Bipolar disorder in adults and lithium: Pharmacology, administration, and management of adverse effects

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INTRODUCTION

The efficacy of lithium for treating mania was discovered in 1949, making it the first medication specifically developed to treat bipolar disorder [1]. Lithium remains a mainstay of treatment for bipolar disorder, especially for acute mania and maintenance treatment [2]. In addition, lithium appears to reduce the risk of suicide in patients with bipolar disorder [2-4], and may possibly have other benefits, such as reducing the risk of developing neurocognitive disorder [5]. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy' and "Geriatric bipolar disorder: Maintenance treatment", section on 'Cognitive impairment'.)

Lithium is the third element of the periodic table and shares certain properties with other monovalent cations such as potassium and sodium, as well as the divalent cations calcium and magnesium [6-8].

The pharmacology, administration, and management of adverse effects of lithium are reviewed here. Choosing a medication (including lithium) to treat acute mania, hypomania, and bipolar depression is discussed separately, as is the choice of medication for maintenance treatment of bipolar disorder, and the epidemiology, clinical manifestations, and diagnosis of bipolar disorder.

- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Bipolar major depression in adults: Choosing treatment".)

- (See "Bipolar disorder in adults: Choosing maintenance treatment".)
- (See "Bipolar disorder in adults: Epidemiology and pathogenesis".)
- (See "Bipolar disorder in adults: Clinical features".)
- (See "Bipolar disorder in adults: Assessment and diagnosis".)

The use of lithium to treat unipolar major depression is also discussed separately. (See "Unipolar depression in adults: Treatment with lithium".)

DEFINITION OF BIPOLAR DISORDER

Bipolar disorder is a mood disorder that is characterized by episodes of mania (table 1), hypomania (table 2), and major depression (table 3) [9]. The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes, and nearly always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Additional information about the clinical features and diagnosis of bipolar disorder is discussed separately. (See "Bipolar disorder in adults: Clinical features" and "Bipolar disorder in adults: Assessment and diagnosis", section on 'Diagnosis'.)

MECHANISM OF ACTION

Lithium's mechanism of action in treating mania is unknown. However, reviews suggest that the overall effect of lithium is such that it stimulates inhibitory neurotransmission and inhibits excitatory transmission [10,11]. As an example, multiple studies suggest that some neurons in patients with bipolar disorder may be hyperexcitable (more easily stimulated) and that lithium may reduce this hyperexcitability in patients who respond to the drug [12].

One hypothesis regarding lithium's specific therapeutic effects is that it inhibits the activity of glycogen synthase kinase 3 beta, which is involved in gene transcription and regulates an intracellular signaling peptide called Wnt [10,11]. Other hypotheses are that lithium works by depleting inositol in the central nervous system and thus dampens neurotransmission dependent upon this second messenger [10,11], or that lithium inhibits overactive protein kinase C intracellular signaling [10,11,13].

Lithium appears to affect multiple neurotransmitter systems including norepinephrine, dopamine, serotonin, and gamma aminobutyric acid; and second messenger systems including cyclic adenosine monophosphate and cyclic guanosine monophosphate [10,11,14]. Other studies also implicate glutamate-induced excitotoxicity in the pathogenesis of bipolar disorder

(particularly mania), and hypothesize that lithium's efficacy may be related to its modulation of abnormal calcium activity at the N-methyl-D-aspartate ionotropic receptor [11,15]. This is further supported by the antidepressant and antisuicidal effects of ketamine in bipolar and unipolar depression, an agent which acts as an antagonist at the N-methyl-D-aspartate receptor. (See "Bipolar major depression in adults: Investigational and nonstandard approaches to treatment", section on 'Ketamine' and "Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects".)

In addition, lithium also appears to increase neurogenesis and neuroprotective factors, and in patients with bipolar disorder, may preserve or increase cortical gray matter, white matter integrity, and limbic structures such as the hippocampus, thalamus, and amygdala [16-24]. As an example:

- A meta-analysis of 15 magnetic resonance imaging studies compared gray matter volume in patients with bipolar disorder who either were treated with lithium (n = 368) or were not (n = 486) [25]. Gray matter volume was greater in lithium treated patients.

- A retrospective study found that hippocampal volumes were smaller in bipolar patients who were never exposed to lithium (n = 15), compared with healthy controls (n = 15) and patients who were exposed for more than two years (n = 15); hippocampal volumes were comparable for the controls and the patients exposed to lithium for more than two years [26].

The neuroprotective effects of lithium may be the result of direct neurochemical effects, rather than indirect effects secondary to treatment or prevention of mood episodes [27].

Response to long-term treatment with lithium (eg, decreased recurrences) may involve genetic factors [28]. A genome-wide association study of patients with bipolar disorder (n >2500), who were treated with lithium monotherapy for a minimum of six months, found that four linked single nucleotide polymorphisms on chromosome 21 were associated with a good response to lithium [29].

ROLE IN TREATING BIPOLAR DISORDER

The three primary considerations in choosing a medication are clinical efficacy, tolerability, and safety. These factors involve issues such as past response to medications, comorbid medical illnesses, concurrent medications, and specific symptoms. Another consideration is cost.

Lithium is one of many medications that can be selected to treat acute mania, hypomania, and bipolar and unipolar depression in adults (as well as children and adolescents), and is also a potential choice for maintenance treatment of bipolar disorder. The choice of pharmacotherapy for bipolar disorder is discussed separately. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Lithium' and "Bipolar major depression in adults: Choosing treatment" and "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Lithium'.)

Lithium is generally avoided in patients with significant renal disease and often not used during the first trimester of pregnancy. In addition, lithium can significantly affect thyroid function. (See "Renal toxicity of lithium" and "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium' and "Lithium and the thyroid".)

Reduced risk of suicide — Long-term treatment with lithium is associated with a reduced risk of suicide attempts and suicide deaths. This is discussed separately. (See "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy' and "Bipolar disorder in adults: Choosing maintenance treatment", section on 'Reduced risk of suicide'.)

Severely ill patients — For patients with severe mania, the combination of lithium plus an antipsychotic is often useful [30,31]. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy", section on 'Severe manic episodes'.)

PHARMACOKINETICS

The absorption, distribution, and elimination of lithium are well described [32-34]. Lithium is rapidly absorbed through the gastrointestinal tract; food does not alter lithium absorption [10,35]. Peak serum levels occur in one to two hours with standard, immediate-release preparations of lithium and within four to five hours with slow-release preparations. Absorption of immediate-release lithium is complete within six to eight hours, and for slow-release preparations in approximately 8 to 12 hours. Lithium is not protein bound and is distributed throughout total body water. Brain levels are highest within two hours of peak serum levels. Steady state is achieved within four to five days after the last dose change.

Lithium is not metabolized and is excreted almost exclusively through the kidneys [10]. Thus, lithium's elimination half-life is determined primarily by renal function. The half-life in healthy young patients is approximately 24 hours and increases as renal function declines with age.

CONTRAINDICATIONS

Lithium is contraindicated in patients with:

- Significant renal impairment
- Sodium depletion
- Dehydration
- Significant cardiovascular disease

Renal impairment, sodium depletion, and dehydration increase the risk of lithium toxicity. In addition, lithium can rarely cause sinus node dysfunction (eg, sinus bradycardia and sinoatrial block), atrioventricular node dissociation with atrioventricular block and junctional rhythms, and ventricular premature beats.

Psoriasis, which lithium exacerbates, is a relative contraindication.

PRESCRIBING LITHIUM

There are several basic points to discuss with patients before prescribing lithium, including potential side effects, the need to take the medication as prescribed rather than on as-needed basis, and to expect that response and remission may not occur until a few days to weeks have elapsed after a therapeutic dose/level has been achieved.

Lithium dose and serum concentrations — The starting dose of lithium is usually 300 mg two or three times daily [36-39]. The total daily dose is then increased by 300 to 600 mg every one to five days based upon response, tolerability, and body mass index. The goal is to reach a therapeutic serum level, which generally occurs with a dose of 900 mg to 1800 mg per day. Dose increases generally occur more frequently at the beginning of treatment and less often as clinicians approach the target dose.

The half-life of lithium is approximately 24 hours. Thus, it takes at least four or five days for serum lithium concentrations to reach steady state after the dose is changed.

Lithium can be dosed either once daily or in a divided dose regimen. Clinicians should start with a twice daily or three times daily dosing schedule to minimize side effects (especially nausea) early in treatment and consolidate the dose schedule to once daily after a number of weeks or months of treatment. Some patients may have to continue taking lithium in two or four divided doses to minimize peak level side effects. However, adherence generally decreases as the frequency of dosing increases [40].

The target serum level for acute phase management and maintenance treatment is between 0.8 and 1.2 mEq/L (0.8 and 1.2 mmol/L), and levels should usually not exceed 1.2 mEq/L (1.2 mmol/L) [39]. Patients who cannot tolerate a level of 0.8 mEq/L (0.8 mmol/L) may respond to a level of 0.6 mEq/L (0.6 mmol/L) [41].

After reaching the estimated therapeutic dose range (generally 900 mg to 1800 mg per day), the serum lithium concentration should be checked. Subsequently, a level should be measured five to seven days after each dose increase. In addition, if the dose is not changed and a level not checked for two or more weeks, a level should be checked before increasing the dose. An office-based instrument for fingerstick tests of lithium levels is available [42].

Lithium levels should be drawn approximately 12 hours after the last dose (12-hour serum trough level) and generally collected in the morning, before the first dose of the day. Changes in the serum level per unit time are not dramatic 12 hours after the last dose. Thus, a level drawn 11 to 13 hours after the last dose, or even 10 to 14 hours, provides meaningful information. In contrast, a serum level drawn a few hours after lithium ingestion is subject to marked fluctuation if the level is drawn one hour sooner or later, leading to unreliable information.

Serum lithium levels are closely related to renal function, salt balance, and water balance. Clinicians can expect lithium concentrations to change as follows:

- Dehydration (may occur with gastrointestinal viral infections or high fever) causes higher lithium levels.
- Increasing sodium intake causes increased sodium and lithium excretion and lower lithium levels.
- Decreased sodium intake causes sodium and lithium reabsorption in the proximal tubule and an increase in serum lithium levels.

When lithium is taken once per day, serum concentrations are approximately 25 percent higher compared with levels that are observed when lithium is taken two or three times per day; this is due to changes in renal excretion [43]. Therefore, a once daily lithium level of 1.0 mEq/L (1.0 mmol/L) is expected to drop to a level of 0.8 mEq/L (0.8 mmol/L) if the patient switches to a divided dose regimen. Virtually all studies examining optimal lithium levels have used divided dose regimens.

Older adult patients — The use of lithium in older adult patients is discussed separately. (See "Geriatric bipolar disorder: Treatment of mania and major depression", section on 'First-line medications'.)

Lithium preparations — Multiple preparations of lithium are available, varying in dose from 100 to 1000 mg. There is no difference in treatment efficacy or serum concentrations among the various lithium preparations.

The most commonly prescribed preparation in the United States contains 300 mg of lithium carbonate, which provides 8 mEq (8 mmol) of lithium. Lithium carbonate is available as a tablet or capsule. In addition, lithium is available in some countries (other than the United States) as a liquid in the form of lithium citrate for patients who have difficulty swallowing pills. A dose of 5 mL contains 8 mEq of lithium and is equivalent in strength to 300 mg of lithium carbonate.

Several slow-release lithium tablets are available. Slow-release lithium may cause less nausea than conventional, immediate-release forms at least in the beginning of treatment, but also a slightly higher incidence of diarrhea, due to more distal gastrointestinal absorption. Slow-release tablets should be swallowed whole, rather than crushed or chewed.

Additional information about lithium preparations is discussed separately.

Lithium toxicity — Excessive lithium levels can lead to toxicity with severe side effects and multisystem dysfunction that can be fatal if not recognized. Lithium toxicity is a clinical diagnosis that is confirmed by serum lithium levels [36]. Relatively mild toxicity usually does not occur until serum lithium reaches a level of 1.5 mEq/L (1.5 mmol/L). Levels ≥2.5 mEq/L (2.5 mmol/L) constitute a medical emergency, even in patients who appear relatively asymptomatic. Symptoms and treatment of toxicity are discussed separately. (See "Lithium poisoning".)

Lithium has a narrow therapeutic index, which means that the dose at which it is clinically effective is only slightly lower than the dose at which it becomes toxic [44]. Many patients thus suffer an episode of lithium toxicity. As an example, a retrospective study of patients (n = 1340) prescribed lithium found that at least one episode of lithium levels ≥1.5 mmol/L occurred in 7 percent [45]. Although acute kidney injury (creatinine ≥26.5 micromole/L/48 hours) occurred in 34 percent of the episodes, renal function returned to baseline in each instance. No fatalities occurred.

The likelihood of lithium intoxication is increased when lithium excretion is impaired. This most commonly occurs with:

- Underlying renal insufficiency
- Effective volume depletion
- Older adult patients (low glomerular filtration rate)

Drug-drug interactions are another risk factor for lithium toxicity. A retrospective study identified patients taking lithium who either utilized acute care services (eg, emergency department) for lithium toxicity (n = 50) or did not (n = 250) [46]. Patients who suffered lithium toxicity were far more likely to have started a medication that can interact with lithium, compared with patients without lithium toxicity (odds ratio 30).

Drug interactions with lithium — Medications that change renal function, salt balance, or water balance can alter lithium excretion and serum lithium concentrations. Lithium levels must be closely monitored in patients taking these medications. These drug interactions are as follows [36]:

- Increases lithium level
  - Thiazide diuretics
  - Nonsteroidal anti-inflammatory drugs except aspirin
  - Angiotensin converting enzyme inhibitors
  - Antibiotics tetracyclines and metronidazole
- Decreases lithium level
  - Potassium-sparing diuretics
  - Sodium-glucose cotransporter 2 (SGLT2) inhibitors
  - Theophylline
- May increase or decrease lithium level
  - Loop diuretics
  - Calcium channel blockers

These medications are not contraindicated for patients taking lithium. Rather, patients receiving medications that may interact with lithium should have their serum levels monitored more closely. Specific interactions of any particular drug with other medications may be determined using the Lexicomp drug interactions tool included in UpToDate.

Laboratory tests and monitoring — Before prescribing lithium and during ongoing treatment, laboratory tests need to be obtained because lithium can adversely affect several organ systems. Management of abnormal test results and adverse effects resulting from lithium are described elsewhere in the topic, as is management of a positive pregnancy test. (See 'Renal' below and 'Thyroid' below and 'Parathyroid' below and 'Cardiac' below and 'Pregnancy' below.)

Prior to beginning lithium, the following tests should be obtained [47-51]:

- Urinalysis, blood urea nitrogen, creatinine, thyroid function studies, and calcium.
- Pregnancy test for women of childbearing potential.
- Electrocardiogram for patients with risk factors for coronary heart disease, including diabetes mellitus, hypertension, dyslipidemia, and cigarette smoking. (See "Overview of established risk factors for cardiovascular disease".)

Lithium levels should be checked five to seven days after the dose is changed. In addition, a lithium level should be checked if a dose increase is under consideration and a level has not been measured for at least two weeks. Patients on steady doses should have their levels checked every 6 to 12 months.

In addition to checking lithium levels during ongoing treatment, renal, thyroid, and parathyroid function should be monitored as follows [10,44,47-51]:

- Urinalysis, blood urea nitrogen, and creatinine every two to three months during the first six months of therapy, and every 6 to 12 months thereafter. (See "Renal toxicity of lithium".)
- Thyroid function tests once or twice during the first six months, and every 6 to 12 months thereafter or more frequently in higher risk patients. (See "Lithium and the thyroid".)
- Serum calcium is monitored yearly.

MANAGING LITHIUM ADVERSE EFFECTS

Lithium can cause many acute and long-term adverse effects that are not necessarily associated with toxicity [52]. Some adverse effects, such as weight gain and cognitive impairment, are more likely to be associated with nonadherence than other adverse effects, such as nausea, polyuria/polydipsia, and tremor [44]. Severe or a sudden worsening of side effects may be a sign of lithium toxicity. (See 'Lithium toxicity' above and "Lithium poisoning".)

General strategies — General strategies for managing adverse effects of lithium include [44]:

- Watchful waiting – Tolerance to some side effects (eg, nausea and tremor) can eventually occur, but is unlikely with other adverse effects (eg, weight gain).
- Changing the time of administration.
- Lowering the dose; however, dose reductions risk compromising efficacy.

- Changing to a different lithium formulation (immediate or slow release).
- Dividing the daily dose to take smaller amounts more often, to decrease peak serum levels.
- Treating adverse effects with a second drug (eg, diuretic for polyuria/polydipsia).
- Discontinuing lithium and switching to a different drug if adverse effects are intolerable and cannot be managed.

Strategies for managing specific adverse effects are discussed in the sections below.

Renal — Renal function is adversely affected by lithium and thus monitored with laboratory tests [50]. (See 'Laboratory tests and monitoring' above.)

Adverse renal effects are often functional and reversible, but may eventually progress to structural, permanent changes [44,53,54]. As an example, a study examined the impact of long-term lithium treatment (mean duration 18 years) on glomerular filtration rate in 312 bipolar disorder patients (mean age = 56 years) [55]. Extended lithium exposure reduced the estimated glomerular filtration rate by approximately 30 percent more than that associated with aging alone. Additional risk factors for decreased estimated glomerular filtration rate were higher serum lithium concentrations, longer exposure, lower initial estimated glomerular filtration rate, general medical comorbidity, and older age. None of the patients developed end-stage kidney disease.

Abnormal renal function tests are managed in collaboration with a nephrologist to determine the need for further testing, a reduction in the dose of lithium, or switching to an alternative medication for treating bipolar disorder. Additional information about lithium and renal toxicity is discussed separately. (See "Renal toxicity of lithium".)

Polyuria and polydipsia — Polyuria is often defined as urinating more than three liters in 24 hours [44]. Polyuria and polydipsia have been observed in up to 70 percent of lithium treated patients; potential risk factors include longer duration of treatment, higher serum lithium concentrations, episodes of lithium toxicity, and use of other psychotropic medications. Polyuria and polydipsia may be a symptom of arginine vasopressin resistance (previously called nephrogenic diabetes insipidus). (See "Renal toxicity of lithium", section on 'Arginine vasopressin resistance (nephrogenic diabetes insipidus)'.)

Clinicians should attempt to prevent polyuria at the onset of lithium treatment by [44]:

- Administering lithium once per day

- Maintaining lithium serum concentrations as low as possible
- Avoiding episodes of lithium toxicity

For patients who develop polyuria, diuretics (eg, the potassium-sparing diuretic amiloride) may decrease polyuria, but caution must be used because many diuretics alter serum lithium concentrations; lithium doses may need to be adjusted and lithium levels checked more often [44]. Use of diuretics that decrease potassium levels necessitates measuring potassium levels and possibly administering potassium supplements.

Specific interactions of lithium with other medications may be determined using the Lexicomp drug interactions tool included in UpToDate.

Thyroid — Thyroid function is adversely affected by lithium and thus monitored with laboratory tests (see 'Laboratory tests and monitoring' above); lithium can cause goiter, hypothyroidism, chronic autoimmune thyroiditis, and possibly hyperthyroidism. The adverse effects of lithium on thyroid function and their management are reviewed separately. (See "Lithium and the thyroid".)

Neither pretreatment hypothyroidism (presumably treated adequately with T4) nor lithium-induced hypothyroidism is a contraindication to lithium therapy [44,56]. Reasonable recommendations are to monitor serum thyrotropin and if it rises much above the upper value of normal, to start T4 while continuing the lithium. Consultation with an endocrinologist may also be indicated. (See "Clinical manifestations of hypothyroidism" and "Treatment of primary hypothyroidism in adults".)

Parathyroid — Lithium may cause hypercalcemia, elevated serum parathyroid hormone, and hyperparathyroidism [44,50]. Patients with lithium-induced hypercalcemia and hyperparathyroidism are generally asymptomatic [57].

An elevated calcium level should prompt a serum parathyroid hormone concentration. If the hormone level is abnormal, an endocrine consult is obtained. Hypercalcemia, hyperparathyroidism secondary to lithium, and measurement of serum calcium are discussed separately. (See "Primary hyperparathyroidism: Pathogenesis and etiology", section on 'Lithium therapy' and "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation", section on 'Serum calcium' and "Primary hyperparathyroidism: Management".)

Tremor — Lithium tremor is common; pooled results from multiple studies suggest that the prevalence is approximately 25 percent [58]. The pathogenesis may involve lithium-induced accumulation of iron in the substantia nigra [59]. Tremor secondary to lithium is classified as an action tremor, and subcategorized as an exaggerated physiologic tremor. Lithium tremors are

also subclassified as a postural tremor that occurs when a specific posture, such as holding the arms outstretched or while standing, is voluntarily maintained. (See "Overview of tremor".)

Onset of lithium tremor typically occurs when the drug is started or titrated up, but tremor can appear at any time during treatment [44,58]. Lithium tremor is generally symmetric, limited to the hands or upper limbs, and nonprogressive. The frequency of the involuntary rhythmic oscillation of the hands is approximately 10 Hertz. Factors that increase the risk of tremor include higher lithium doses and serum concentrations, anxiety, caffeine, medications (eg, antiarrhythmics, beta-adrenergic agents, carbamazepine, and valproate), emotional and physical stress, fatigue, and older age.

The differential diagnosis of lithium tremor includes metabolic abnormalities, benign essential tremor, Parkinson disease, and lithium toxicity [58]. Tremor caused by lithium toxicity is more coarse and severe than is otherwise observed in patients treated with lithium; in addition, lithium toxicity may affect body parts other than the upper extremity, and is likely to occur with other symptoms of toxicity. (See 'Lithium toxicity' above and "Lithium poisoning", section on 'Signs and symptoms'.)

Clinicians evaluating lithium tremor should obtain a history, physical examination, and laboratory tests (including a serum lithium concentration), to rule out other causes of tremor [58]. Additional information about the evaluation of lithium tremor is discussed separately. (See "Overview of tremor", section on 'Evaluation'.)

Watchful waiting is a reasonable approach to lithium tremor because it often is relatively mild and resolves over time [44,58]. Management of lithium tremor that is troublesome and/or persistent starts with modifying aggravating factors (eg, decreasing caffeine intake). In addition, it may help to change the lithium preparation from long acting to short acting, or to a different salt (ie, from carbonate to citrate), or to divide the daily dose to take smaller amounts more often.

For lithium tremor that still persists and causes moderate to severe functional problems, we suggest add-on pharmacotherapy (eg, beta blockers such as propranolol) [44,58]. Alternatively, the total daily dose of lithium can be reduced if feasible. Choosing and administering add-on pharmacotherapy for lithium tremor is discussed separately in the context of essential tremor. (See "Essential tremor: Treatment and prognosis".)

Nausea — Nausea secondary to lithium is observed in 10 to 20 percent of patients [44]. Management strategies include the following, listed from most to least preferable:

- Taking lithium with food or after meals.

- Using a sustained release formulation of lithium (to decrease peak serum concentrations because nausea may be related to higher peak levels).
- Dividing the daily dose to take smaller amounts more often (to decrease peak serum concentrations).
- Treatment with a second drug. (See "Approach to the adult with nausea and vomiting", section on 'Antiemetics and prokinetics'.)
- Reducing the total daily dose.

Nausea often abates over time, which allows patients to resume a higher dose and once daily dosing [44].

Vomiting secondary to lithium is uncommon and can indicate lithium toxicity, especially in the context of other adverse effects, such as coarse tremor and ataxia [44]. (See 'Lithium toxicity' above.)

Loose stools/diarrhea — Lithium-induced loose stools/diarrhea is seen in up to 10 percent of patients [44]. Higher serum lithium concentrations (eg, greater than 0.8 mEq/L [0.8 mmol/L]) may correlate with loose stools/diarrhea; thus, management strategies include:

- Using an immediate-release formulation of lithium (to avoid distal absorption of the drug).
- Treatment with a second drug. (See "Approach to the adult with chronic diarrhea in resource-abundant settings", section on 'Symptomatic therapy'.)
- Reducing the daily dose.

Weight gain — Lithium can cause weight gain through several mechanisms, such as carbohydrate craving, increased thirst, and fluid consumption, water retention related to salt retention, and reduced metabolism secondary to hypothyroidism. A meta-analysis of five randomized trials compared lithium with placebo in patients with bipolar disorder; four trials lasted to 12 or 18 months (n = 899 patients) and one trial lasted 3 months (n = 325) [50]. Clinically significant weight gain, defined as an increase >7 percent from baseline, occurred in nearly twice as many patients treated with lithium than placebo (relative risk 1.9, 95% CI 1.3-2.8). In addition, weight gain is relatively distressing, compared with other adverse effects [44].

Preventing and managing weight gain during lithium treatment is based upon nonspecific measures [44]:

- Discussing the likelihood of weight gain at the outset of treatment.

- Encouraging patients to drink low caloric drinks when thirsty.
- Dietary strategies, exercise, and drug therapy. (See "Obesity in adults: Overview of management", section on 'Drug therapy'.)
- Treating polyuria/polydipsia-induced weight gain with a diuretic, and treating hypothyroidism-induced weight gain with thyroid supplementation. (See "Renal toxicity of lithium", section on 'Treatment' and "Treatment of primary hypothyroidism in adults".)

Cognitive impairment — Lithium-induced cognitive impairment appears to be one of the most distressing adverse effects of the drug and often leads to nonadherence [10,44]. Cognitive dysfunction secondary to lithium needs to be distinguished from the cognitive impairment that is associated with bipolar disorder per se, including patients who are euthymic or depressed [44,60]. Concomitant medications (eg, antipsychotics, antidepressants, and benzodiazepines) may also contribute to cognitive dulling that occurs in patients receiving lithium. In addition, it appears that the neurocognitive effects are worse at higher doses and are cumulative over time. Cognitive impairment that is due to bipolar disorder itself is discussed separately. (See "Bipolar disorder in adults: Clinical features", section on 'Cognition'.)

Multiple cognitive domains are adversely affected by lithium. As an example, a meta-analysis of six studies included patients with remitted mood disorders (n = 326, primarily bipolar disorder) and found that use of lithium was associated with small to moderate impairment of immediate verbal learning and memory, creativity, and psychomotor performance [61]. However, lithium may preserve other domains of neurocognition [60].

Management strategies include dividing the daily dose to take smaller amounts more often; in addition, lowering the dose of lithium may help, because cognitive dulling may be dose related [44]. Among patients receiving polypharmacy, especially complex psychotropic regimens that include three or more drugs, discontinuing one or more drugs may improve cognitive dysfunction without exacerbating mood symptoms. Adding stimulants such as modafinil and armodafinil may possibly help, but there is no high quality evidence to support this approach.

Sexual dysfunction — Lithium-induced sexual dysfunction appears to be common. One study assessed clinically stable patients with bipolar disorder who were treated with lithium for an average of 10 years (n = 100 patients; mean age 44 years); 85 percent were receiving lithium monotherapy and the mean dose in the entire sample was 800 mg/day [62]. Sexual dysfunction across multiple domains (eg, arousal, sexual drive, and penile erection/vaginal lubrication) was present in 37 percent and was associated with poor adherence. Risk factors for sexual dysfunction included older age and the presence of other adverse effects.

Management strategies, beyond the general strategies for managing adverse effects (see 'General strategies' above), are discussed in the context of treating the general population of patients with sexual dysfunction. (See "Treatment of male sexual dysfunction" and "Overview of sexual dysfunction in females: Management".)

Cardiac — Lithium may rarely cause cardiac dysrhythmias in patients without pre-existing cardiac disease [36,52,63]. In addition, lithium may lead to the following abnormalities on the electrocardiogram, which may anticipate the onset of dysrhythmias [52]:

- Repolarization abnormalities of the T wave or ST segment.
- Findings consistent with sinus node dysfunction. (See "Sinus node dysfunction: Epidemiology, etiology, and natural history", section on 'Other'.)
- An unmasked or modulated Brugada pattern. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on 'Provoking factors'.)

These electrocardiogram findings should prompt a cardiology consult.

PREGNANCY

Although lithium is generally regarded as teratogenic due to increased risks of cardiac defects (eg, Ebstein anomaly) [64-66], many authorities consider the absolute risk small [67-71]. The use of lithium during pregnancy and risks of lithium exposure during pregnancy and breastfeeding are discussed separately.

- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium' and "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Refractory patients' and "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders", section on 'Lithium'.)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium' and "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section on 'Refractory patients' and "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders", section on 'Lithium'.)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy", section on 'Lithium' and "Bipolar disorder in women: Preconception and prenatal maintenance pharmacotherapy", section

on 'Refractory patients' and "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders", section on 'Lithium'.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Coping with high drug prices (The Basics)")
- Beyond the Basics topics (see "Patient education: Bipolar disorder (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

The United States National Library of Medicine and National Institutes of Health have created an educational document entitled "Lithium" that explains the use of lithium. It is available online at the website, and copies may be printed free of charge.

The United States National Institute of Mental Health has a document entitled, "Mental Health Medications," that is available at the website, or through the toll-free number 866-615-6464. Copies may be printed free of charge.

The Depression and Bipolar Support Alliance (available at the website or 800-826-3632) is a national organization whose mission is to educate members about bipolar disorder and how to cope with it. Other functions include increasing public awareness of the illness and advocating for more research and services. The organization is administered and maintained by patients and family members, and has local chapters.

The National Alliance on Mental Illness (available at the website or 800-950-6264) is a similarly structured organization devoted to providing education, support, and advocacy for

patients with any mental illness. Bipolar disorder is one of their priorities.

SUMMARY

- **Indications for lithium in bipolar disorder** – Lithium is one of many medications that can be selected to treat acute mania, hypomania, and bipolar depression, and is also a potential choice for maintenance treatment of bipolar disorder. In addition, lithium may reduce the risk of suicide. (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy" and "Bipolar major depression in adults: Choosing treatment" and "Bipolar disorder in adults: Choosing maintenance treatment" and "Suicidal ideation and behavior in adults", section on 'Pharmacotherapy'.)

- **Pharmacokinetics** – Lithium is rapidly absorbed through the gastrointestinal tract. Peak serum levels occur in one to two hours with immediate-release preparations of lithium and within four to five hours with slow-release preparations. Lithium is distributed throughout total body water. Steady state is achieved within four to five days after the last dose change. Lithium is excreted almost exclusively through the kidneys. The half-life is approximately 24 hours in healthy young patients and increases as renal function declines with age. (See 'Pharmacokinetics' above.)

- **Contraindications** – Lithium is contraindicated in patients with significant renal impairment, sodium depletion, dehydration, and significant cardiovascular disease. (See 'Contraindications' above.)

- **Dose** – The starting dose of lithium is usually 300 mg two or three times daily. The dose should be increased by 300 to 600 mg every one to five days based upon response, tolerability, and body mass index. The goal is to reach a therapeutic serum level, which generally occurs with a dose of 900 mg to 1800 mg per day. Dose increases generally occur more frequently at the beginning of treatment, and less often as clinicians approach the target dose. (See 'Lithium dose and serum concentrations' above.)

- **Target serum levels** – The target serum level for acute phase management and maintenance treatment is generally between 0.8 and 1.2 mEq/L (0.8 and 1.2 mmol/L). Patients who cannot tolerate a level of 0.8 mEq/L (0.8 mmol/L) may respond to a level of 0.6 mEq/L (0.6 mmol/L). (See 'Lithium dose and serum concentrations' above.)

- **Monitoring serum levels** – Levels should generally be measured five to seven days after each dose increase. In addition, a lithium level should be checked if a dose increase is considered and a level has not been measured within the past two weeks. Patients on

steady doses should have their levels checked every 6 to 12 months. Lithium levels should be drawn 12 hours after the last dose (12-hour serum trough level) and generally collected in the morning, before the first dose of the day. (See 'Lithium dose and serum concentrations' above and 'Laboratory tests and monitoring' above.)

- **Lithium toxicity** – Excessive lithium levels can lead to toxicity with severe side effects and multisystem dysfunction, which can be fatal if not recognized. Lithium toxicity is a clinical diagnosis that is confirmed by serum lithium levels. Relatively mild toxicity usually does not occur until serum lithium reaches a level of 1.5 mEq/L (1.5 mmol/L). Levels ≥2.5 mEq/L (2.5 mmol/L) constitute a medical emergency, even in patients who appear relatively asymptomatic. (See 'Lithium toxicity' above and "Lithium poisoning".)

- **Drug-drug interactions** – Multiple medications can alter lithium concentrations. As an example, lithium levels are increased by thiazide diuretics and nonsteroidal anti-inflammatory drugs except aspirin. Lithium levels are decreased by potassium-sparing diuretics and theophylline. (See 'Drug interactions with lithium' above.)

- **Laboratory tests prior to and during lithium therapy** – Prior to beginning lithium, clinicians should obtain a urinalysis, blood urea nitrogen, creatinine, thyroid function studies, calcium, and pregnancy test for women of childbearing potential; for patients over age 40 years, an electrocardiogram is also obtained. Blood urea nitrogen and creatinine should be checked every two to three months during the first six months of therapy, and every 6 to 12 months thereafter. Thyroid function should be checked once or twice during the first six months, and every 6 to 12 months thereafter. (See 'Laboratory tests and monitoring' above.)

- **Adverse effects** – Lithium can cause several side effects, including those that involve the kidneys and thyroid gland. In addition, cardiac rhythm disturbances have been described; these almost always occur in patients with preexisting cardiac disease. Severe or a sudden worsening of side effects may be a sign of lithium toxicity. (See 'Managing lithium adverse effects' above and 'Lithium toxicity' above and "Lithium poisoning".)

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