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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

TREATMENT WITH LITHIUM AND LITHIUM TOXICITY PREVENTION

EMILY SCHUTZENHOFER, MD MPH, PGY-5

UW CONSULTATION-LIAISON PSYCHIATRY FELLOWSHIP

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

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.

Mark Duncan MD
Rick Ries MD
Kari Stephens PhD
Barb McCann PhD
Anna Ratzliff MD PhD
Betsy Payn MA PMP
Esther Solano
Cara Towle MSN RN

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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)

EVIDENCE

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)

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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)

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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)

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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)

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CASE: LITHIUM INTOXICATION

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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)

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LITHIUM TOXICITY

	Acute/Acute on Chronic	Chronic
Thyroid	None	Hypothyroidism
GI	Nausea, vomiting, abdominal pain, diarrhea	Minimal
CNS	Rare, if seen then same symptoms as chronic	Tremor, ataxia, confusion, agitation, neuromuscular excitability, seizures, coma
Cardiac	Rare: QTc prolongation, arrhythmia, T-wave changes	Myocarditis
Heme	Leukocytosis	Aplastic anemia
Renal	Urine concentrating defect	Chronic interstitial nephritis, nephrogenic diabetes insipidus, renal failure
Skin	None	Dermatitis, localized edema
Recovery	Rapid	Delayed, possible incomplete resolution

HYPERCALCEMIA

COARSE TREMOR

SINUS NODE DYSFUNCTION

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)

EMBoardsBombs.com

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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)

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TREATMENT

1. Admission to hospital for any signs of lithium toxicity (even if normal serum lithium level!)
    1. ICU if moderate or severe sxs
2. IV fluids (forced diuresis)
3. No role for activated charcoal. Rarely, might do bowel irrigation
4. If severe sxs (seizure, AMS, coma) OR if sxs 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)

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PREVENTING LITHIUM TOXICITY

1. Excessive intake
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    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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        - Medications that reduce GFR -> chronic toxicity

OPPORTUNITIES FOR INTERVENTION?

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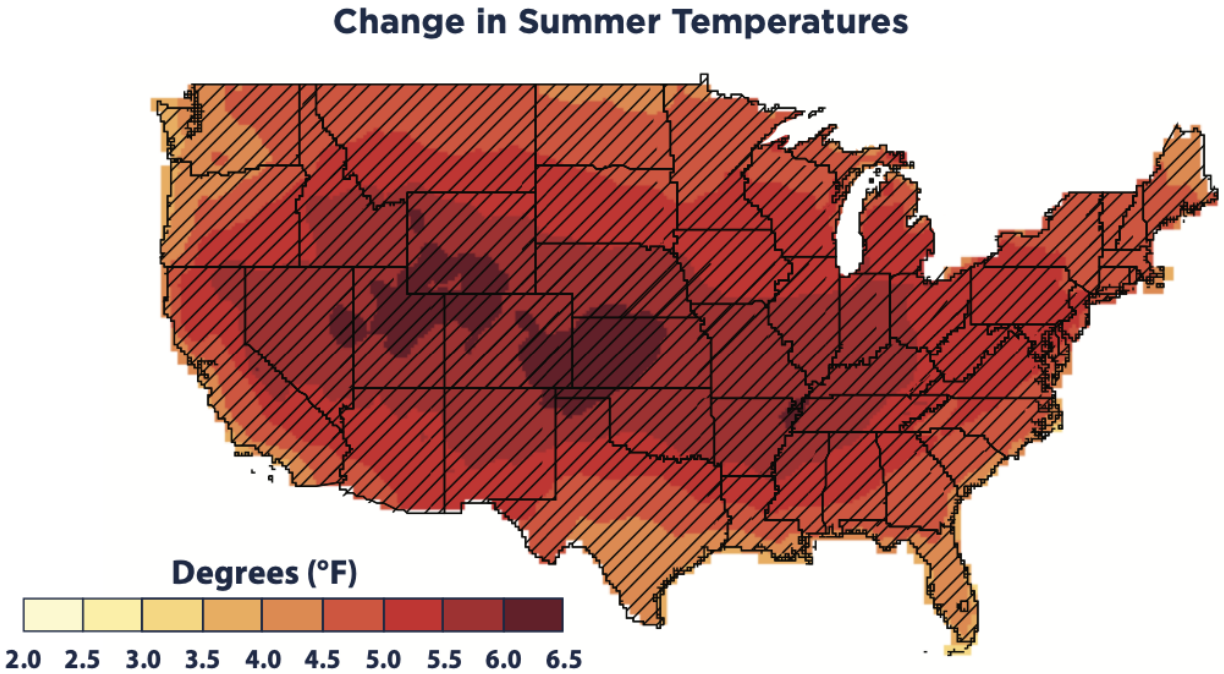
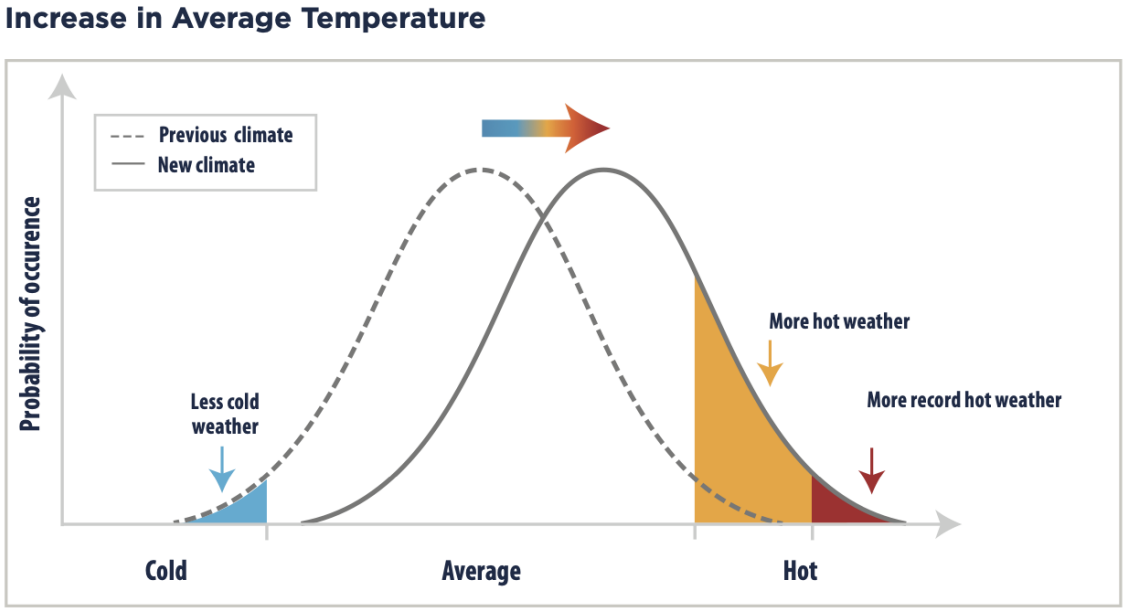
LITHIUM AND CLIMATE CHANGE

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)





When average temperatures increase, the average temperature of "hot weather" and "record hot weather" will become even hotter. Source: IPCC, 2001[7]

(CDC Extreme Heat Guidebook, 2016; Hayes et al., 2018)

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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

Do

- Use air conditioners or spend time in air-conditioned places, such as cooling centers, malls, or libraries.
- Use electric fans to provide comfort when the temperature is below 95°F.[18] Fans can make sweat evaporate more quickly from your body. More evaporation means more heat can leave your body.
- Take a cool shower or bath to help cool off.
- Minimize direct exposure to the sun.
- Stay hydrated—drink water or beverages **without** caffeine, sugar, or alcohol throughout the day.
- Eat light, cool, and easy-to-digest foods such as fruit or salads.
- Wear loose-fitting, light-colored clothes.
- Know the symptoms of heat-related illnesses and the appropriate responses.
- Check the local news for health and safety updates.[13]

(CDC Extreme Heat Guidebook, 2016)

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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)

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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)

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LITHIUM AND PREGNANCY

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 $\geqslant$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)

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QUESTIONS?

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