



## CRACKCast E160 – Lithium

### Key concepts;

- The clinical pattern of acute and chronic toxicity is different. Gastrointestinal symptoms occur early and neurological toxicity manifest late in acute toxicity.
- Neurological findings (such as, tremors, clonus, and somnolence) often are presenting signs of chronic lithium toxicity and gastrointestinal symptoms may be absent.
- Neither activated charcoal nor whole bowel irrigation (WBI) is indicated in the routine management of acute or chronic lithium toxicity.
- Serial lithium concentrations should be obtained every 2 to 4 hours initially to determine the peak level and the need for dialysis.
- Fluid hydration with crystalloid is essential to enhance the removal of lithium through the kidney. Diuretics are contraindicated.**
- We recommend dialysis for acute lithium concentrations  $>4$  mEq/L (4 mmol/L), and chronic lithium concentrations  $>2.5$  mEq/L (2.5 mmol/L), or for patients with signs of severe neurological toxicity regardless of the concentration.

### Core questions

1. How does lithium work?
2. What is the clinical presentation of lithium toxicity?
3. List risk factors for toxicity in the setting of chronic lithium use.
4. List 4 factors which impair renal filtration of Li
5. List 2 disease states caused by Li
6. Describe the management of lithium toxicity.
7. What are the indications for dialysis in a patient with lithium toxicity?

### Wisecracks:

1. List 4 common clinical scenarios for Li toxicity and describe the clinical syndromes
  2. List the ECG changes potentially seen in lithium toxicity
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## Rosen's In Perspective:

***Lithium was approved for the treatment of bipolar disorder in 1970, and it remains one of the most effective agents for both depressive and manic symptoms.***

*“Lithium is a monovalent cation with a narrow therapeutic range, and significant toxicity can result when outside of this range.”*

***Lithium largely has no effect when given in therapeutic doses to patients without mood disorders.***

*“Lithium toxicity is nonspecific and may present in a manner similar to many systemic and neurologic disorders, so obtaining a history of use or ingestion is critical to making the diagnosis.”*

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### [1] How does lithium work?

*In spite of long-term therapeutic use, the mechanism by which lithium acts is still not fully understood. Its efficacy in the treatment of psychiatric illnesses is thought to be due to the modulation of neurotransmitters, which has downstream effects through cell signaling and molecular mechanisms.*

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### [2] What is the clinical presentation of lithium toxicity?

***Lithium is rapidly absorbed from the gastrointestinal tract and peaks in the serum 1 to 2 hours after ingestion of immediate release preparation and 4 to 5 hours with sustained release preparations.***

*“In overdose situations, absorption and peak concentrations may be delayed. Once absorbed, lithium enters the serum followed by a delayed distribution to the tissues.”*

**Lithium is NOT metabolised (it's a metal) and is excreted unchanged in the urine.**

**Unless the patient intentionally overdoses, most toxicity occurs in the setting of acute or chronic intravascular volume depletion or renal impairment**

***The classic presentation of significant lithium toxicity comprises altered mental status; tremors; hyperreflexia, clonus, or fasciculations; and vomiting or diarrhea.***

*However, clinical features of lithium toxicity **depend on whether it is acute or chronic in nature** (Table 154.1). Thus, evaluation of the potentially lithium toxic patient requires*



knowledge of whether the patient was previously taking lithium, the timing of the last dose, and the amount of drug ingested.

**Acute toxicity = GI symptoms predominate**

- Patient wasn't on lithium and wanted to OD on it

**Chronic toxicity = neurologic symptoms predominate**

- an increase in serum levels of lithium in a patient who is regularly taking lithium. This can either be from reduced excretion, renal insufficiency, or dose adjustment (either by a clinician or by the patient). **Chronic lithium toxicity causes predominantly neurological symptoms.**
- Acute-on-chronic toxicity occurs when a patient with a stable steady-state lithium level takes a substantial additional amount of lithium, whether intentional or accidental. These patients present with a combination of both acute and chronic toxicity signs and symptoms. Either acute or chronic toxicity can result in cardiac conduction abnormalities or bradycardia;

**Table 154.1: Clinical Features of Lithium Toxicity**

CLINICAL FEATURES	TYPE OF TOXICITY	
	ACUTE	CHRONIC
<b>Gastrointestinal</b> <sup>1</sup>	Nausea Vomiting Diarrhea	Mild or nonexistent
<b>Neurological</b> <sup>11,12</sup>	Similar to chronic toxicity, occurs several hours after lithium distribution to the brain	Tremors Clonus Hyperreflexia Somnolence Extrapyramidal symptoms Coma Seizures
<b>Cardiac</b> <sup>13-14</sup>	Sinus node dysfunction AV blockade Brugada pattern on ECG Ischemic changes on ECG QTc prolongation	

AV, Atrioventricular; ECG, electrocardiogram.

**Mnemonic time:**

- Leukostasis
- Insipidus
- Tremor / teratogen
- Hypothyroidism
- Increased weight



- Vomiting ? nausea
- Myocardium = ecg changes
- Serotonin syndrome / nms like effect

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### [3] List risk factors for toxicity in the setting of chronic lithium use.

- Nephrogenic DI
- Renal impairment
- Acute illness
- Diuretic use, NSAIDS, ACE/ARB drugs
- Dementia
- Increased age
- SILENT: cerebellar findings with pseudodementia

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### [4] List 4 factors which impair renal filtration of Lithium

- Volume depletion
- Kidney injury
- Nephrogenic DI
- Diuretic use

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### [5] List 2 disease states caused by Lithium

Here's a bunch:

- *nephrogenic diabetes insipidus*
- *Hypothyroidism (and hyperthyroidism)*
  - *Both of these conditions are reversible with discontinuation of the medication and respond well to conventional management.*
- *Hypercalcemia and hyperparathyroidism also can occur and reverse upon discontinuation of lithium.*
- *Patients chronically taking lithium can develop the syndrome of irreversible lithium-effectuated neurotoxicity (SILENT). Patients with SILENT will often have persistent cerebellar and brainstem dysfunction, dementia, and extrapyramidal signs even after lithium use has been discontinued for more than 2 months.*

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### [6] Describe the management of lithium toxicity.

Think about other ingestants or your ddx:

- Toxins:



- **Salicylates, iron, ASA, acetaminophen, substance withdrawal, serotonin syndrome!**

*“Lithium concentrations should be obtained in all patients who are taking lithium, or have access to lithium, and present with potential toxicity. Because of the insidious and nonspecific nature of chronic lithium toxicity, a serum lithium level is also advisable in patients who are on lithium maintenance, regardless of their reason for presentation (normal levels 0.6 - 1.2 mmol/L)”*

**Box 154.1: Diagnostic Testing For Lithium:**

- Serum lithium level
- Serum electrolytes
- Electrocardiogram (ECG)
- *If the clinical picture dictates:*
  - Acetaminophen/salicylate levels
  - Thyroid function tests

***No specific antidote exists for lithium toxicity, and activated charcoal does not bind lithium.***

***Supportive care and enhanced elimination are the mainstays of treatment. Because lithium is primarily excreted unchanged by the kidney, intravenous crystalloid should be administered early.***

***Most patients who are lithium-toxic are dehydrated because of gastrointestinal losses in acute toxicity or from underlying dehydration leading to chronic toxicity.***

***Crystalloid should be infused as a 1 L bolus followed by a continuous infusion at 150% of the calculated maintenance rate if there are no contraindications, such as congestive heart failure.***

***Diuretics are contraindicated, because they can cause worsening dehydration and reabsorption of lithium. Electrolyte abnormalities, if significant, should be corrected.***

***We do not recommend the use of whole bowel irrigation (WBI) in routine lithium ingestions. “ - Rosen’s***

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## **[7] What are the indications for dialysis in a patient with lithium toxicity?**

**Lithium is highly dialyzable and dialysis is indicated for patients exhibiting signs of severe lithium toxicity**



**Dialysis can remove lithium at a rate five to seven times the rate of typical renal elimination.**

**Box 154.2: Indications For Dialysis in Lithium Poisoned Patients**

1. Severely symptomatic patients
2. Unable to tolerate fluid hydration
3. Renal impairment
4. Acute toxicity: Levels above 4 mEq/L
5. Chronic toxicity: Levels above 2.5 mEq/L

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**Wisecracks:**

**[1] List 4 common clinical scenarios for Li toxicity and describe the clinical syndromes**

- **Acute toxicity**
  - *a recent ingestion in a patient who is not therapeutically taking lithium.*
  - **Acute toxicity typically manifests with gastrointestinal symptoms such as vomiting and diarrhea and can mimic many other disease states.**
  - *Neurologic consequences of an acute lithium overdose (such as, altered mental status and seizures) **occur several hours later** after lithium redistributes to the brain, but in some cases where lithium has delayed-release properties, this can occur even 12 or more hours after ingestion.*
  - May have cardiac toxicity
- **Acute on chronic toxicity**
  - Overlap of GI, Neuro, and cardiotoxicity (AV blockade, qtc prolonged, ischemic changes)
- **Chronic toxicity** (*reduced excretion, renal insufficiency, dose adjustment (either by a clinician or by the patient).*)
  - *predominantly neurological symptoms = ataxia, EPS, tremors, seizures, coma/somnolence.*
- Lithium has also been implicated in **serotonin syndrome** when combined with other drugs, such as monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitor (SSRIs), dextromethorphan, and meperidine.

***Any changes in renal excretion due to conditions such as dehydration, hyponatremia, or renal dysfunction will lead to increases in serum lithium levels.***

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## **[2] List the ECG changes potentially seen in lithium toxicity**

These are usually seen in acute overdose

- Bradycardia**
- Junctional rhythm / AV blockade**
- ST changes**
- QT prolongation**
- Flattened or inverted T-waves**
- Brugada pattern on ECG**
- Ischemic changes on ECG**