

LITHIUM USAGE GUIDELINES (revised December 2002)

UHS Drug Formulary/Therapeutic Guide

INDICATIONS

Lithium salts are used in the treatment of a variety of psychiatric illnesses. The most common indications are (1) **acute mania and the acute manic phase of mixed bipolar disorder**, (2) **prophylaxis of bipolar disorder**, and (3) **treatment of cyclothymic disorder**. Less common indications (which are currently not included in the labeling approved by the FDA) include major depression, adjunctive therapy with antidepressants, schizoaffective and schizophrenic disorders, adjunctive treatment with neuroleptics, disorders of impulse control, aggression, organic affective disorder (bipolar type), neutropenia and anemia secondary to a variety of causes (particularly drug-induced), psychiatric disorders in children, and alcohol dependence.

WORK-UP

Prior to beginning of lithium therapy, the patient should have the following:

| Baseline Determination | Rationale |
|---|---|
| SrCr, BUN | Lithium is excreted renally |
| Urine specific gravity | Lithium may cause polyuria |
| Electrolytes (including calcium & phosphorus) | Hyponatremia & dehydration lead to increased renal reabsorption of lithium & subsequent lithium toxicity; hypokalemia may increase the risk of lithium-induced cardiac toxicity |
| ECG (every pt>50, younger if warranted) | Lithium may worsen severe cardiac disease |
| CBC with differential | Lithium may cause a 15% - 45% increase in the numbers of all WBC lines except basophils; lithium may also cause an increase in platelet counts |
| T ₄ , TSH | Lithium may induce hypothyroidism |
| Glucose | Lithium may induce weight gain and complicate the presentation of diabetes mellitus |
| Weight | Lithium may cause weight gain |
| Lithium level | Manic patients may at times not give an accurate medication history |
| Pregnancy test | Lithium is a potential teratogen |
| This table was reproduced from the reference by Love & Grothe | |

The routine work-up should also include a complete history which should include reference to the presence of medical diseases or conditions in which risks of lithium therapy are increased (eg, hypothyroidism, goiter, impaired renal function, congestive heart failure, arrhythmias, cirrhosis, low-salt diets, and excessive diaphoresis). History should also include reference to medications which may increase lithium toxicity (e.g., thiazide diuretics).

If warranted by the clinical situation, the following should be included in the initial or subsequent work-up:

- A complete physical examination
- Hemoglobin, and hematocrit
- Serum electrolytes including calcium and phosphorus

These lab tests and assessments should be repeated at 6 -12 month intervals thereafter, or whenever the patient becomes ill. Lithium blood levels should be monitored every 3 months.

MONITORING OF SERUM LEVELS AND DOSAGE INFORMATION

Careful monitoring of serum lithium concentrations **and** clinical status of the patient is mandatory, and **patients should be carefully instructed in the safe use of the drug.** (Patient care instructions are available and should be given to all outpatients on lithium.)

There is wide variation in the doses required to achieve certain serum concentrations, and the concentrations needed to achieve a therapeutic response. The established therapeutic range is based on data obtained from monitoring steady-state levels obtained in the morning **12 hours after a dose** in patients receiving divided doses. (Even if a patient is receiving only one daily dose, levels should still be drawn 12 hours after the dose.)

Total reliance must not be placed on serum concentrations alone. Accurate patient evaluation requires interpretation of both clinical response and laboratory data. Dosage should be adjusted and serum concentration determined when a patient exhibits signs and symptoms of adverse nervous system, GI, or renal effects (see section on adverse effects).

INITIAL THERAPY FOR ACUTE EPISODES

A typical starting dose is 300 mg 3 times/day (lower in the elderly) **Serum levels should be determined every 5-7 days during this acute phase of therapy** until the serum concentration and clinical condition have stabilized. The **target range for this acute phase is usually 0.6-1.2 mEq/L.** This target range is usually obtained with daily doses of 900mg to 2400mg. In the elderly, levels <1.0 mEq/L are preferred. In other patients, levels up to 1.5 mEq/L may be required. Levels >2 mEq/L warrant temporarily stopping the drug.

MAINTENANCE THERAPY

Usual doses range from 900-1200 mg/day. The usual maximum dose is 2400 mg, however doses up to 3600 mg have been used. The **target serum concentration range for maintenance therapy is usually 0.6-1 mEq/L.** Rarely, up to 1.2 mEq/L may be required; and in the elderly, levels of 0.4 mEq/L may be adequate. *The dose should be adjusted down to the lowest possible dose that prevents recurrence of symptoms.* A higher risk of relapse may exist in some patients if maintenance levels are <0.8 mEq/L. **Serum lithium levels should be monitored at least every 1-3 months during the first year, then at 3- to 6-month intervals, or more often if clinically indicated.**

DOSAGE FORMS AVAILABLE :

Capsule, as carbonate: 300 mg

Syrup, as citrate: 300 mg/5 mL

Tablet, controlled release, as carbonate: 450 mg

ADMINISTRATION

Lithium salts are administered **orally**, preferably with meals to avoid stomach upset. Extended-release products should be swallowed whole, **not chewed or crushed.** The drug is usually given in divided doses to prevent GI side effects. The liquid should be diluted with juice prior to administration.

Scheduled doses of the liquid should be separated from other antipsychotic liquid doses by at least 1 hour.

SIDE EFFECTS, ADVERSE REACTIONS, AND TOXICITIES

Patients should be monitored closely – especially during initiation of treatment.

Patient complaints of lethargy, difficulties in concentrating, and easy loss of balance are common and often respond to small dosage reductions.

The following "minor" side effects can occur with normal serum lithium levels **or** may be signs of mild toxicity: abdominal pain, diarrhea, nausea, polyuria, thirst, leukocytosis, muscle weakness, and tremor. The GI effects usually diminish with time and may be alleviated by taking with food, or by switching to a slow-release preparation or from the carbonate salt to the citrate salt. Tremor may be reduced by decreasing the dose, decreasing caffeine intake, or by the addition of low doses of propranolol. Thiazide diuretics and amiloride (**nonformulary**) can be used to reduce polyuria and increase urinary concentrating ability, but the dose of lithium usually must be reduced by 30% to 50% and close monitoring is necessary.

The following "major" side effects can occur with therapeutic doses, but usually are associated with toxic serum levels (>1.5 mEq/L): ataxia, muscle fasciculations, confusion, slurred speech, blurred vision, hypotension, and renal failure.

"Severe" toxicities which are usually associated with levels >2.5 mEq/L include seizures, stupor, coma, cardiovascular collapse, and death.

Long-term side effects of lithium therapy include goiter and/or hypothyroidism. Signs and symptoms include fatigue, coarse skin, brittle hair, cold intolerance, vague somatic complaints, decreased interest in activities, and depression. Thyroid function tests will help differentiate lithium-induced hypothyroid symptoms from symptoms associated with an acute depressive episode in a bipolar patient.

Other long-term side effects include facial and truncal acneiform eruptions, weight gain, nephrogenic diabetes insipidus, and decreased creatinine clearance. Polyuria is the most commonly reported adverse effect in maintenance therapy. Stress incontinence and/or urinary urgency may accompany this symptom. Traditionally, doses were divided to prevent high peaks and hopefully to prevent toxicities, but recent evidence indicates that single daily doses of the controlled-release lithium may actually **reduce** polyuria. (GI intolerance may prevent single daily doses above 900-1200 mg.)

The **patient care instructions** mentioned earlier will help the patient differentiate common side effects from those which require medical attention and what activities to avoid (or to begin) to deal with certain side effects.

PRECAUTIONS AND CONTRAINDICATIONS

Lithium should **generally** not be used (or used with extreme caution) in patients with **severe** renal or cardiovascular disease or **severe** dehydration, sodium depletion, or debilitation since **the risk of toxicity is increased**.

Although pregnancy is **not** an absolute contraindication, risks of congenital (especially cardiac) abnormalities are increased. **Lithium should not be used in the first trimester** (unless risk of withdrawing the drug is considered to be greater). Doses usually must be increased during pregnancy due to various physiological changes that increase lithium clearance. **Serum levels should be monitored every 1-3 months during the first 8 months of pregnancy (more often if clinically indicated). Monitoring is especially important during the last month of pregnancy and may be required weekly.** Salt-restricted diets and diuretics should be used with

extreme caution. When labor begins, the lithium dose should be reduced to prepregnancy doses or reduced by 50%.

Breast-feeding should be discouraged since lithium concentrations in breast milk can reach 30% to 60% of the concentration in the maternal serum.

History of anaphylactic reaction or severe hypersensitivity to this drug is a **contraindication**.

DRUG INTERACTIONS

All reported drug interactions with lithium are too numerous to list here. Only a few of the more significant interactions will be addressed. If a drug interaction is suspected, contact the Drug Information Service (567-4280) or Pharmacy Service (358-2890).

Diuretics

This is a well-documented interaction that results in increased lithium levels. All diuretics can contribute to sodium depletion which in turn can result in an increased proximal reabsorption of sodium and lithium. Thiazides cause the greatest increase in lithium levels. Loop diuretics and potassium-sparing diuretics appear to have less of an effect on lithium levels.

ACE-inhibitors and Angiotensin II receptor blockers

May increase the lithium levels.

Antipsychotics

May increase lithium's neurotoxicities. Monitor for altered response to either drug.

Phenothiazine levels may be increased. Seizures and diabetic ketoacidosis has been reported with clozapine.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

May increase lithium levels as much as 25% - 60%. This is probably due to an enhanced reabsorption of sodium and lithium secondary to inhibition of prostaglandin synthesis. Sulindac may have a minimal effect. Appropriate adjustment of lithium dose may be necessary upon initiation and discontinuation of NSAIDs.

Antidepressants

May cause a **switch into mania and may increase tremors**. Fluoxetine may increase toxicity. Sertraline may increase nausea and tremor.

Xanthines

Increase renal excretion of lithium resulting in **decreased lithium levels (in the range of 20%)**. May also contribute to tremors.

Carbamazepine

May increase neurotoxicity

REFERENCES

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