MOOD STABILIZER

Lithium

Lithobid, Eskalith (discontinued), lithium carbonate, lithium citrate

The reference mood stabilizer for bipolar I disorder and the only agent with replicated evidence for reducing suicide risk.

USUAL ADULT RANGE	TARGET LEVEL	HALF-LIFE	ONSET
900-1800 mg/day PO divided	Acute 0.8-1.2; maint 0.6-1.0	18-36 h; longer in elderly	5-7 days for antimanic effect

⚠ FDA BOXED WARNING

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic levels; facilities for prompt and accurate serum lithium determinations must be available before initiating therapy.

INDICATIONS

- FDA-approved for the treatment of acute manic and mixed episodes of bipolar I disorder in adults and in children aged 7 years and older.
- FDA-approved for maintenance therapy of bipolar I disorder to reduce the frequency and intensity of subsequent manic episodes.
- Off-label but strongly supported for reducing suicide and all-cause mortality in recurrent mood disorders, an effect not shown for other stabilizers.
- Off-label augmentation of antidepressants in treatment-resistant unipolar depression, typically targeting a level of 0.6 to 0.8 mEq/L.
- Off-label adjunct for schizoaffective disorder, for aggression and impulsivity, and for cluster headache prophylaxis in specialist practice.
- Preferred over valproate for classic euphoric mania with fewer episodes and a family history of lithium response.

DOSING & TITRATION

- Start immediate-release lithium carbonate at **300 mg** two or three times daily, or extended-release **450 mg** twice daily in healthy adults.
- Titrate by 300 mg every 5 to 7 days guided by 12-hour trough levels, with most adults stabilizing on **900-1800 mg/day** in divided doses.
- Target **0.8-1.2 mEq/L** for acute mania and **0.6-1.0 mEq/L** for maintenance; levels above **1.5 mEq/L** carry substantial toxicity risk.
- Once-nightly extended-release dosing reduces peak-related tremor and may lower the risk of long-term renal concentrating defects.
- Reduce the dose by roughly one-third to one-half when creatinine clearance falls below 50 mL/min, and avoid lithium below 30 mL/min.
- Discontinue by tapering over at least 2 to 4 weeks; abrupt cessation markedly increases the risk of rebound mania within weeks.

MECHANISM OF ACTION

- Inhibits inositol monophosphatase, depleting myo-inositol and dampening phosphatidylinositol second-messenger signaling in overactive neurons.
- Inhibits glycogen synthase kinase-3 beta, shifting downstream transcription toward neuroprotection, circadian regulation, and synaptic plasticity.
- Modulates dopamine and glutamate transmission and enhances GABAergic tone, which underlies the antimanic and antiaggressive effects.
- Increases expression of neurotrophic proteins such as BDNF and Bcl-2, consistent with the gray matter preservation seen on imaging.
- Effects are gradual because they depend on gene expression changes rather than acute receptor blockade, giving a 5 to 7 day antimanic onset.

PHARMACOKINETICS

- Absorption is complete with peak levels at 1 to 2 hours for immediate-release salts and 4 to 5 hours for extended-release tablets.
- Lithium is not metabolized and not protein bound; it is eliminated unchanged by the kidney, so renal function drives all dosing decisions.
- The elimination half-life is 18 to 36 hours, lengthening to 36 hours or more in older adults and in chronic kidney disease.
- Steady state is reached in about 5 days, so serum levels are drawn 5 days after any dose change and 12 hours after the last dose.
- Roughly 80 percent of filtered lithium is reabsorbed in the proximal tubule in competition with sodium, so sodium depletion raises levels sharply.

ADVERSE EFFECTS

- Fine hand tremor affects roughly a quarter of patients, along with polyuria and polydipsia in up to 30 to 40 percent from nephrogenic diabetes insipidus.
- Gastrointestinal upset, nausea, and diarrhea are common early and often improve with extended-release tablets taken with food.
- Weight gain, acne, psoriasis exacerbation, cognitive dulling, and benign leukocytosis are frequent reasons patients ask to stop.
- Hypothyroidism develops in up to 20 percent, especially women, and hyperparathyroidism with hypercalcemia occurs in about 10 percent.
- Long-term use causes chronic tubulointerstitial nephropathy in a minority, with slow decline in eGFR over decades of exposure.
- Toxicity above 1.5 mEq/L brings coarse tremor, ataxia, vomiting, confusion, and at higher levels seizures, renal failure, and death.

MONITORING

- Draw serum lithium as a 12-hour trough 5 days after any dose change, then every 3 months for the first year and every 6 months once stable.
- Check creatinine with eGFR and TSH at baseline, at 3 months, and then every 6 to 12 months, with calcium at baseline and annually.
- Obtain baseline electrolytes, CBC, urinalysis, pregnancy test, and an ECG in patients over 40 or with known cardiac disease.
- Recheck levels urgently during any illness with vomiting, diarrhea, fever, dehydration, or when a diuretic, NSAID, or ACE inhibitor is started.
- Track weight and waist circumference at each visit, and reassess renal function more often once eGFR falls below 60 mL/min.

INTERACTIONS & CAUTIONS

- NSAIDs other than aspirin reduce renal lithium clearance and can raise levels by 25 to 60 percent within days of regular use.
- Thiazide diuretics increase proximal reabsorption and commonly raise lithium levels by 25 to 40 percent; loop diuretics are less problematic.
- ACE inhibitors and angiotensin receptor blockers reduce clearance, with the greatest risk in older adults and in volume depletion.
- Dehydration, sodium restriction, vomiting, diarrhea, and heavy sweating all concentrate lithium and are frequent precipitants of toxicity.
- Combining lithium with haloperidol or other antipsychotics rarely causes an encephalopathic syndrome; carbamazepine adds neurotoxicity risk.

SPECIAL POPULATIONS

- First-trimester exposure raises the risk of Ebstein anomaly; absolute risk remains under 1 percent and cardiac malformation risk is dose-related.
- If lithium is continued in pregnancy, check levels every 4 weeks, weekly near term, and hold at labor onset because clearance falls abruptly.
- Lithium enters breast milk at 10 to 50 percent of maternal levels; breastfeeding is possible with infant level, thyroid, and renal monitoring.
- Approved from age 7; children clear lithium faster and may need weight-based dosing with more frequent level checks during titration.
- In older adults reduce doses substantially, target the lower end of the range, and expect neurotoxicity even at therapeutic levels.

PRESCRIBING PEARLS

- Always draw the level 12 hours post-dose; a random level is uninterpretable and drives wrong dose changes.
- Any new NSAID, thiazide, or ACE inhibitor should trigger a lithium level within one week.
- Stopping lithium abruptly causes rebound mania; taper over at least 2-4 weeks whenever possible.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.