# LITHIUM: ANTIMANIC AND OFF-LABEL USES

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## Topic Overview

Lithium is well known as an antimanic agent and is administered for mood stabilization in patients diagnosed with bipolar disorder. More recently, Lithium's use has been recognized off-label as an adjuvant treatment for conditions other than mania. An understanding of lithium treatment and monitoring requirements, as well as potential complications of treatment, is crucial to ensure patient awareness of symptoms and compliance. This is of particular importance in patients with comorbidities and in the elderly. Clinicians who do not regularly prescribe lithium to treat bipolar disorder may be unfamiliar with all of its uses, especially in special populations and for patients diagnosed with mixed mood states.

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**Target Audience:** This continuing education activity is intended for licensed pharmacists and associates to update knowledge on the anti-manic and off-label uses of lithium.

**How to Earn Credit:** From April 1, 2021, through March 31, 2024, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
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3) Complete the Course Test and Evaluation form. The Course Test will be graded automatically. Following successful completion of the Course test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

**Educational Objectives:** Upon completion of this educational activity, participants should be able to:

1. **Identify** the basic pharmacological profile of lithium treatment, with monitoring requirements and recommended serum levels
2. **Describe** the primary use and clinical outcomes of treatment with lithium, including off-label uses, and use in patients with comorbidities and the elderly.
3. **Compare** conditions for which lithium is prescribed, with potential side effects and adverse reactions
4. **Identify** lithium toxicity

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## Introduction

Lithium is a first-line choice for treating and preventing manic episodes in patients diagnosed with bipolar disorder. While it is generally accepted as a safe and effective drug for bipolar disorder, lithium has a narrow therapeutic window so that close monitoring of laboratory trends of lithium levels and of patient symptoms are needed. Before the patient begins lithium therapy, they should be provided with a thorough understanding of the potential complications and adverse effects that could occur. The following sections will discuss the basic pharmacological profile and uses of lithium.

## Lithium Treatment

Lithium is categorized as an antimanic and mood stabilizing agent.[1-3] The goal of lithium therapy is to attain mood stabilization in patients who have bipolar disorder; however, lithium's mechanism of action is unknown. Lithium is rapidly absorbed and there is no metabolism of lithium, so it is excreted in the urine unchanged.[1-3] Lithium has a labeled use for the treatment of patients with mood disorders. There is evidence; however, that lithium can also be useful in combination with other medications and for other off-label uses.

### Bipolar Disorder

Lithium is used as a treatment of manic episodes and as maintenance treatment in patients who have bipolar disorder.[1-3] Lithium can also be used off-label for bipolar depression as an adjunct with an antidepressant to treat symptoms of depression.[1-3]

Bipolar disorder is considered a chronic mental illness that is characterized by episodes of mania, hypomania, and major depression.[4,5] Bipolar disorder can be managed by medication treatment but not cured. The mania, hypomania, and depression seen in bipolar disorder can be severe with significant functional consequences that accompany a patient's mood episodes.[5,6]

Two subtypes of bipolar disorder include *type I* and *type II.* In bipolar disorder type 1, manic episodes, major depressive and hypomanic episodes can be experienced.[6,7] Bipolar disorder type II episodes can include hypomania and at least one major depression. Lithium is the first line treatment for manic episodes associated with Bipolar I disorder.[6,7] For severe mania, lithium can be combined with an antipsychotic medication, such as olanzapine and/or other mood stabilizer, such as valproic acid, depending on the patient's history and prior response to treatment.[7]

Mild to moderate manic episodes can also be treated with lithium.[7,8] When used as maintenance treatment for bipolar disorder, lithium can lower the relapse rate. Long-term treatment with lithium may depend on genetic factors;[9] a single nucleotide polymorphisms on chromosome 21 has been shown to correspond with a good lithium response.[10]

Manic Episode: DSM-5 Criteria

Criteria A through D of the Diagnostic and Statistical Manual Fifth Edition (DSM-5) set forth the criteria to diagnose a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.[11] A manic episode is characterized by an abnormally and persistently elevated, expansive, or irritable mood and increased level of energy and activity, lasting at least one week and for most of the day, nearly every day.[11]

For patients observed to have a mood disturbance and increased energy or activity, three or more of the following symptoms (four symptoms if the mood is only irritable) can exist to a significant degree, representing a noticeable change in a patient's usual behavior:[11]

1. Grandiosity or inflated self-esteem.
2. A reduced need for sleep.
3. Hyperverbal or pressured speech.
4. Flight of ideas or racing thoughts.
5. Distractibility, by patient report or observation.

6. High energy or activity (sexually, socially, work, school) or psychomotor agitation.
7. Impulsivity or involved in risky activities (excessive spending, business dealings, sexual behavior).

The patient with a bipolar disorder can display a mood disturbance that is severe enough to cause significant impairment in social and/or occupational functioning and may require hospitalization to prevent harm to self or to others. The mood disturbance can coincide with an episode of psychosis.[11] Bipolar disorder may or may not be attributable to the physiological effects of substance use or to another medical condition.[11]

**Lithium and Circadian Rhythm**

Bipolar disorder is known to be associated with altered circadian rhythm and insomnia. Research has focused on how lithium works at the cellular level to target the biological clock. Chronotypes may be divided into preferences: morning people who like to rise early, or evening people who stay awake late.[12] McCarthy, *et al.* (2019) reported that lithium responders, people who respond well to lithium treatment, were found to show a "difference in chronotype, with higher levels of morningness," when compared to lithium non-responders.[12] Lithium responders tended to have a "short circadian period, a linear relationship between period and phase, and period shortening effects of lithium."[12] On the other hand, *evening chronotype* corresponded with higher incidence of mood symptoms (depression, mania, and insomnia).[12] Individual variations in circadian rhythm in patients with bipolar disorder may impact lithium maintenance treatment and treatment outcomes.

Gold and Kinrys (2019) reported that sleep dysregulation affects an estimated 70% of patients with bipolar disorder and can persist even during euthymic periods. Depressed and manic patients can experience changes in sleep onset, mixed insomnia/hypersomnia, an altered circadian phase, and can become preoccupied and anxious about their sleep pattern.[13] Reference was made by Gold and Kinrys to prior studies where researchers raised bipolar chronotypes, described as preference for wakefulness in the morning versus

the evening, revealing that individuals with bipolar disorder had "a common pattern of eveningness preference."[13] Eveningness chronotype associated with mood disorders were also associated with delayed circadian phase, delayed melatonin onset.[13] More studies are underway to explore the link with circadian rhythm, bipolar disorder and the use of lithium.

**Lithium and Aggression**

The use of lithium to control symptoms of aggression in youth and adults has been studied. A Canadian review of lithium efficacy in aggressive youth with comorbid drug use and attention deficit hyperactivity disorder (ADHD) showed mixed outcomes.[14] While one study showed no difference in behaviors in youth with co-occurring disorders who were prescribed lithium as compared to placebo, other studies reported multiple behavioral outcomes. Data extracted from multiple studies suggested that lithium use was associated with a higher remission rate in aggressive youth than placebo.[14] The general consensus in psychiatry is that lithium can show benefit in combination with other medication targeting symptoms of anxiety, mood disorder, mixed states, hostility, aggression or violent behavior.

The presence of co-occurring conditions are not uncommon in youth and adults with bipolar disorder. This can include substance use and anxiety disorders, attention deficit/hyperactivity disorder, personality disorders and other complicating conditions.[15] Comorbid psychiatric disorders can cover a range of psychopathology seen in individuals with bipolar disorder, which can make the treatment choice difficult.

The initial dose of lithium is typically 300 mg two or three times daily with a goal to reach a therapeutic dose that is often reached between 900 mg to 1800 mg per day.[16] The serum lithium level to reach therapeutic value is 0.8 - 1.2 mEq/L. Some patients may tolerate a serum level of 0.6 mEq/L better than 0.8 and higher.[16] Lithium has been compared with placebo in prison settings where patients showed chronic impulsive aggressive behavior that decreased significantly with the addition of lithium.[16]

## Lithium Side Effects and Adverse Outcomes

Patients that are prescribed lithium are routinely monitored for physical symptoms of toxicity and for elevated serum levels that could lead to serious side effects, such as renal impairment or thyroid dysfunction. There are considerable drug-drug interactions with the combined use of lithium and other drugs that require close monitoring to prevent a serious outcome.

For adult patients with renal impairment and a CrCl of 30 to 89 mL/minute, therapy should be initiated with low dose and titrated slowly with frequent monitoring. In patients with a CrCl of < 30 mL/minute, the use of lithium should be avoided.[1]

Lithium is associated with nephrogenic diabetes insipidus but there is mixed review of the association between long-term lithium use and renal dysfunction.[17] Long-term lithium use can lead to deterioration in eGFR. Age, comorbidities, use of other nephrotoxic drugs, and history of lithium toxicity (lithium level > 0.80 mmol/L) have been associated with lower eGFR. In the majority of patients prescribed long-term lithium, treatment is tolerated without renal dysfunction.[17]

The potential of renal dysfunction can occur at serum levels > 0.8 mmol/L, so cautious dosing should be considered in some people, such as elderly, and for people taking medications known to increase lithium levels like nonsteroidal anti-inflammatory drugs (NSAIDS) and certain blood pressure and diuretic agents.[17] Symptoms of acute lithium toxicity include "nausea, vomiting, diarrhea, dysrhythmia and neurological manifestations such as coarse tremor, muscle weakness, cerebellar signs and delirium."[17] Seizures, coma and permanent neurological damage, such as dementia can result from severe lithium toxicity. The risk of lithium toxicity is higher with sodium or volume depletion.[17]

Monitoring of lithium levels and renal function are important when looking for signs of toxicity.[17] Long-term lithium use leads to a steady-state concentration in the brain and serum.[17] There are variations of serum lithium

levels between individuals. In patients on chronically high doses of lithium, accumulation of the drug in central nervous system tissue can lead to lithium toxicity. If a patient failed to take a prescribed dose of lithium prior to a neurological toxicity test, the patient may test for a normal serum level even though neurological toxicity is present.[17] Serum levels should be tested within 12 hours of taking lithium to avoid a false normal.[17]

Lithium can show diverse side effects in individuals. Those suspected to have lithium toxicity need to be treated with caution. In elderly patients on long-term lithium, a lithium level at the low end of the normal range should be a target goal.[17]

## Case Study: Lithium Toxicity

The following case study was obtained from a PubMed search that focused on a 62-year-old male who had been diagnosed with bipolar disorder 25 years prior and prostate cancer.[17]

The patient had been stable on lithium with one documented stress-related hypomanic relapse. Symptoms of hypomania included high energy, insomnia, grandiosity and irritability. The patient became highly elated, disinhibited and disorganized while in the community prior to admission. On admission to the hospital, he displayed pressured speech, flight of ideas and appeared delusional. His adherence to medication was unknown. He was described as labile, tearful, laughing, anxious, pacing constantly, and made inappropriate odd statements. He required emergency hold and admission to the psychiatric unit.

A medical history was obtained that he was diagnosed with low-risk prostate cancer with conservative treatment and monitoring. The patient had no documented allergies to medication. A bilateral fine tremor was noted and Parkinson’s disease was ruled out with an initial trial of selegiline. Propranolol was also trialed for essential tremor, but discontinued due to lack of efficacy. Routine medications included: lithium 800 mg at bedtime, trazodone 50 mg at bedtime and tadalafil 20 mg as required.

Family history was negative for mental illness. Social history and substance use showed that he lived in a shelter, was unemployed with documented disability due to bipolar disorder; and he denied tobacco, alcohol or illicit drug use.

On physical examination, the patient's vital signs included heart rate 91 per minute, blood pressure 135/79 mmHg, temperature 36.5 celsius and oxygen saturations 96% on room air. The patient appeared malnourished and had bilateral tremors and slurred speech, but had no other acute health concerns.

Laboratory testing showed a complete blood count (CBC), liver function tests, which were all normal, and thyroid-stimulating hormone within normal limits. The comprehensive metabolic panel showed a creatinine elevation of 123 μmol/L, with urea 10.1 mmol/L estimated glomerular filtration rate (eGFR) of 52 mL/min and was otherwise within normal limits. The PSA was 6.82 μg/L. The serum lithium level was at the high end of normal range at 0.95 mmol/L (> 12 hours after his last dose). The urinalysis and urine drug screen were negative.

Initial treatment included rehydrating the patient with oral fluids. Lithium was initially stopped and replaced with olanzapine 10 mg at bedtime. Lithium was later restarted two weeks later due to worsening mania and coarse tremors recurred. Chronic renal impairment and the recurrence of symptoms indicating toxicity led to the discontinuance of lithium. Sodium valproate was started as second-line medication for bipolar disorder. The discontinuance of lithium corresponded with a vast improvement of tremor within 2 weeks. The authors believed that the patient developed chronic renal impairment during episodes of toxicity while taking lithium.

After three months, the patient transitioned to a lesser restrictive level of care. He continued to show poor insight and judgment but overall improved in mood and thought, less labile and showing gradual awareness of his mental condition. Medications were reported as olanzapine 20 mg at bedtime. He developed side effects to olanzapine, described as rigidity and lip smacking.

Procyclidine was started and sodium valproate was increased to 500 mg in the morning and 1000 mg at bedtime. There was no further deterioration of chronic kidney disease. He eventually discharged to community mental health services on olanzapine and sodium valproate.

## Summary

Lithium is a first-line choice for the treatment of patients with bipolar disorder, and with careful prescribing and close monitoring it can be used effectively and safely. Lithium should be used cautiously in patients with comorbid health conditions. Patients should be counseled on lithium drug interactions and made aware of lithium toxicity symptoms. Neurological status and the serum lithium level must be closely followed in patient's prescribed long-term lithium. Careful monitoring of the serum lithium level through observation and laboratory testing is important to trend for ongoing safe utilization.

**Course Test:**

1. **Lithium is an antimanic agent that acts as _____ in patients who have bipolar disorder.**

    a. a hallucinogen
    b. a mood stabilizer
    c. an antipsychotic
    d. an antidepressant

2. **For treatment of _____, lithium can be combined with an antipsychotic.**

    a. tremors
    b. severe mania
    c. mild mania
    d. ADHD

3. **Bipolar disorder is a psychiatric disorder characterized by episodes of**

    a. depression followed by periods of lethargy.
    b. anxiety and concomitant depression.
    c. mania, hypomania, and major depression.
    d. anger and anxiety, followed by periods of pseudo-mania.

4. **An adult patient with renal impairment and a CrCl of 30 to 89 mL/minute may**

    a. NOT take lithium.
    b. take lithium without adjusting the dose since lithium does not affect renal function.
    c. take lithium with an initial low dose, titration and monitoring.
    d. take lithium but a high sodium diet is recommended.

5. **True or False: Lithium is *not* useful to treat mild to moderate manic episodes.**

    a. True
    b. False

6. **In patients on chronically high doses of lithium, accumulation of the drug in central nervous system tissue can lead to**

    a. lithium toxicity.
    b. Brugada syndrome.
    c. hyperthyroidism.
    d. the development of thyroid auto-antibodies.

7. **A patient taking chronically high doses of lithium may have neurological toxicity but test normal because**

    a. the patient took lithium within 12 hours of being tested.
    b. the patient developed thyroid auto-antibodies.
    c. the patient failed to take a prescribed dose within 12 hours of being tested.
    d. the results were masked by the patient's high sodium diet.

8. **True or False: Lithium, in combination with other medication, may benefit patients who are hostile, aggressive or violent.**

    a. True
    b. False

9. **When comparing bipolar disorder patients who do not respond well to lithium treatment with bipolar disorder patients who do, those who respond well to lithium treatment tend to**

    a. have long circadian periods.
    b. prefer an evening chronotype.
    c. have higher levels of morningness.
    d. have a higher incidence of depression, mania, and insomnia.

10. **Which of the following medications are known to increase a patient's lithium levels?**

    a. Nonsteroidal anti-inflammatory drugs (NSAIDS)
    b. Blood pressure agents
    c. Diuretic agents
    d. All of the above

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