TREATMENT WITH LITHIUM AND LITHIUM TOXICITY PREVENTION

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SPEAKER DISCLOSURES

✓ I have no conflicts of interest

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. To identify the indications and pharmacokinetics relevant to safe prescribing of lithium
2. To recognize symptoms of lithium toxicity and link these symptoms to potential etiologies
3. To apply understanding of lithium toxicity etiology to design interventions that can be taken by the clinician and the mental health care team to prevent lithium toxicity
INDICATIONS FOR LI USE

FDA Approved:
1. Bipolar disorder, acute mania
2. Bipolar disorder, maintenance with hx of manic episode

Off-Label:
1. MDD (adjunct tx)
2. Reduction in suicidal behavior in affective disorders
3. Bipolar disorder without hx of mania (but not rapid cycling or mixed state types)

(Chokhawala et al., 2023)
1. "Gold Standard" and first line agent for treatment of acute mania and maintenance tx for bipolar disorder (Tondo, 2019)

2. Two-thirds of lithium-treated patients have satisfactory mood stabilization over 6-12 months
   1. One-third of lithium-treated patients will have no recurrences of mania in 3 years! (Grof 2006)

3. Meta-analysis in 2014 by Miura et al. reinforced “gold standard” status – one of the most effective tx for prevention of both manic and depressive episodes with most robust and unbiased evidence
PRESCRIBING LITHIUM

- Narrow therapeutic index – 0.6-1.0 mmol/L (sometimes 1.2 mmol/L)
- Monitor serum (extracellular) lithium levels
  • After 1 week of starting treatment, or 5-7 days after change of dose
  • Every month for 3 months
  • Once stable, monitor every 6 months
- Before starting, test: Cr and BUN, Na, K, Ca, thyroid and parathyroid hormones, EKG. Repeat annually.
- Dosing:
  • Divided in elderly, pregnant women, and those on doses > 1200 mg daily
  • Otherwise can use controlled-release once daily dosing

(Tondo, 2019)
PHARMACOKINETICS

• 95% excretion through kidneys
  – Kidneys treat Li+ like Na+
• Other 5% divided between sweat and feces
• Half-life: 12-27 hours
  – In chronic intoxication, half-life can be prolonged to up to 48 hrs

(Hedya et al., 2023)
EXPECTED SIDE EFFECTS

1. Dry mouth, polydipsia, and polyuria (70% of pts)
2. Fine Tremor (symmetric, postural) (25% of pts)
3. Weight gain (~70% of pts, average increased of 13 lbs)
4. Cognitive Impairment (memory, verbal learning, creativity, dose-dependent)
5. Renal Impairment – Decreased urine concentrating ability, sometimes to point of nephrogenic Diabetes Insipidus
6. Nausea, diarrhea (10-20% of patients, early in tx only)

(Gitlin, 2016)
DOES CHRONIC LITHIUM USE LEAD TO RENAL DYSFUNCTION?

• 2015 population-based cohort study (Clos et al.) showed renal dysfunction (reduced eGFR) is predicted by:
  – Baseline eGFR, age, comorbidities, co-prescription of nephrotoxic drugs, and episodes of lithium toxicity (defined as serum levels >0.80 mmol/L)
  – NOT duration of exposure
  – NOT average lithium level

• Li may not cause GFR reduction above natural life course, if levels not toxic; but studies are mixed on how Li is associated with ESRD
  – Note rates of ESRD in lithium-treated patients are improving as mean therapeutic doses are decreasing with time

(Gitlin, 2016)
(Clos et al., 2015)
CASE: LITHIUM INTOXICATION
LITHIUM TOXICITY: ETIOLOGIES

1. Excessive intake
   1. Suicidal intent
   2. Accidental ingestion of excessive amounts

2. Impaired excretion
   1. Sodium and volume depletion (dehydration)
      • Vomiting or diarrhea
      • Febrile illness
      • Renal insufficiency
      • Water restriction
      • Excessive sweating and/or exercise
      • Diuretics
      • Low sodium diet
      • Congestive Heart Failure
      • Medications that reduce GFR -> chronic toxicity

(Hedya et al., 2023)
**Clinical toxicity can be seen even when measured lithium level is normal – don’t treat the numbers!** Treat clinical symptoms. (Though 1.5 mmol/L is often called Li intoxication)

(Alexander, 2008; Foulser, 2017)
VICIOUS CYCLE OF LITHIUM TOXICITY

• Li can induce nephrogenic diabetes insipidus
• Decreased urine concentrating capacity →
• Dehydration as well as decreased excretion of lithium →
• More injury to kidney from both increased lithium and decreased blood volume, causing more impaired GFR →
• Toxicity builds

(Hedya et al., 2023)
TREATMENT

1. Admission to hospital for any signs of lithium toxicity (even if normal serum lithium level!)
   1. ICU if moderate or severe sx

2. IV fluids (forced diuresis)

3. No role for activated charcoal. Rarely, might do bowel irrigation

4. If severe sx (seizure, AMS, coma) OR if sx and serum Li is 2.5 mmol/L or more OR if serum Li is 4 mmol/L or more, will do hemodialysis

(Hedya et al., 2023)
(Tondo, 2019)
PREVENTING LITHIUM TOXICITY

1. Excessive intake
   1. Suicidal intent
   2. Accidental ingestion of excessive amounts

2. Impaired excretion
   1. Sodium and volume depletion (dehydration)
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   • Febrile illness
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   • Diuretics
   • Low sodium diet
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OPPORTUNITIES FOR INTERVENTION?
LITHIUM AND CLIMATE CHANGE

1. Dehydration elevates risk of Li toxicity
2. Increased exposure to heat from increased ambient temperatures and increased frequency and severity of extreme heat events (heat waves)

(CDC Extreme Heat Guidebook, 2016; Hayes et al., 2018)
PREVENTION & HARM REDUCTION

1. **Assess**: Talk to patient about environmental heat exposures

2. **Counsel**: Hydration and cooling recs →

3. **Prepare**: Help patients identify cooling centers and LIHEAP programs

4. **Monitor**: Consider heat in periods to watch closely for signs of toxicity, timing to redraw Li levels

(CDC Extreme Heat Guidebook, 2016)
PREVENTION IN LIGHT OF CLIMATE CHANGE: WEIGHING LITHIUM VS ANTIPSYCHOTICS

1. Antipsychotics and other mood stabilizers (anti-epileptics) impair central thermoregulatory processes, as well as decrease sweating (our main cooling mechanism!)
   → mortality from heat exhaustion, heat stroke
   – Dopaminergic and serotonergic pathways implicated

2. Lithium has not been established to impair central thermoregulation or impair sweating

(Bouchama et al., 2007)
PREVENTION: CO-MORBIDITIES TO LOOK OUT FOR TO AVOID INDUCED TOXICITY

1. CHF or renal failure (diuretics, volume shifts)
2. Renal clearance of lithium decreased in elderly patients
   - Half-life: 58 hrs in elderly, compared to 12-27 hrs in non-elderly
   - Lower target serum levels to 0.5-0.8 mmol/L
3. Acute illness - fever above 38°C, dehydration, diarrhea
   - Best to decrease dose by half or hold dose
4. Surgery (with general anesthesia) – stop 48-72 before due to NPO
5. Medication interactions which increase level:
   - NSAID, diuretics (thiazides, but caution with all), ACE-inhibitors, metronidazole, carbamazepine, phenytoin, and methyldopa
6. Pregnancy

(Tondo, 2019)
(Hedya et al., 2023)
Pregnancy:

1. Monitor Li blood levels and Cr frequently (once every 3 weeks) until 34 weeks, and then at least once weekly until delivery.
2. Before 17 weeks of pregnancy, anticipate progressively decreasing lithium levels. Afterwards, expect lithium levels to begin increasing.
3. Li blood levels should be maintained using a therapeutic blood level as low as possible and based on the personal history of the patient. It is therefore important to obtain preconception (reference) Li and creatinine blood levels, and the corresponding Li doses.
4. Consider twice-daily Li dosing to minimize peak lithium blood levels.
5. Increase the frequency of Li and Cr blood level monitoring for women exhibiting signs of preterm birth, pre-eclampsia, dehydration or other illnesses that can affect renal function.

Delivery/postpartum:

1. Obtain Li blood levels after delivery and twice weekly during the first 2 postpartum weeks.
2. Consider increasing the target therapeutic Li blood level immediately after delivery and during the first month postpartum to optimize relapse prevention (for example $\geq 0.8$ mmol/L).
3. Be aware of pharmacokinetic interactions with other medications such as non-steroidal anti-inflammatories

**Risk of congenital malformations, particularly Ebstein anomaly, if Li in use during first trimester**

(Wesseloo et al., 2017)
QUESTIONS?