests
• Before initiating treatment, kidney function tests (including creatinine and urine specific gravity) and thyroid function tests; electrocardiogram for patients over 50
• Repeat kidney function tests 1–2 times/year
Life-Threatening or Dangerous Side Effects
- Lithium toxicity
- Renal impairment (interstitial nephritis)
- Nephrogenic diabetes insipidus
- Arrhythmia, cardiovascular changes, sick sinus syndrome, bradycardia, hypotension
- T wave flattening and inversion
- Rare pseudotumor cerebri
- Rare seizures

Weight Gain
- Many experience and/or can be significant in amount
- Can become a health problem in some
- May be associated with increased appetite

Sedation
- Many experience and/or can be significant in amount
- May wear off with time

What To Do About Side Effects
- Wait
- Wait
- Wait
- Lower the dose
- Take entire dose at night as long as efficacy persists all day long with this administration
- Change to a different lithium preparation (e.g., controlled release)
- Reduce dosing from 3 times/day to 2 times/day
- If signs of lithium toxicity occur, discontinue immediately
- For stomach upset, take with food
- For tremor, avoid caffeine
- Switch to another agent

Best Augmenting Agents for Side Effects
- Propranolol 20–30 mg 2–3 times/day may reduce tremor
- For the expert, cautious addition of a diuretic (e.g., chlorothiazide 50 mg/day) while reducing lithium dose by 50% and monitoring plasma lithium levels may
reduce polydipsia and polyuria that does not go away with time alone
• Many side effects cannot be improved with an augmenting agent

**DOSING AND USE**

**Usual Dosage Range**
• 1,800 mg/day in divided doses (acute)
• 900–1,200 mg/day in divided doses (maintenance)
• Liquid: 10 mL three times/day (acute mania); 5 mL 3–4 times/day (long-term)

**Dosage Forms**
• Tablet 300 mg (slow-release), 450 mg (controlled-release)
• Capsule 150 mg, 300 mg, 600 mg
• Liquid 8 mEq/5 mL

**How to Dose**
• Start 300 mg 2–3 times/day and adjust dosage upward as indicated by plasma lithium levels

**Dosing Tips**

✽ Sustained-release formulation may reduce gastric irritation, lower peak lithium plasma levels, and diminish peak dose side effects (i.e., side effects occurring 1–2 hours after each dose of standard lithium carbonate may be improved by sustained-release formulation)
• Lithium sulfate and other dosage strengths for lithium are available in Europe
• Check therapeutic blood levels as “trough” levels about 12 hours after the last dose
• After stabilization, some patients may do best with a once daily dose at night
• Responses in acute mania may take 7–14 days even with adequate plasma lithium levels

✽ Some patients apparently respond to doses as low as 300 mg twice a day, even with plasma lithium levels below 0.5 mEq/L
• Use the lowest dose of lithium associated with adequate therapeutic response
• Lower doses and lower plasma lithium levels (<0.6 mEq/L) are often adequate and advisable in the elderly

✽ Rapid discontinuation increases the risk of relapse and possibly suicide, so lithium may need to be tapered slowly over 3 months if it is to be discontinued after long-term maintenance

**Overdose**
• Fatalities have occurred; tremor, dysarthria, delirium, coma, seizures, autonomic instability

**Long-Term Use**
• Indicated for long-term prevention of relapse
• May cause reduced kidney function
• Requires regular therapeutic monitoring of lithium levels as well as of kidney function and thyroid function

**Habit Forming**
• No

**How to Stop**
• Taper gradually over 3 months to avoid relapse
• Rapid discontinuation increases the risk of relapse, and possibly suicide
• Discontinuation symptoms uncommon

**Pharmacokinetics**
• Half life 18–30 hours

**Drug Interactions**

✽ Non-steroidal anti-inflammatory agents, including ibuprofen and selective COX-2 inhibitors (cyclooxygenase 2), can increase plasma lithium concentrations; add with caution to patients stabilized on lithium
• Diuretics, especially thiazides, can increase plasma lithium concentrations; add with caution to patients stabilized on lithium
• Angiotensin-converting enzyme inhibitors can increase plasma lithium concentrations; add with caution to patients stabilized on lithium
• Metronidazole can lead to lithium toxicity through decreased renal clearance
• Acetazolamide, alkalizing agents, xanthine preparations, and urea may lower lithium plasma concentrations
• Methyldopa, carbamazepine, and phenytoin may interact with lithium to increase its toxicity
• Use lithium cautiously with calcium channel blockers, which may also increase lithium toxicity
• Use of lithium with an SSRI may raise risk of dizziness, confusion, diarrhea, agitation, tremor
• Some patients taking haloperidol and lithium have developed an encephalopathic syndrome similar to neuroleptic malignant syndrome
• Lithium may prolong effects of neuromuscular blocking agents
• No likely pharmacokinetic interactions of lithium with mood-stabilizing anticonvulsants or atypical antipsychotics

**Other Warnings/Precautions**

- Toxic levels are near therapeutic levels; signs of toxicity include tremor, ataxia, diarrhea, vomiting, sedation
- Monitor for dehydration; lower dose if patient exhibits signs of infection, excessive sweating, diarrhea
- Closely monitor patients with thyroid disorders

**Do Not Use**

- If patient has severe kidney disease
- If patient has severe cardiovascular disease
- If patient has severe dehydration
- If patient has sodium depletion
- If there is a proven allergy to lithium

**Pregnancy**

- Risk category D [positive evidence of risk to human fetus; potential benefits may still justify its use during pregnancy]
- Evidence of increased risk of major birth defects (perhaps 2–3 times the general population), but probably lower than with some other mood stabilizers (e.g., valproate)
- Evidence of increase in cardiac anomalies (especially Ebstein's anomaly) in infants whose mothers took lithium during pregnancy
- Lithium administration during delivery may be associated with hypotonia in the infant
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- Taper drug if discontinuing

- For bipolar patients, lithium should generally be discontinued before anticipated pregnancies
- Recurrent bipolar illness during pregnancy can be quite disruptive
- For bipolar patients, given the risk of relapse in the postpartum period, lithium should generally be restarted immediately after delivery, but this generally means no breastfeeding
- Atypical antipsychotics may be preferable to lithium or anticonvulsants if treatment of bipolar disorder is required during pregnancy
- Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary

---

**SPECIAL POPULATIONS**

**Renal Impairment**

- Not recommended for use in patients with severe impairment

**Hepatic Impairment**

- No special indications

**Cardiac Impairment**

- Not recommended for use in patients with severe impairment

**Elderly**

- Likely that elderly patients will require lower doses to achieve therapeutic serum levels
- Elderly patients may be more sensitive to adverse effects
- Neurotoxicity, including delirium and other mental status changes, may occur even at therapeutic doses in elderly and organically compromised patients

- Lower doses and lower plasma lithium levels (<0.6 mEq/L) are often adequate and advisable in the elderly

**Children and Adolescents**

- Safety and efficacy not established in children under age 12
- Use only with caution
- Younger children tend to have more frequent and severe side effects
- Children should be monitored more frequently

---

 Laurie Hitchcock, MD
Lithium

Seems to be more effective in treating manic episodes than depressive episodes in bipolar disorder (treats from above better than it treats from below)

May also be more effective in preventing manic relapses than in preventing depressive episodes (stabilizes from above better than it stabilizes from below)

May decrease suicide and suicide attempts not only in bipolar I disorder but also in bipolar II disorder and in unipolar depression

Due to its narrow therapeutic index, lithium’s toxic side effects occur at doses close to its therapeutic effects

Close therapeutic monitoring of plasma drug levels is required during lithium treatment; lithium is the first psychiatric drug that required blood level monitoring

Probably less effective than atypical antipsychotics for severe, excited, disturbed, hyperactive, or psychotic patients with mania

Due to delayed onset of action, lithium monotherapy may not be the first choice in acute mania, but rather may be used as an adjunct to atypical antipsychotics, benzodiazepines, and/or valproate loading

After acute symptoms of mania are controlled, some patients can be maintained on lithium monotherapy

However, only a third of bipolar patients experience adequate relief with a monotherapy, so most patients need multiple medications for best control

Lithium is not a convincing augmentation agent to atypical antipsychotics for the treatment of schizophrenia

Lithium is one of the most useful adjunctive agents to augment antidepressants for treatment-resistant unipolar depression

Lithium may be useful for a number of patients with episodic, recurrent symptoms with or without affective illness, including episodic rage, anger or violence, and self-destructive behavior; such symptoms may be associated with psychotic or nonpsychotic illnesses, personality disorders, organic disorders, or mental retardation

Lithium is better tolerated during acute manic phases than when manic symptoms have abated

Breast Feeding

- Some drug is found in mother’s breast milk, possibly at full therapeutic levels since lithium is soluble in breast milk
- Recommended either to discontinue drug or bottle feed
- Bipolar disorder may recur during the postpartum period, particularly if there is a history of prior postpartum episodes of either depression or psychosis
- Relapse rates may be lower in women who receive prophylactic treatment for postpartum episodes of bipolar disorder
- Atypical antipsychotics and anticonvulsants such as valproate may be safer than lithium during the postpartum period when breast feeding

ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Euphoric mania
- Treatment-resistant depression
- Reduces suicide risk
- Works well in combination with atypical antipsychotics and/or mood-stabilizing anticonvulsants such as valproate

Potential Disadvantages
- Dysphoric mania
- Mixed mania, rapid-cycling mania
- Depressed phase of bipolar disorder
- Patients unable to tolerate weight gain, sedation, gastrointestinal effects, renal effects, and other side effects
- Requires blood monitoring

Primary Target Symptoms
- Unstable mood
- Mania

Pearls
- Lithium was the original mood stabilizer and is still a first-line treatment option but may be underutilized since it is an older agent and is less promoted for use in bipolar disorder than newer agents
- May be best for euphoric mania; patients with rapid-cycling and mixed state types of bipolar disorder generally do less well on lithium
• Adverse effects generally increase in incidence and severity as lithium serum levels increase.
• Although not recommended for use in patients with severe renal or cardiovascular disease, dehydration, or sodium depletion,
lithium can be administered cautiously in a hospital setting to such patients, with lithium serum levels determined daily.
• Lithium-induced weight gain may be more common in women than in men.