Don't You (Forget About Me): Lithium in Contemporary Psychiatry
Learning Objectives

• Implement dosing strategies for lithium that maximize efficacy, tolerability, and safety

• Apply appropriate monitoring strategies for patients receiving lithium

• Apply management strategies for the side effects of lithium in order to optimize tolerability and adherence
Patrick is a 54-year-old patient with a history of bipolar II disorder. He recently began taking lithium with good response and is curious about how lithium works to stabilize mood. You explain to him that the mechanism of action of lithium is thought to involve:

1. Reduction in arachidonic acid turnover
2. Inhibition of glycogen synthase kinase (GSK) 3β
3. Inhibition of inositol monophosphatase (IMP)
4. Inhibition of protein kinase C (PKC)
5. Modulation of serotonergic neurotransmission
6. All of the above
7. None of the above

Pretest Question 1
A 24-year-old man with bipolar disorder is being initiated on lithium, with monitoring of his levels until a therapeutic serum concentration is achieved. Once the patient is stabilized, how often should his serum lithium levels be monitored (excluding one-off situations such as dose or illness change)?

1. Every month
2. Every 6-12 months
3. Every 1-2 years
4. Routine monitoring is not necessary
A 36-year-old woman has been taking lithium for 3 years. Her most recent laboratory results reveal that she has polyuria. Based on this fact, what might be the best dosing schedule and formulation option for this patient?

1. Once-daily, immediate-release
2. Twice-daily, immediate-release
3. Once-daily, sustained-release
4. Twice-daily, sustained-release
Postulated Mechanisms of Action of Lithium
Mechanisms
Postulated Mechanisms

• Inositol monophosphatase (IMP) inhibition
• Glycogen synthase kinase (GSK) 3β inhibition
• Protein kinase C (PKC) inhibition
• Reduction in arachidonic acid turnover
  – Li ↓ phosphatidylinositol turnover 83% and phosphatidylcholine by 73%, while VPA achieves ↓ of 34% and 36%, respectively
• 5HT effects
  – Li increases 5HT presynaptic release through desensitizing actions at 5HT1B sites; it also antagonizes mouse behaviors induced by the administration of selective 5HT1B agonists

Efficacy of Lithium in Bipolar Disorder

How Does it Compare to Other Mood Stabilizers?
Lithium Reduces Suicide More Effectively Than DVX or CBZ

• Study sample: 20,638 health plan members (2 sites) age ≥ 14 years with at least 1 outpatient diagnosis of bipolar disorder
  – All subject records must reflect at least 1 filled prescription for lithium, divalproex, or carbamazepine from 1/1/1994–12/31/2001

Goodwin FK et al. JAMA 2003;290:1467-73.
Results: Lithium vs. Divalproex

• Unadjusted rates were greater during treatment with divalproex than during treatment with lithium for:
  
  – Emergency department suicide attempt*
    • 31.3 vs. 10.8 per 1000 person-years; p<.001
    • Adjusted hazard ratio 1.8 (95% CI 1.4–2.2, p<.001)
  
  – Suicide attempt resulting in hospitalization
    • 10.5 vs. 4.2 per 1000 person-years; p<.001
    • Adjusted hazard ratio 1.7 (95% CI 1.2–2.3, p=.002)
  
  – Suicide death
    • 1.7 vs. 0.7 per 1000 person-years; p=.04
    • Adjusted hazard ratio 2.7 (95% CI 1.1–6.3, p=.03)

*Site 1 only (n=16,248) because codes for suicide attempt were not included on encounter forms for Site 2 for the majority of the study period

Goodwin FK et al. JAMA 2003;290:1467-73.
Results: Lithium vs. Carbamazepine

• Unadjusted rates were greater during treatment with carbamazepine than during treatment with lithium for:
  
  – Emergency department suicide attempt*
    • 22.1 vs. 10.8 per 1000 person-years; p<.001
    • Adjusted hazard ratio 1.4 (95% CI 1.0–2.0, p=.09)
  
  – Suicide attempt resulting in hospitalization
    • Adjusted hazard ratio 2.9 (95% CI 1.9–4.4, p<.001)
  
  – Suicide death
    • Adjusted hazard ratio 1.5 (95% CI 0.3–7.0, p=.61)

Note: With smaller sample sizes in the CBZ cohort, certain results are statistically not significant

*Site 1 only (n=16,248) because codes for suicide attempt were not included on encounter forms for Site 2 for the majority of the study period

Goodwin FK et al. JAMA 2003;290:1467-73.
Lithium Prevents Suicide: Meta-analysis

Risk of suicides & attempts was 5 times higher among subjects not treated with lithium

1. All suicidal acts: \( RR = 4.91 \) (95% CI 3.82–6.31, \( p < 0.0001 \))
   - Completed: \( RR = 4.86 \) (95% CI 3.36–7.02, \( p < 0.01 \))
   - Attempted: \( RR = 4.98 \) (95% CI 3.56–6.96, \( p < 0.01 \))

2. Bipolar: \( RR = 5.34 \) (95% CI 3.59–7.93, \( p < 0.01 \))

3. MDD/SAD: \( RR = 4.66 \) (95% CI 3.43–6.33, \( p < 0.01 \))

4. Reduced lethality
   - All studies: 2.5-fold reduction by lithium
   - Bipolar: 2.9-fold reduction by lithium

MDD: major depressive disorder; SAD: schizoaffective disorder

Efficacy of Lithium in Bipolar Disorder: Summary

• Established efficacy in acute mania
• Established efficacy for mania prophylaxis
• Effects are modest in bipolar depression
• Lithium has proven anti-suicide data, suggesting that its impact on suicidality may be somewhat independent of its modest antidepressant properties
  – Lithium is superior to other agents, including divalproex, for suicide reduction
Target Levels of Lithium

How to Dose Within a Narrow Therapeutic Index
"Consensus" Recommendations

Acute Mood Episode Target Levels

• Mania: recommended 1.0–1.5 mEq/L
  – Limited dose-finding studies
  – Efficacy demonstrated for levels up 2.0 mEq/L, but tolerability is poor at levels >1.5 mEq/L
  – Response in 3–7 days, depending on method of treatment initiation
  – Loading is possible! (and will be discussed later)

• Depression: recommended 0.6–1.0 mEq/L
  – Same as maintenance dosing
  – No dose-response studies

Maintenance Levels in Bipolar Disorder

• 0.7/0.8–1.0 mEq/L have lower rates of relapse
  – Based on 7 studies of patients randomly assigned to
different serum levels during long-term follow-up

• Some studies (but not all) show higher relapse
  rates at lower levels

• No a priori way to determine who will do well at
  lower vs. higher levels

• Increased side effects at higher maintenance
  levels, especially GI, tremor, and metallic taste

Advantages of Single Daily Dosing

• Compared with multiple-dose schedules, single-dose schedules have:
  – Same PK properties
  – Same brain lithium concentrations
  – Increased adherence
  – Less polyuria
  – Possibly less risk of renal damage
  – Lower dose by 25% (if administered at night)
    • Reduces peak-related and overall adverse effects

Initiating Treatment: Can Lithium Be Loaded?

• Only 2 studies have examined loading strategies
  – Moscovich et al: based dosing in 9 patients on clinical data (age, gender, weight) without a specific formula
Can Lithium Dosing Be Loaded?

• Formula of 30 mg/kg in 3 divided doses of Lithobid at 4 pm, 6 pm, and 8 pm
  – Predicted to achieve 12-hour trough level of 0.9–1.1 mEq/L

• Demographics
  – N = 38 (20 M/18 F) inpatients
  – Mean age: 36.2 ± 2.95 yrs
  – Mean weight: 70.1 ± 3.50 kg
  – Calculated creatinine clearance: 46–128 mL/min
  – Female loading doses: 1200–2400 mg
  – Male loading doses: 1800–3000 mg

Can Lithium Dosing Be Loaded?

- No dropouts!
- No patient experienced any adverse effects during the loading procedure or in the 12 hours afterwards
- Males
  - 12-hour levels range: 0.58–1.10 mEq/L
  - Mean error: 0.16 ± 0.09
- Females
  - 12-hour levels range: 0.45–1.29 mEq/L
  - Mean error: 0.28 ± 0.14
  - 3 of 4 with elevated levels (1.28–1.40) were obese

Lithium Loading: Practical Data

• Auckland practice guideline used 30 mg/kg loading strategy (max daily dose 2000 mg) based on review of outcomes in patients treated with loading (n=12) vs. usual titration (n=15)

• Faster time to therapeutic levels in loading group
  – Mean dose on day 2: 1679 mg loading vs. 994 mg titration

• Length of stay significantly shorter for loading
  – 20.2 ± 7.11 days vs. 39.9 ± 24.2 days (p=.011)

• Side effect rates higher for loading (63.6%) vs. titration (38.7%) (p=0.05)
  – Higher than in Kook et al.; likely related to use of standard release form and 1 vs. 3 daily doses

Lithium Levels and Acute Toxicity

Causes

- Overdose
- Kinetic drug interactions
- Sodium depletion (diuretics, diarrhea, sweating)

Symptoms by serum level (mEq/L)

- 1-5 – 2.0: mild, managed by dose interruption
- 2.1 – 2.9: EKG monitoring, supportive measures
- ≥ 3.0: ICU stay, dialysis

Review of 213 cases (1948-84)

- Complete recovery with mean max level of 2.5 mEq/L
- Permanent CNS sx with mean max level of 3.2 mEq/L
- Death with mean max level of 4.2 mEq/L

Signs of Acute Lithium Toxicity

Peripheral signs
• EKG: bradycardia due to decreased sinus node automaticity
• Fasciculations

CNS signs
• Cortical depression
  – Apathy, drowsiness
  – Lethargy
  – Stupor, coma, death
• Upper motor neuron toxicity
  – Hypertonia, hyperreflexia
  – Muscle rigidity, myoclonus
  – Spasticity
• Cerebellar toxicity
  – Ataxia, dysmetria
  – Dysarthria, tremor
## CNS Outcomes of Acute Lithium Toxicity

(≥ 6-Month Follow-Up)

<table>
<thead>
<tr>
<th>Age (Gender)</th>
<th>Sequelae</th>
<th>Max Lithium Level (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 (male)</td>
<td>Ataxia, tremor, dysarthria</td>
<td>7.6</td>
</tr>
<tr>
<td>50 (female)</td>
<td>Ataxia, tremor, choreoathetosis</td>
<td>5.0</td>
</tr>
<tr>
<td>53 (female)</td>
<td>Ataxia, choreoathetosis, hyperreflexia</td>
<td>2.3</td>
</tr>
<tr>
<td>55 (female)</td>
<td>Ataxia</td>
<td>2.9</td>
</tr>
<tr>
<td>39 (male)</td>
<td>Ataxia</td>
<td>6.2</td>
</tr>
<tr>
<td>?? (male)</td>
<td>Dysarthria, spasticity, memory impairment</td>
<td>4.8</td>
</tr>
<tr>
<td>62 (female)</td>
<td>None</td>
<td>2.7</td>
</tr>
<tr>
<td>38 (male)</td>
<td>Ataxia, choreoathetosis, dysmetria</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Permanent CNS sx after severe overdose may relate to white matter spongiform changes and cerebellar Purkinje cell loss

Monitoring Lithium Levels

• CNS to serum ratio: 0.45–0.56 (± 0.12–0.24)
  – May be somewhat higher during periods of euthymia

• Brain concentrations correlate best with serum lithium level (r=0.66), not with RBC lithium level (r=0.44)

• Initial monitoring: every 1–2 weeks until desired serum concentration is achieved, then every 2–3 months for the first 6 months

• Stable monitoring: every 6–12 months

• One-off monitoring after dose change, other medication change, illness change (not before 1 week)

# Factors Affecting 12-Hour Trough Levels

## Time of Blood Draw

<table>
<thead>
<tr>
<th>Time Since Last Dose</th>
<th>10 hrs</th>
<th>12 hrs</th>
<th>14 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>1.28</td>
<td>1.20</td>
<td>1.12</td>
</tr>
</tbody>
</table>

## Dosing Schedule

<table>
<thead>
<tr>
<th>Author</th>
<th>QD</th>
<th>BID</th>
<th>TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amdisen</td>
<td>1.37</td>
<td>1.07</td>
<td>1.00</td>
</tr>
<tr>
<td>Swartz</td>
<td>0.90</td>
<td>0.70</td>
<td>--</td>
</tr>
<tr>
<td>Greil</td>
<td>1.04</td>
<td>0.81</td>
<td>--</td>
</tr>
</tbody>
</table>

## Preparation

Slow-release: 10% higher mean troughs (≥30% increase in 1/5 of patients)
Side Effects of Lithium

Benign but Common
Managing Common Lithium Side Effects

• Tremor: dose dependent
  – Modest dose reduction, avoid caffeine and other meds that increase tremor
  – Propranolol up to 160 mg/day

• GI distress: dose dependent
  – Consider sustained-release lithium or BID dosing (increased severity of polyuria with either)

• Hair loss
  – Daily multivitamin (≥100 mcg selenium, 15 mg zinc)
Managing Common Lithium Side Effects

• Metallic taste
  – Try modest dose reduction

• Skin reactions
  – Try usual acne meds

• Weight gain (mean 1 year ↑ up to 4 kg, with 13% or more gaining >5%)
  – Good luck!

• Peripheral edema (10% incidence)
  – Try modest dose reduction, maintain adequate Na+ intake

Lithium ECG Effects

• Benign and reversible T-wave flattening in approximately 20% of patients and the appearance of U waves; not related to depletion of sodium or potassium

• At therapeutic levels, rare reports of effects on cardiac conduction and pacemaker automaticity
  – Pronounced during overdose; lead to sinus bradycardia, atrioventricular blocks, and possible cardiovascular compromise

• Routine ECG monitoring not recommended in younger patients, but may be considered in older patients, particularly those with a history of arrhythmia or coronary heart disease

Lithium Thyroid Effects

• Lithium interferes with the iodination of tyrosine and therefore the synthesis of thyroxine

• Most remain euthyroid; only 7–10% develop overt hypothyroidism and 23% have subclinical disease, with women at 3–9 times greater risk

• No plateau in the incidence of hypothyroidism in studies covering up to 10 years of exposure

• Ongoing monitoring of TSH and free T4 is recommended throughout lithium treatment

Pregnancy and Lactation (1)

- Lithium is classified as risk category D
- Basal risk of Ebstein's anomaly is ~ 1 per 20,000 live births and probably not above 1 per 2500 on lithium
- Typically detectable in utero by ultrasonography and often surgically correctable after birth
- Important to evaluate the risk of inadequate prophylaxis for bipolar disorder and the subsequent risk that mania poses to the patient and the fetus
- Maternal polyuria may be exacerbated by lithium
  - Concomitant use of lithium with medications that waste sodium or a low-sodium diet can contribute to maternal and neonatal lithium intoxication

• Significantly lower Apgar scores are observed in infants with levels >0.64 mEq/L at delivery

• Most recommend withholding lithium therapy for 24–48 hours before delivery
  – Results in a mean decrease of 0.28 mEq/L in maternal lithium concentrations

• Physical and CNS sequelae of late-term neonatal lithium exposure are reversible once lithium exposure has ceased; no long-term neurobehavioral consequences are observed based on extended follow-up (5 years)

• Lithium is secreted in breast milk; low infant serum lithium levels are not associated with any observable physical or behavioral effects

Rarer Lithium Side Effects

• Hypercalcemia
  – Usually asymptomatic; possibly related to lithium effects on parathyroid function, including hyperplasia and adenomas
  – Rarely a need for medical intervention
  – Monitoring of serum calcium every 6–12 months is recommended

• Intracranial hypertension
  – Stop drug

Renal Effects of Lithium
Renal Handling

• Freely filtered and 80% reabsorbed in the proximal tubules (competes with Na+ for reabsorption)

• Distal reabsorption in collecting ducts through epithelial sodium channels (ENaC) (competes with Na+)

• Levels increased by:
  – Hyponatremia (less competition with Na+)
  – ACE inhibitors (lisinopril > others)
  – Distal loop diuretics (cause Na+ wasting, thereby increasing reabsorption of both Na+ and lithium proximally)
    • Triamterene, amiloride, spironolactone, methylxanthines
  – Ibuprofen, naproxen, indomethacin
  – Less effects: ASA, loop diuretics
Normal Renal Parameters

- **eGFR**: ≥60 mL/min (typically 90–140)
- **Urine osmolality (concentrating ability)**
  - Normal: >750 mOsm/kg of H2O
  - Partial NDI: 300–750 mOsm/kg of H2O
  - NDI: <300 mOsm/kg of H2O
- **Creatinine clearance**
  - Men: 97–137 mL/min
  - Women: 88–128 mL/min
- **24-hr urine volume**: up to 2000 mL

## Renal Sequelae: Single vs. Multiple Daily Dosing

<table>
<thead>
<tr>
<th></th>
<th>Aarhus (n=95)</th>
<th>Copenhagen (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SR, BID Dosing</td>
<td>IR, QD Dosing</td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
</tr>
<tr>
<td>F/M</td>
<td>45/50</td>
<td>21/7</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>43.2</td>
<td>12.1</td>
<td>50.5</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>73.7</td>
<td>16.8</td>
<td>69.7</td>
</tr>
<tr>
<td>Li use (yrs)</td>
<td>6.5</td>
<td>3.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Li dose (mg)</td>
<td>1125</td>
<td>349</td>
<td>960</td>
</tr>
<tr>
<td>12-hr Li trough</td>
<td>0.82</td>
<td>0.19</td>
<td>0.87</td>
</tr>
<tr>
<td>Urine vol (L/day)</td>
<td>2.83 (median value)</td>
<td>2.38 (median value)</td>
<td>0.05</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>99.5</td>
<td>26.6</td>
<td>90.3</td>
</tr>
<tr>
<td>Li Cl (mL/min)</td>
<td>21.2</td>
<td>7.6</td>
<td>21.1</td>
</tr>
</tbody>
</table>

**Conclusion:** The 2 regimens did not impact GFR or proximal reabsorption (Li clearance) differently, but urine volume was 19% lower in patients given conventional tablets once daily than in those given slow-release tablets twice daily.

Renal Sequelae After 7 Years

- 7-yr follow-up of previously lithium naïve patients, primarily on SR preparations; data analyzed for those on lithium 4 years (n=39)
- Mean dose 870 mg; mean level 0.68 mEq/L

<table>
<thead>
<tr>
<th></th>
<th>Before Lithium</th>
<th>After Lithium</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr Cl (mL/min)</td>
<td>85.4 ± 22.1</td>
<td>82.6 ± 19.6</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Cr (µmol/L)</td>
<td>87.4 ± 10.6</td>
<td>91.8 ± 12.7</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Urine Vol (mL/24 h)</td>
<td>1697 ± 543</td>
<td>2086 ± 726</td>
<td>NS</td>
</tr>
<tr>
<td>Concentrating Ability (after DDAVP test) (mOsm/kg H2O)</td>
<td>845 ± 170</td>
<td>764 ± 151</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Conclusions
- Nonsignificant changes in Cr clearance
- 5% increase in Cr, weakly related to age (r=0.13) and lithium concentration (r=0.19)
- Increased urinary volume and decreased concentrating ability; most change in urine Osm in first 2 years of Tx, stable afterwards

Renal Sequelae After Another 10 Years

Follow-up of cohort of 46 subjects reassessed 10 years after prior evaluation with renal biopsy; at second follow-up, mean exposure was 19.5 years of Li use

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>27</td>
</tr>
<tr>
<td>Still on Li</td>
<td>19</td>
</tr>
<tr>
<td>F/M</td>
<td>19/8</td>
</tr>
<tr>
<td>Mean age</td>
<td>58</td>
</tr>
<tr>
<td>Li use (yrs)</td>
<td>19.5</td>
</tr>
<tr>
<td>Li dose (mg)</td>
<td>708.75</td>
</tr>
<tr>
<td>12-hr Li trough</td>
<td>0.80</td>
</tr>
<tr>
<td>QD dosing</td>
<td>16 (of 19)</td>
</tr>
<tr>
<td>IR lithium</td>
<td>17 (of 19)</td>
</tr>
</tbody>
</table>

## Renal Sequelae After Another 10 Years

<table>
<thead>
<tr>
<th></th>
<th>Creat (mmol/L)</th>
<th>24-hr Urine Vol (mL)</th>
<th>GFR (mL/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>On Li</td>
<td>.090 ± .01</td>
<td>.110 ± .02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3033</td>
</tr>
<tr>
<td>Off Li</td>
<td>.094 ± .02</td>
<td>.130 ± .07</td>
<td>3101</td>
</tr>
<tr>
<td>QD Li Dosing</td>
<td>.093 ± .01</td>
<td>.107 ± .01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2319</td>
</tr>
<tr>
<td>BID/TID Dosing</td>
<td>.110 ± .02</td>
<td>.150 ± .07&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4375</td>
</tr>
</tbody>
</table>

<sup>a</sup> p<.001; <sup>b</sup> p<.05

- Age-dependent decrease in GFR, increase in Cr, all of which were stable over the nearly 20 years of exposure and matched expected changes based on age
- Urinary volume unchanged over 10 years
- Single dose 33% less urinary volume
- Prior biopsy data showed greater tubular atrophy in multiple dose

Does Urinary Volume Always Remain Unchanged After the First 5–10 Years of Treatment?

Cross-sectional data from 45 lithium-treated mood disorder patients

<table>
<thead>
<tr>
<th></th>
<th>Ur Osm &gt; 750 mOsm/kg</th>
<th>Ur Osm 300 - 750 mOsm/kg</th>
<th>Ur Osm &lt; 300 mOsm/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M</td>
<td>19/11</td>
<td>5/8</td>
<td>2/0</td>
</tr>
<tr>
<td>Mean Age</td>
<td>43</td>
<td>51</td>
<td>48.5</td>
</tr>
<tr>
<td>Yrs Li Therapy</td>
<td>13.5 ± 2.4</td>
<td>20.8 ±2.7</td>
<td>25, 28</td>
</tr>
<tr>
<td>Creatinine</td>
<td>83 ± 3</td>
<td>95 ±5</td>
<td>135, 116</td>
</tr>
<tr>
<td>Plasma Osm</td>
<td>292 ±1</td>
<td>296 ± 2</td>
<td>298, 314</td>
</tr>
<tr>
<td>Vasopressin Level</td>
<td>6.5 ± 0.8</td>
<td>6.3 ±0.9</td>
<td>14.7, 18.2</td>
</tr>
<tr>
<td>Li Level</td>
<td>.73 ± .06</td>
<td>.83 ± .05</td>
<td>.71, 1.06</td>
</tr>
</tbody>
</table>

Comments

- Urine osmolality was lower in those with mean 20+ years of lithium exposure compared to 13.5 years
- Suggests that strategies to minimize polyuria (e.g., use of single daily dosing of immediate-release lithium) may be of benefit, even with long-term exposure, to minimize further decreases in urine concentrating ability

Who Gets More Than Expected Increases in Serum Creatinine?

• 114 Israeli patients
  – Diagnosis: bipolar n=71; MDD n=27; schizoaffective n=16
  – Mean follow-up: 16.75 ± 7.89 years
  – Mean age at lithium initiation: 43.1 ± 12.1

• Examined 2 groups based on long-term Cr:
  – No renal insufficiency (**NRI**)
  – Renal insufficiency (**RI**) defined as Creat ≥ 1.5 on 2 consecutive measures repeated 4-6 weeks apart

Who Gets More Than Expected Increases in Serum Creatinine?

Who Gets More Than Expected Increases in Serum Creatinine?

- **Risk factors for RI**
  - Hypertension or DM
    - 41.7% for RI vs. 22.0% for NRI (p=0.05)
  - Use of nephrotoxic medications
    - 33.3% for RI vs. 13.2% for NRI (p<0.05)

- **Not risk factors for RI**
  - Mean dose
  - Mean serum lithium level
  - Gender
  - Age at onset of lithium therapy
  - Psychiatric diagnosis

Does Renal Failure Occur?

• Rarely reported before 1990

• French data from dialysis centers indicate that lithium-induced nephropathy represented only 0.14–0.22% of all dialysis patients

• New Zealand data: 0.2%

• Factors
  – Age at onset of lithium therapy, mean daily dose, and mean serum level were not predictive
  – Low baseline Cr Cl seemed to be the only predictive variable

Managing Polyuria and Increased Creatinine
Renal Impact of Switching From Multiple to Daily Lithium Dosing

- Switched to single daily dosing for 12–18 months

<table>
<thead>
<tr>
<th>Group</th>
<th>Age Range</th>
<th>Mean Age</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>&lt; 5 years</td>
<td>43.8</td>
<td>21</td>
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<tr>
<td>II</td>
<td>5–10 years</td>
<td>45.6</td>
<td>14</td>
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<tr>
<td>III</td>
<td>11–22 years</td>
<td>55.7</td>
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<tr>
<th>Group</th>
<th>Male</th>
<th>Female</th>
<th>Baseline Creatinine</th>
<th>Final Creatinine</th>
<th>Baseline Urinary Vol</th>
<th>Final Urinary Vol</th>
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<tr>
<td>I</td>
<td>6</td>
<td>15</td>
<td>94.5 µmol/L</td>
<td>100.0 µmol/L</td>
<td>1865 mL</td>
<td>1380 mL</td>
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<td>72.8</td>
<td>70.9</td>
<td>2026</td>
<td>1827</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>10</td>
<td>99.0</td>
<td>107.0</td>
<td>3379</td>
<td>3275</td>
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<td></td>
<td>78.5</td>
<td>79.3</td>
<td>2785</td>
<td>2723</td>
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<tr>
<td>III</td>
<td>7</td>
<td>9</td>
<td>108.6</td>
<td>108.5</td>
<td>3371</td>
<td>3020</td>
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<td>77.9</td>
<td>84.2</td>
<td>2922</td>
<td>2988</td>
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</table>

Switching to Once-Nightly Dosing: Comments

• Greatest improvement in renal function (decrease in polyuria) seen for patients on lithium <5 years

• Study limitation: no control group
  – Although those on Li ≥5 years who switched to QHS dosing did not have significant decreases in urinary volume, the switch may have minimized further changes in renal function
Collecting Duct and Lithium: How NDI Occurs

- Li reabsorbed through epithelial sodium channels (ENaC) (1.5–2.0x greater permeability than Na+)

- Intracellular removal dependent on Na/K-ATPase; Li is a poor substrate for this pump → high intracellular levels

- Li accumulation leads to inhibition of GsK-3β; this enzyme controls water transport via AQP2 and sodium transport via ENaC; as a result, the cell becomes partially insensitive to aldosterone and vasopressin

- Amiloride blocks ENaC and may minimize renal injury and nephrogenic DI by ↓ intracellular Li levels

Amiloride for Polyuria

• Blocks ENaC and may minimize renal injury and NDI by decreasing intracellular Li levels
  – Practical issue: amiloride causes Na+ wasting, so may need to lower lithium dosage

• Consider when:
  – 24-hr volume >3 liters, especially >4 liters
  – Urine Osm <300 mOsm/kg (NDI)

• Starting dose: 5 mg/day

• Effective in studies at doses up to 20 mg/day; no significant change in lithium levels at doses ≤10 mg/day
  – Carefully watch Li levels due to potential for lithium toxicity secondary to Na+ wasting and increased lithium retention

Who Benefits From Lithium Discontinuation?

- Lepkifker et al. (n=114): after Li stopped or reduced in renal insufficiency group (Cr ≥1.5)
  - 12/24: improvement or stabilization of Cr in high normal range
  - 3/24: nonsignificant increases in creatinine
  - 9/24: further declines in renal function

- Presne et al. (n=74, mean exposure 19.8 years)
  - Creatinine clearance at time lithium was stopped
    - >40 mL/min: 5/7 improved
    - ≤40 mL/min: 12/18 experienced further declines
    - <25 mL/min: all experienced further declines

Managing Renal Parameters

• Normal eGFR is ≥60 mL/min

• Single estimations of eGFR can be unreliable, emphasizing need for serial monitoring

• As Cr Cl (or eGFR) approaches 40 mL/min, need to consider risks vs. benefits of stopping lithium

Managing Renal Parameters

• Dosing and preparation
  – Once-daily immediate-release lithium causes less polyuria

• Monitoring
  – BUN, Creat, and eGFR every 6 months, Li every 3 months
    • Strongly recommend annual 24-hr urine collection
    • Added workup for rise in Cr on 3 or more occasions
  – When eGFR is 30–59 mL/min, increase renal lab frequency to every 3 months (or more) and perform routine urinalysis

• Referral
  – eGFR drops >4 mL/min per year on 3 or more determinations
  – Rise in Cr on 3 or more occasions
  – Proteinuria or hematuria
  – eGFR <30 mL/min

Conclusions: Renal Issues

- BID or TID regimens or extended-release preparations: increased risk of non-progressive impairment in concentrating ability
  - Once-daily dosing has been the standard of care in Europe for over 20 years to minimize polyuria

- Long-term lithium use is not associated with changes in GFR in the majority of patients, even after 30 years of exposure
  - Lithium is associated with modest nonsignificant changes in serum creatinine proportional to age-predicted declines
  - 20% may experience greater than expected changes (creatinine creep), typically those with prior histories of lithium intoxication, comorbid illnesses that can impair renal function, or the use of nephrotoxic medications

- Difficulty with urine concentrating ability appears in the first 5 years of treatment and remains stable for a decade or more but may change over very long periods (e.g., 20 years)
  - Amiloride has evidence for treating lithium-induced NDI
Summary

• Lithium has therapeutic advantages, including superiority on reduction in suicidality

• Clinicians must educate patients about benefits and expected side effects

• The ability to manage common side effects is critical to keeping patients on lithium

• Once-daily dosing is possible and may have renal advantages

• Rapid loading (total dose of 30 mg/kg), split into several doses of 10 mg/kg, is feasible without side effects