BACK IN TIME: AN UPDATE ON THE USE OF LITHIUM
Learning Objectives

• Understand the data supporting lithium's use for suicidality and in rapid cycling patients

• Implement the latest findings from the literature to minimize risk of lithium-related renal dysfunction and manage polyuria

• Understand how to safely treat older patients with lithium and the neuroprotective benefits in that population
Please check out the APPENDIX section in the downloadable slides for additional information regarding the use of lithium.
Lithium and Suicidality
Swedish national registry study of 51,535 individuals with bipolar disorder followed from 2005-13 receiving treatment with lithium or valproate. Stratified Cox regression was used to estimate the hazard ratios of suicide-related events during treated periods compared with untreated periods.

**Sensitivity analyses:** Examined year of diagnosis, use of concomitant meds, varying definitions of bipolar Dx, mixed vs. non-mixed episodes, starting lithium within 1 year of BPD Dx, varying definitions of suicidal events, and the following:

- **Bias due to suicidality:** To test whether lithium was biased towards those with a suicide Hx, the main analysis was repeated excluding periods containing switch to lithium within 7, 14, and 30 days after a suicide attempt, respectively.

- **Monotherapy vs. combination:** Repeated analysis by defining medication periods with lithium alone, VPA alone, and lithium plus VPA. As patients on lithium monotherapy might be different from patients who have switched between lithium and valproate, the analysis was repeated for the subgroup with lithium monotherapy.

Lithium Reduces Suicidality More Effectively Than VPA

10,403 suicide-related events occurred in 4405 subjects

- The rate was significantly decreased by 14% during periods with lithium treatment: HR 0.86 (95% CI 0.78–0.95) but not VPA HR 1.02 (95% CI 0.89–1.15; p=0.038).
  - None of the sensitivity analyses showed any substantive difference from the main results. Analyses for lithium + VPA yielded no substantial difference from lithium alone.

- Patients had an increased rate of suicidal behavior within 30 days of lithium discontinuation (HR 1.33, 95% CI 1.09–1.61).

- Substance use: most events occurred in those with comorbid substance use (7976 events in 15,927 pts). Lithium also reduced events in this group (HR 0.84, 95% CI 0.75–0.94).

**Conclusions:** For valproate, there was no protective effect for suicide-related events, with a significant difference between lithium and valproate. Estimates suggested that 12% (95% CI 4% - 20%) of suicide-related events could have been avoided if patients had taken lithium during the entire follow-up.

Lithium Reduces Suicide More Effectively Than VPA, Olanzapine, or Quetiapine

• Propensity score (PS) adjusted and matched UK cohort using EHR data from 1995 - 2013. Included all patients with bipolar Dx prescribed lithium (n=2148), VPA (n=1670), olanzapine (n=1477), or quetiapine (n=1376) as maintenance mood stabilizer.

• The PS model was based on factors decided *a priori* to affect MD prescribing choice (sex, age, year, race/ethnicity, medical disease (CV, htn, CKD, thyroid, liver, DM2, seizure), EtOH use (by severity), illicit drug use, smoking status (by severity), BMI (grouped as < 25, 25-30, or > 30 kg/m²), anxiety Sx or Dx, depressive Sx or Dx, sleep disturbance, use of study drug at or before baseline, and h/o of previous self-harm).

• To remove patients with multiple drug exposures, individuals were excluded if they were prescribed more than one study drug at the start of follow-up or in the 28 days preceding this date.

Lithium Reduces Suicide More Effectively Than VPA, Olanzapine, or Quetiapine

Self-harm rate hazard ratio comparisons after PS adjustment and matching:

- VPA, olanz, quet vs. lithium: 1.51 (95% CI, 1.21-1.88)
- VPA vs. lithium: 1.31 (95% CI, 1.01-1.70)

Unintentional injury hazard ratio comparisons after PS adjustment and matching:

- VPA, olanz, quet vs. lithium: 1.19 (95% CI, 1.01-1.41)
- VPA vs. lithium: 1.34 (95% CI, 1.09-1.65)

Figure 2. Cumulative Self-harm Rate in Patients Prescribed Lithium vs Valproate, Olanzapine, or Quetiapine

<table>
<thead>
<tr>
<th></th>
<th>Valproate, olanzapine, or quetiapine fumarate</th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>4523</td>
<td>2148</td>
</tr>
<tr>
<td>1 y</td>
<td>2482</td>
<td>1458</td>
</tr>
<tr>
<td>2 y</td>
<td>1561</td>
<td>1066</td>
</tr>
<tr>
<td>3 y</td>
<td>1026</td>
<td>804</td>
</tr>
<tr>
<td>4 y</td>
<td>708</td>
<td>649</td>
</tr>
<tr>
<td>5 y</td>
<td>493</td>
<td>509</td>
</tr>
</tbody>
</table>
Lithium and Rapid Cycling
Issues With Older Literature on Rapid Cycling (RC)

• **Rapid cycling (RC):** First recognized in 1974 paper which associated RC with lower lithium response.⁵ 9/11 rapid cycling patients had a mood relapse compared to 18/44 non rapid cycling.

• **Issues in RC literature:** Only six randomized, controlled prospective studies have specifically examined treatment outcomes in RC bipolar patients, and many of these were small, statistically underpowered, or focused on those with a specific mood state (e.g., depressed). Much of the literature is naturalistic, or post-hoc analyses of RC patients in other bipolar studies.

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Do Rapid Cycling Bipolar Patients Respond to Lithium?

Data: Bipolar I or II adults followed from 1974-98 in a Stanley Foundation Network study in Sardinia (pop 1.6M). Those who used other mood agents ≥ 8 weeks at any time were excluded from the analysis.

- **Total Sample (n=360):** BP I: 60.6%; 63.6% F, 39.4%; mean 8.83 ± 8.38 years of historical mood info prior to study. Mean 4.49 ± 4.10 years of follow-up on lithium (pts seen q 2-3 months).

- **RC subgroup (n=56):** BP I 6.0% of total sample; BP II 30.3% of total sample; female 17.9% of sample; male 11.5% of sample. 30.4% of the RC group averaged ≥ 4 mood episodes per year prior to study entry.

# RC and Lithium Response

## Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>Episodes/Yr Mania/Hyp</th>
<th>Episodes/Yr Depression</th>
<th>Episode Duration Mania/Hyp (mos)</th>
<th>Episode Duration Depression (mos)</th>
<th>% Time Mania/Hyp</th>
<th>% Time Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>1.83 ± 1.79</td>
<td>2.08 ± 1.88</td>
<td>2.29 ± 1.50</td>
<td>3.09 ± 3.38</td>
<td>25.5 ± 18.2</td>
<td>34.9 ± 22.5</td>
</tr>
<tr>
<td>Non-RC</td>
<td>0.59 ± 0.47</td>
<td>0.58 ± 0.44</td>
<td>3.33 ± 2.05</td>
<td>5.16 ± 4.16</td>
<td>16.1 ± 16.0</td>
<td>21.9 ± 19.9</td>
</tr>
</tbody>
</table>

## Outcomes

1. The clinical status of RC and non-RC groups was comparable, including: % of time spent ill, the annual rate of mania, annual hospitalizations, percentage improvement in time spent ill

2. For RC patients, % time spent ill did not correlate with RC status (prior 12 months vs. historical), or baseline episode frequency: ≥ 3.5 episodes/yr were ill 23.0 ± 27.9%; fewer annual episodes were ill 18.6 ± 22.7% (p=.762)

3. RC patients had three times more depressive episodes/yr, and fewer RC pts had zero recurrences during follow-up compared to the non-RC group (17.9% vs. 31.6%, p=.04)

Lithium vs. VPA: A 20-Month Double-Blind Maintenance Trial in RC Patients

Subjects: 254 adults with RC bipolar disorder I or II, defined as any h/o ≥ 4 episodes in the past 12 months, and at least one episode of mania, hypomania, or mixed episode in the 3 months prior to study entry.

Exclusions: Prior h/o combined lithium + divalproex use, intolerance of lithium level 0.8 meq/L or VPA level 50 mcg/ml; substance dependence criteria for EtOH or drugs in the prior 6 months; on steroids; pregnant or planning to become pregnant.

Method - Two phase study design:

• Open-label stabilization: subjects initially titrated on lithium to target level 0.80 meq/L over 4-6 weeks, then divalproex added to target level 50 mcg/ml over 4-6 weeks. During this phase 28% were lost due to poor adherence, 26% for nonresponse (19% depression, 7% mania/hypo/mixed), and 19% for adverse effects.

• Double-blind maintenance: For those who maintained stability for 4 consecutive weeks, with HAM-D$_{24}$ ≤ 20, YMRS ≤ 12, and serum drug levels at or above the targets. 24% (n=60) met these criteria and were randomized to lithium or divalproex monotherapy, stratified by bipolar I or II type.

Lithium vs. VPA: A 20-Month Double-Blind Maintenance Trial in RC Patients

**Outcomes:** There were no between group differences in time to treatment for a mood episode, time to discontinuation for any reason, nor was there any impact of bipolar I vs. II diagnosis.

**Conclusion:** "The hypothesis that divalproex is more effective than lithium in the long-term management of rapid-cycling bipolar disorder is not supported by these data. Preliminary data suggest highly recurrent refractory depression may be the hallmark of rapid-cycling bipolar disorder."

Lithium and Neuroprotection
The Hypotheses

1. Based on positive animal and human data, very low exposure (e.g., 300 µg/d) is sufficient to exert neuroprotective effects across a wide range of diseases and disease models.¹

2. This may be related to lithium’s inhibitory effects on glycogen synthase kinase (GSK) 3-β, an enzyme implicated in the pathogenesis of neurodegenerative disorders due to effects on neurotrophic response, autophagy, oxidative stress, inflammation, and mitochondrial function.¹

3. Lithium has been shown to increase gray matter volume in healthy humans and those with bipolar disorder.² In addition, the less active GSK3-β rs334558*C gene promoter SNP, and the long-term administration of lithium, both positively influence white matter structure by tensor diffusion imaging.²


2. **Inclusion:** Bipolar diagnosis (based on one inpt or 2 outpt claims), no diagnosis of dementia or MCI, and not receiving dementia-related medications or services during the prior year. Schizophrenia or other psychotic disorders were excluded. Each follow-up day was classified by past-year cumulative lithium use (0, 1-60, 61-300, and 301-365 days). Anticonvulsants commonly used as mood stabilizers served as a negative control.

3. **Demographics:** Mean age 60.4 yrs, 66.4% white, 71.4% female. There were 66,258 person-years of follow-up (**mean 19 months**). 1538 patients (3.7%) were newly diagnosed with dementia during follow-up (2.32 cases per 100 patient-years).

4. **Results:** 301-365 days of lithium exposure significantly reduced dementia risk (**HR = 0.77**, 95% **CI 0.60-0.99**).

Lithium, Bipolar Disorder & Dementia Risk: Meta-Analysis

1. **Meta-analysis** of 10 studies (6859 BD; 487,966 controls) to test whether bipolar disorder is a risk factor for dementia. 5 studies (6483 lithium; 43,496 non-lithium) were then examined to look at the potential protective effect of lithium in bipolar disorder.

2. **Results:**
   - **Bipolar disorder increases dementia risk almost 3-fold:** OR 2.96 (95% CI 2.09–4.18, P < 0.001)
   - The risk of progression to dementia is higher in bipolar disorder than in major depressive disorder. Moreover, the number of mood episodes predicted the development of dementia in bipolar disorder.
   - **Treatment with lithium decreases the risk of dementia in bipolar disorder by 50%:** OR: 0.51 (95% CI: 0.36–0.72, P < 0.0001)

Impact of Serum Levels and Kinetics on Risk of Renal Dysfunction
Terminology of Chronic Kidney Disease

- Individuals with GFR <60 ml/min/1.73 m² for 3 months are classified as having chronic kidney disease (CKD)

- When discussing lithium’s renal impact the term “renal failure” is alarming and inappropriate, as renal failure (as defined below) is a rare outcome

- The term renal dysfunction is preferred

<table>
<thead>
<tr>
<th>Stage</th>
<th>eGFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Normal</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2. Mild</td>
<td>60-89</td>
</tr>
<tr>
<td>3a. Moderate</td>
<td>45-59</td>
</tr>
<tr>
<td>3b. Moderate</td>
<td>30-44</td>
</tr>
<tr>
<td>4. Severe</td>
<td>15-29</td>
</tr>
<tr>
<td>5. Failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

Staging of CKD:

Lithium: Renal Handling and Drug Interactions

- Freely filtered and 80% reabsorbed in the proximal tubules (competes with sodium for reabsorption)
- Distal reabsorption occurs in the collecting ducts via epithelial sodium channels (ENaC) where it also competes with sodium

Levels increased by:
- **Hyponatremia** (less competition with Na$^+$)
- **ACE Inhibitors:** *lisinopril use is particularly dangerous* compared to other ACEIs, as lisinopril is 100% renally cleared; any decrement in renal function increases lisinopril levels which further increases lithium levels and may rapidly cause lithium toxicity$^1$
- Distal tubule (K-sparing) diuretics cause sodium wasting thereby increasing reabsorption of both sodium and lithium proximally: triamterene, amiloride, spironolactone, **HCTZ**
- Ibuprofen, naproxen, indomethacin
- Less effects: ASA, loop diuretics (e.g., except loop diuretics in the elderly)

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The Collecting Duct and Lithium - How NDI Occurs

1. Distally, lithium is reabsorbed through epithelial sodium channels (ENaC) which have 1.5 - 2.0x greater permeability for lithium than for Na⁺.

2. Intracellular removal is dependent on Na/K-ATPase - lithium is a poor substrate for this pump which leads to high intracellular levels.

3. Lithium accumulation leads to inhibition of GSK-3β, a kinase involved in control of H₂O transport via aquaporin-2 (AQP2) channels and Na⁺ transport via ENaC.

**Net effect:** insensitivity to aldosterone and vasopressin actions at AQP2 leading to AQP2 channel downregulation.

**NB:** PKCα inhibition may also play a role, since PKCα knockout mice do not get polyuria from lithium exposure.

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Lithium Kinetics

Rapidly absorbed in the upper GI tract
• $T_{\text{max}}$ 1-3 hours (regular lithium carbonate) vs. $T_{\text{max}}$ 4-12 hours (SR)
• **Half-life: 20-24 hours at steady state**

CNS levels: distributed unequally in the brain, white matter > grey matter
• $T_{\text{max}}$ 24 hours
• **CNS Half-life: 28 hours at steady state**
• CNS to serum ratio: surprising amount of variability. In a $^7\text{Li}$ MRI imaging study of 23 depressed bipolar pts, a significant association between CNS and peripheral lithium levels was found only in remitters ($r = 0.7, P = 0.004$) but not in non-remitters ($r = -0.12, P = 0.76$). Also, brain lithium (but not plasma) was inversely correlated with age ($r = -0.46, P = 0.025$).

## Factors Impacting 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>

**Comment:** Once daily lithium should never be qam or qnoon as the levels obtained at 6 am will be 18-hr or 24-hr trough values.

### Dosing Schedule

<table>
<thead>
<tr>
<th></th>
<th>QD</th>
<th>BID</th>
<th>TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amdisen ¹</td>
<td>1.37</td>
<td>1.07</td>
<td>1.00</td>
</tr>
<tr>
<td>Swartz ²</td>
<td>0.90</td>
<td>0.70</td>
<td>--</td>
</tr>
<tr>
<td>Greil ³</td>
<td>1.04</td>
<td>0.81</td>
<td>--</td>
</tr>
</tbody>
</table>

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Largest Study on Risk For Renal Insufficiency (RI) in Lithium-Treated Patients

Method

• New England EHR database, pts age ≥ 18, with at least one lithium prescription between 2006-13 based on e-prescribing data. RI defined: eGFR < 60 ml/min or by ICD-9 code

• Lithium-treated patients with RI (n=1445) were matched 1:3 with 4306 lithium-exposed patients without RI

Aims

• To develop and validate a risk stratification tool

• To examine possible medication-related risks including lithium preparation (citrate, carbonate standard-release, sustained-release), lithium dosing frequency, mean and most recent lithium level, and concomitant psychotropic medications (FGA & SGA, newer antidepressants)
**Treatment-Related Factors Associated With RI**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate, odds ratio</th>
<th>Adjusted for clinical model, odds ratio</th>
<th>Fully adjusted for clinical model plus other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-daily dosing</td>
<td>0.86</td>
<td>0.79</td>
<td>0.80</td>
</tr>
<tr>
<td>Extended release (vs immediate/citrate)</td>
<td>0.90</td>
<td>1.09</td>
<td>1.13</td>
</tr>
<tr>
<td>Concomitant first-generation antipsychotic</td>
<td>1.55</td>
<td>1.40</td>
<td>1.48</td>
</tr>
<tr>
<td>Concomitant second-generation antipsychotic</td>
<td>0.67</td>
<td>0.87</td>
<td>0.95</td>
</tr>
<tr>
<td>Concomitant SSRI/SNRI</td>
<td>0.73</td>
<td>0.67</td>
<td>0.68</td>
</tr>
</tbody>
</table>

**Comments:** Certain variables such as receiving a 1st generation antipsychotic or an SSRI/SNRI may be related to the quality of care received by these individuals (i.e., confounding by indication), since prior studies have not shown a signal based on the antipsychotic or antidepressant received.

Maximum Level: 285 cases & 299 controls had at least one outpatient level > 1.2 mEq/L prior to first recorded RI Dx. In adjusted regression models, presence of one supratherapeutic level was associated with risk for renal insufficiency with OR 1.72 (95% CI 1.38-2.14).

Mean outpatient level (excluding values within 90 days of the RI diagnosis): In fully adjusted models with a level < 0.60 mEq/L as the reference, the odds ratios were:

- Level 0.6 - 0.8 mEq/L: 1.42 (95% CI= 1.14–1.77)
- Level 0.8 - 1.0 mEq/L: 2.03 (95% CI= 1.56–2.65)
- Level > 1.0 mEq/L: 2.20 (95% CI= 1.43–3.38)

Comments:

a. In presumably stable patients (i.e., outpatients) excessively high levels contribute to risk for renal dysfunction.

b. Once patients are stable, every attempt must be made to get levels below 1.2 mEq/L and preferably below 1.0 mEq/L.

c. The maintenance level must be balanced against the risk of manic relapse.
Monitoring for and Managing Polyuria and Increasing eGFR
Managing Renal Parameters

Monitoring
• Initially: eGFR q 3 months, lithium q 3 months. Consider urine osmolality to detect NDI.
• Stable patients: eGFR and lithium level every 6 months. Consider urine osmolality to detect NDI.

Parameters
• Normal eGFR is ≥ 60 mL/min. Reported lab eGFR may be inaccurate if the lab lacks essential demographic info (e.g., race).
  • Online calculator: www.qxmd.com/calculate/egfr-using-ckd-epi
• Single estimations of eGFR can be unreliable, emphasizing need for serial monitoring.
• As eGFR becomes closer to 50 mL/min, need to consider risks:benefits of stopping lithium.
  • Lithium should be stopped for eGFR < 50 mL/min.

Study: 79 lithium-treated outpatients received comprehensive screening including questionnaires on polyuria, polydipsia, and nocturia; 24-hour urine collection; early morning urine osmolality; and 24-hour fluid intake recollection (FIR).

Results: Urine osmolality distinguished those with polyuria, but the FIR was more significantly associated with polyuria.

- FIR < 2000 mL/24 hrs associated with very low likelihood of polyuria
- FIR > 3500mL/24 hrs associated with very high likelihood

Comments:

- 24-hour urine collection is the gold standard, but impractical and often inaccurate if the patient forgets to use the “jug.” Its impracticality also precludes use as a tracking tool if NDI is treated.
- 24-hour FIR is a great screening tool for outpatients and for less cooperative inpatients who will not provide a urine specimen for osmolality.

Amiloride for Polyuria

**Principle:** Blocks lithium reabsorption through epithelial sodium channels (ENaC) in distal tubules. These channels have 1.5 - 2.0x greater permeability for lithium than for sodium.

**Amiloride:** Blocks ENaC and minimizes renal injury and nephrogenic DI by decreasing intracellular lithium levels.

**Practical issue:** Amiloride causes sodium wasting, but less than HCTZ.

- Monitor sodium levels along with lithium levels, eGFR while on amiloride
- Cannot be used with K-sparing diuretics including HCTZ, ACE inhibitors, or ARBs

Method: crossover design, double-blind, placebo-controlled, order of arms randomized. Dosing: Amiloride: 5 mg/day x 2 wks, then 10 mg/d x 4 wks:

a. 6 weeks of placebo or amiloride
b. 6-week washout
c. 6 weeks of amiloride or placebo

Eleven subjects (9F/2M), mean age 58 ± 4 yrs, mean lithium exposure 20 ± 3 yrs

• Mean urine osm 296-298 ± 3. Mean lithium level 0.70 – 0.73 ± .09 mEq/L.

Results

• During amiloride treatment, 164.5% ± 8% increase in urine osm
• Increase of 104% ± 32% in aquaporin 2 water channel excretion (a measure of aquaporin 2 channel density)
• No significant changes in serum lithium level

Long-Term Impact on eGFR
Impact of Long-Term Lithium Exposure on eGFR

**Method:** Longitudinal data on 312 bipolar patients at 12 European sites

**Demographics:** (6412 person-years of lithium exposure)
- Patients treated for mean 18 yrs (range 8-48 yrs), and 57.7% were female
- Mean age 37.9 ± 12.9 years at time of lithium initiation (range 11-76)
- Mean age 55.8 ± 14.2 years at the time of the analysis (range 20-89)
- 78.2% bipolar I; 21.8% bipolar II; average age at illness-onset of 28.5 ± 11.1 years

**Results:** eGFR declined from a mean 94.2 ml/min to 62.2 ml/min, an average rate of decline of $0.915\%/yr$
- This rate falls into the range for general population estimates of $0.637\%/yr - 0.917\%/yr$
- This overall observed annual rate of decline ($0.915\%/yr$) was 28.9% greater for years of lithium treatment than for years of age ($0.710\%/yr$)
- eGFR < 60 ml/min: Based on the accepted criterion of ≥ 2 low values, the risk of eGFR < 60 ml/min was 18.1%; 29.5% had at least one estimated eGFR below 60 ml/min

Stefansson VTN et al. Metabolic syndrome but not obesity measures are risk factors for accelerated age-related glomerular filtration rate decline in the general population. Kidney Int. 2018;93:1183-90.
Low eGFR Risk Factors During Lithium Exposure

Risk factors:

• Older age, female gender, lower baseline eGFR, longer lithium duration and antipsychotic use were associated with low eGFR risk

• Medical comorbidities (CV disease, DM, Htn, hypothyroidism, hypercholesterolemia, hypertriglyceridemia, or respiratory diseases)

Why lower risk with anticonvulsants but higher risk with antipsychotics?

• A multiple variable logistic regression model adjusted for age/sex, found that mood stabilizing anticonvulsants were associated with shorter lithium exposure & lower serum levels. Antipsychotic use was significantly greater among bipolar I than bipolar II disorder, and this was also associated with shorter exposure to lithium but at higher doses and serum concentrations.

Factors not associated with low eGFR: (a) Bipolar I vs. II diagnosis; (b) educational level; (c) metabolic syndrome; (d) abuse of alcohol or drugs; (e) cigarette smoking; (f) lifetime suicidal behavior; (g) serum TSH.

Does Bipolar Disorder Contribute to Risk of CKD?

Method: Danish nationwide population-based study

Cohort 1 (n= 1,800,591): randomly selected sample of 1.5 million individuals, all patients with a diagnosis of a single manic episode or bipolar disorder between January 1, 1994, and December 31, 2012 (n =10,591), and all patients exposed to either lithium (n = 26,731) or anticonvulsants (n=420,959). Provides population rates of CKD, ESRD.

Cohort 2: the subgroup of 10,591 patients diagnosed as having bipolar disorder. Provides rates of CKD, ESRD for bipolar patients.

Outcome measures:

• 1st hospital contact with discharge Dx of CKD (by ICD-10 codes)

• End-stage CKD, defined as irreversible end-stage CKD with either dialysis or transplantation

Absolute Risks: Bipolar Disorder Is Associated With Nearly 3-Fold Higher CKD Risk Than That in the General Population


<table>
<thead>
<tr>
<th></th>
<th>Definite CKD</th>
<th>Possible CKD</th>
<th>End-Stage CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- General Pop</td>
<td>0.80%</td>
<td>1.0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>(n)</td>
<td>(14,727)</td>
<td>(18,762)</td>
<td>(3407)</td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bipolar Only</td>
<td>2.6%</td>
<td>3.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>(n)</td>
<td>(278)</td>
<td>(319)</td>
<td>(62)</td>
</tr>
</tbody>
</table>
Table 1. Hazard Ratios of CKD for 1800591 Individuals in Cohort 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definite CKD (n = 14727)</th>
<th>Possible CKD (n = 18762)</th>
<th>End-Stage CKD (n = 3407)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Lithium prescriptions, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.09 (0.81-1.45)</td>
<td></td>
<td>1.01 (0.79-1.30)</td>
</tr>
<tr>
<td>1-2</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>3-9</td>
<td>1.68 (1.17-2.42)</td>
<td>&lt;.001</td>
<td>1.38 (1.00-1.89)</td>
</tr>
<tr>
<td>10-19</td>
<td>1.93 (1.33-2.78)</td>
<td>&lt;.001</td>
<td>1.73 (1.26-2.38)</td>
</tr>
<tr>
<td>20-29</td>
<td>2.54 (1.75-3.67)</td>
<td>&lt;.001</td>
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<td>20-29</td>
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<td>40-59</td>
<td>1.02 (0.89-1.16)</td>
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<td>0.98 (0.87-1.10)</td>
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<td>≥60</td>
<td>0.92 (0.83-1.03)</td>
<td>&lt;.001</td>
<td>0.90 (0.81-0.99)</td>
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Cohort 2 (Bipolar Disorder) Is Associated With Increased CKD Risk With Lithium or Anticonvulsants


<table>
<thead>
<tr>
<th>Variable</th>
<th>Definite CKD (n = 278)</th>
<th>Possible CKD (n = 319)</th>
<th>End-Stage CKD (n = 62)</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value(^b)</td>
<td>HR (95% CI)</td>
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<td>1-2</td>
<td>0.89 (0.39-2.06)</td>
<td>0.12 (0.65-2.43)</td>
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<td>3-9</td>
<td>1.40 (0.84-2.33)</td>
<td>1.24 (0.76-2.01)</td>
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<td>10-19</td>
<td>1.11 (0.66-1.88)</td>
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<td>20-29</td>
<td>1.53 (0.92-2.53)</td>
<td>1.82 (1.15-2.89)</td>
<td>2.07 (1.42-3.03)</td>
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<td>30-39</td>
<td>2.03 (1.26-3.28)</td>
<td>2.07 (1.42-3.03)</td>
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<td>40-59</td>
<td>2.24 (1.50-3.35)</td>
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<td>0.32 (0.09-1.11)</td>
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<tr>
<td>≥60</td>
<td>2.54 (1.81-3.57)</td>
<td>2.48 (1.80-3.42)</td>
<td>0.32 (0.09-1.11)</td>
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Anticonvulsant prescriptions, No.

<table>
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<tr>
<th>Variable</th>
<th>Definite CKD (n = 278)</th>
<th>Possible CKD (n = 319)</th>
<th>End-Stage CKD (n = 62)</th>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value(^b)</td>
<td>HR (95% CI)</td>
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<td>1 [Reference]</td>
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<td>1.74 (1.16-2.61)</td>
<td>1.71 (1.18-2.49)</td>
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<td>30-39</td>
<td>2.58 (1.57-4.24)</td>
<td>2.24 (1.45-3.45)</td>
<td>2.64 (1.07-6.49)</td>
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<td>40-59</td>
<td>2.28 (1.43-3.64)</td>
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<td>2.06 (0.82-5.16)</td>
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<tr>
<td>≥60</td>
<td>2.30 (1.53-3.44)</td>
<td>1.97 (1.34-2.90)</td>
<td>2.06 (0.82-5.16)</td>
</tr>
</tbody>
</table>
Using Lithium in Older Bipolar Patients
Lithium vs. VPA in Older Bipolar Patients

1. **Double-blind 9 week** trial of lithium (target level 0.80–0.99 mEq/L) or divalproex (target level 80–99 mcg/mL) in 224 inpts and outpts age ≥ 60 with bipolar I disorder (manic, hypomanic, or mixed episode). If inadequate response after 3 weeks, adjunctive risperidone given. Exclusions: dementia, delirium, rapid cycling, contraindication to the study medications.

2. **Demographics:** Mean age 68.0 ± 6.4 years, 49% F, 87% white, 50% inpatient. 64% manic, 13% hypomanic, 23% mixed. 34% had psychotic symptoms.

3. **Serum levels:** Similar proportions in the lithium (57%) and divalproex (56%) groups achieved target concentrations.

Lithium vs. VPA in Older Bipolar Patients - Results

1. **Safety results**: Attrition rates were similar for lithium and divalproex (14% and 18% at wk 3, 51% and 44% at wk 9, respectively). The groups did not differ significantly in sedation. The lithium group tended to have more tremor.

2. **Efficacy results**: Week 9 response rates did not differ significantly between Li⁺ (79%) and VPA (73%). The need for adjunctive risperidone was similar (17% and 14%, respectively). **A longitudinal mixed model of improvement (YMRS change from baseline)** favored lithium by 3.90 points (97.5% CI=1.71, 6.09).

Lithium Toxicity in Older Bipolar Patients

1. **Nested case-control study** of 10,615 pts ages ≥ 66 in Ontario 1992-2001. 413 were admitted at least once for lithium toxicity and matched with four controls. Prescriptions for any diuretic, ACEI, or NSAID before the index date were examined. Thiazide and loop diuretics were examined independently.

2. **Results:** Any use of **ACEI or loop diuretic** in the prior month increased risk of lithium toxicity, but this effect was greatly magnified among new users. Neither thiazides nor NSAIDs were associated with increased risk.

3. **Comment on loop diuretics:** Increase lithium clearance ~20% in healthy younger individuals and are the diuretics of choice for most patients on lithium. However, older patients, particularly with some degree of renal dysfunction, may become sufficiently volume contracted and sodium depleted during furosemide therapy that virtually all filtered lithium is reabsorbed in the proximal tubule leading to risk of toxicity.

# Lithium Toxicity in Older Bipolar Patients

## Table 1. Association Between Hospitalization for Lithium Toxicity and Any Use of Other Medications

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Cases (n = 413)</th>
<th>Controls (n = 1,651)</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td>Primary (dispensed within 28 days)</td>
<td></td>
<td></td>
<td>Multivariate*</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>16 (3.9)</td>
<td>37 (2.2)</td>
<td>1.8 (1.0–3.3)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>54 (13.1)</td>
<td>71 (4.3)</td>
<td>3.4 (2.3–5.0)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>63 (15.3)</td>
<td>110 (6.7)</td>
<td>2.5 (1.8–3.5)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>63 (15.3)</td>
<td>187 (11.3)</td>
<td>1.4 (1.0–1.9)</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>29 (7.0)</td>
<td>75 (4.5)</td>
<td>1.6 (1.0–2.5)</td>
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</tbody>
</table>

## Table 2. Association between Hospitalization for Lithium Toxicity and New Use of Other Medications

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Cases (n = 413)</th>
<th>Controls (n = 1,651)</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multivariate*</td>
</tr>
<tr>
<td>Primary (dispensed within 28 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>5 (1.2)</td>
<td>6 (0.4)</td>
<td>3.3 (1.0–10.9)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>12 (2.9)</td>
<td>6 (0.4)</td>
<td>8.0 (3.0–21.3)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>14 (3.4)</td>
<td>5 (0.3)</td>
<td>11.2 (4.0–31.1)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>4 (1.0)</td>
<td>17 (1.0)</td>
<td>0.9 (0.3–2.8)</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>4 (1.0)</td>
<td>15 (0.9)</td>
<td>1.1 (0.4–3.2)</td>
</tr>
</tbody>
</table>

What About Renal Outcomes in Older Bipolar Patients?

1. **Prevalence and correlates of renal dysfunction** in a cross-sectional sample of 2480 lithium users aged ≥ 70 in Ontario 2005-11

   a. Results: the 6-year prevalence rates of CKD and NDI were 13.9% and 3.0%, respectively

   b. Htn (OR 2.05; 95% CI 1.50-2.79), DM (OR 1.86; 95% CI 1.45-2.38), IHD (OR 1.65; 95% CI 1.24-2.20), NDI (OR 2.54; 95% CI 1.47-4.40), AKI (OR 11.7; 95% CI 5.26-26.1), loop diuretic use (OR 1.74; 95% CI 1.26-2.41), HCTZ use (OR 1.48; 95% CI 1.07-2.05) were all independently associated with CKD

   c. Lithium use > 2 years (OR 1.71; 95% CI 1.05-2.81) and atypical antipsychotic use (OR 1.49; 95% CI 1.17-1.89) were also independently associated with CKD

2. **Comparative prevalence of CKD in older lithium users compared to age matched general population samples:**

   a. When followed over 4 years, more lithium treated patients age 65 and older had significant declines in eGFR (> 8 ml/min) than matched controls in a family medicine clinic: 40.2% vs. 29.5%

   b. Nonetheless, prevalence estimates of CKD range from 42-50% among older lithium users compared to 37.8% for community-dwelling non-psychiatric cohorts

---

Acute Medical Events in Older Bipolar Patients: Lithium vs. Valproate vs. Neither


2. **Results:** No significant differences in % with medical admissions, time to medical admission, or % with ER visits. VPA users had longer length of stay for medical admissions than did lithium users, but a fewer number of ER visits.

# Acute Medical Events: Lithium vs. Valproate


<table>
<thead>
<tr>
<th></th>
<th>Lithium (n=279)</th>
<th>VPA (n=452)</th>
<th>Neither Li/VPA (n=657)</th>
<th>P</th>
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</thead>
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<tr>
<td>Age</td>
<td>72.4 ± 5.7</td>
<td>71.8 ± 5.4</td>
<td>72.5 ± 5.8</td>
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<tr>
<td>Female</td>
<td>61.6%</td>
<td>63.7%</td>
<td>65.0%</td>
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<tr>
<td>LT Care Resident</td>
<td>7.2%</td>
<td>8.8%</td>
<td>5.3%</td>
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<tr>
<td>Dementia</td>
<td>35.1%</td>
<td>36.7%</td>
<td>35.9%</td>
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<tr>
<td>Length of stay during index psych admit (d)</td>
<td>35.6 ± 47.3</td>
<td>36.7 ± 71.2</td>
<td>33.5 ± 74.2</td>
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<tr>
<td>Psych admit in prior 1 yr to index psych admit</td>
<td>25.1%</td>
<td>32.1%</td>
<td>30.9%</td>
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<tr>
<td>Nonpsychiatric admit (1 yr prior to index date)</td>
<td>21.9%</td>
<td>21.9%</td>
<td>22.7%</td>
<td>--</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>11.5%</td>
<td>15.9%</td>
<td>12.0%</td>
<td>--</td>
</tr>
<tr>
<td>Inpt medical hospitalization</td>
<td>20.8%</td>
<td>21.2%</td>
<td>23.0%</td>
<td>NS</td>
</tr>
<tr>
<td>Mean time to medical hospitalization (days)</td>
<td>310.8</td>
<td>317.9</td>
<td>312.7</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay (95% CI)</td>
<td>14.8 (7.1, 22.5)</td>
<td>24.5 (10.8, 38.2)</td>
<td>9.6 (7.3, 11.9)</td>
<td>VPA &gt; Li</td>
</tr>
<tr>
<td>ER visit</td>
<td>35.1%</td>
<td>36.9%</td>
<td>41.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Number of ER visits</td>
<td>2.2 (1.7, 2.8)</td>
<td>1.7 (1.5, 1.9)</td>
<td>2.9 (2.3, 3.4)</td>
<td>VPA &lt; Li</td>
</tr>
</tbody>
</table>
Conclusions Part I

Lithium has a > 24 hour CNS half-life

- There is no efficacy advantage from multiple daily doses
- Lithium should only be dosed as a single qhs dose and outpt levels kept < 1.2 meq/L
- Single daily lithium dosing using qD, qam, or qnoon schedules must be avoided as the trough levels will be greatly distorted
- Patients on BID or TID regimens have increased risk of renal dysfunction with no discernible advantage over QHS dosing

Lithium is associated with modest non-significant changes in eGFR, *changes that are only slightly different than age-predicted declines*

- Some of this risk may be due to the Dx of bipolar disorder itself

**Difficulty with urine concentrating ability can be monitored with urine osmolality and FIR**

- Amiloride has evidence for treating lithium-induced NDI
Conclusions Part II

Lithium has demonstrable neuroprotective properties

• Older patients can take lithium, but need careful monitoring, and may not tolerate furosemide in the manner seen with younger patients

Lithium has anti-suicide properties

• These properties exist regardless of indication
• The effect is comparable in those with substance use disorders, a group a higher risk for self-harm and suicide
• There is no data supporting a similar effect for VPA
Lithium has been shown in numerous studies to reduce the incidence of completed suicide in bipolar patients compared to which of the following?

1. Placebo  
2. Depakote  
3. Antipsychotics  
4. 1 and 2  
5. All of the above
Lithium has a steady state half-life of 20-24 hours. The advantages of single daily lithium dosing include:

1. Decreased long term renal dysfunction (polyuria)
2. Decreased inpatient staff time or outpatient inconvenience
3. Increased efficacy
4. 1 and 2
5. All of the above
A nested case-control study was performed among patients age 66 and older in Ontario, Canada which compared 413 who were admitted with lithium toxicity and 4 matched lithium-treated controls. Drug-related factors that were associated with increased risk for lithium toxicity included:

1. Use of loop diuretics (e.g., furosemide)
2. Use of ACE inhibitors
3. Use of thiazide diuretics (e.g., HCTZ)
4. 1 and 2
5. All of the above
APPENDIX
• Lithium has superior data to other mood stabilizers for suicidality, and is effective in rapid cycling patients

• Lithium can be safely used in older patients; moreover, there are neuroprotective advantages over other mood agents seen in studies of older bipolar patients

• **Kinetics and dosing:** Lithium has a half-life > 24 hours in the CNS – multiple daily dosing is not more effective and is associated with greater risk for renal dysfunction
  
  • Outpatient lithium levels > 1.2 mEq/L are also associated with greater risk for renal dysfunction
• **Risk for renal dysfunction:** lithium plays a role as does the patient population, as many have risk factors for renal dysfunction due to higher prevalence of htn and cardiometabolic disease
  
  • In capable hands, no patient on lithium should develop stage 4 or 5 CKD

• **Managing polyuria:** urine osmolality and 24-hour fluid intake record are the preferred methods for polyuria screening – 24-hour urine collection is not feasible or necessary
  
  • Amiloride is the treatment of choice for lithium induced nephrogenic diabetes insipidus by blocking lithium entry in distal tubular cells through ENaC
Lithium Prevents Suicide

• Meta-analysis of 45 studies involving 85,229 person-years of risk-exposure during treatment of bipolar and other major affective disorder patients with lithium for an average of 18 months.

• Papers must provide data on attempted and completed suicide to be eligible for analysis
  • Studies excluded with zero events in lithium and non-lithium arms

• 31 of 45 papers met criteria for analysis

# Lithium Reduces Suicidal Events 5-Fold

1. **All Suicidal Acts:**
   \[ RR = 4.91 \ (95\% \ CI \ 3.82-6.31, \ p < 0.0001) \]

2. **Completed or Attempted Suicides:**
   - **Completed:**
     \[ RR = 4.86 \ (95\% \ CI \ 3.36-7.02, \ p < 0.01) \]
   - **Attempted:**
     \[ RR = 4.98 \ (95\% \ CI \ 3.56-6.96, \ p < 0.01) \]

3. **Bipolar vs. MDD/SAD:**
   - **Bipolar:**
     \[ RR = 5.34 \ (95\% \ CI \ 3.59-7.93, \ p < 0.01) \] (14 studies)
   - **MDD/SAD:**
     \[ RR = 4.66 \ (95\% \ CI \ 3.43-6.33, \ p < 0.01) \] (17 studies)

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

Results were independent of type of trial (RCT vs. open label), method of study analysis

<table>
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<tr>
<th>Characteristic</th>
<th>Cycling type</th>
<th>F or $\chi^2$</th>
<th>P</th>
</tr>
</thead>
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<td>Rapid $(N=56)$</td>
<td>Non-rapid $(N=304)$</td>
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</tr>
<tr>
<td>Years on lithium</td>
<td>4.96±4.31</td>
<td>4.41±4.07</td>
<td>0.86</td>
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<tr>
<td>Mean serum lithium (mM)</td>
<td>0.596±0.116</td>
<td>0.616±0.143</td>
<td>0.95</td>
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<td><em>Annual cycling rate</em>&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>All episodes</td>
<td>1.49±1.94</td>
<td>0.73±0.92</td>
<td>20.9</td>
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<tr>
<td>Manias</td>
<td>0.49±0.73</td>
<td>0.36±0.55</td>
<td>2.19</td>
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<tr>
<td>Depressions</td>
<td>1.00±1.52</td>
<td>0.37±0.60</td>
<td>28.3</td>
</tr>
<tr>
<td>Hospitalizations/ year</td>
<td>0.087±0.351</td>
<td>0.073±0.015</td>
<td>0.12</td>
</tr>
<tr>
<td><em>Proportion of time ill (%)&lt;sup&gt;b&lt;/sup&gt;</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All episodes</td>
<td>21.2±25.2</td>
<td>18.5±22.6</td>
<td>0.66</td>
</tr>
<tr>
<td>Mania</td>
<td>6.99±10.5</td>
<td>8.04±13.0</td>
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<tr>
<td>Depression</td>
<td>14.2±17.2</td>
<td>10.5±17.7</td>
<td>2.17</td>
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<tr>
<td><em>Percentage improvement</em>&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Episodes/year</td>
<td>56.5±41.4</td>
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<tr>
<td>Manias/year</td>
<td>66.4±42.5</td>
<td>63.1±44.5</td>
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<tr>
<td>Depressions/year</td>
<td>54.5±42.8</td>
<td>54.6±46.0</td>
<td>0.00</td>
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<tr>
<td>Time in all episodes</td>
<td>61.4±37.4</td>
<td>48.3±41.6</td>
<td>0.26</td>
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<tr>
<td>Time in mania</td>
<td>68.8±39.6</td>
<td>64.0±43.3</td>
<td>0.61</td>
</tr>
<tr>
<td>Time in depression</td>
<td>59.3±39.1</td>
<td>57.9±44.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Lithium vs. VPA in RC Patients

Subjects: 525 adults with bipolar disorder enrolled in the Bipolar Collaborative Network 1996 - 2002. Patients could be on multiple agents. RC: any history of ≥ 4 episodes/year (58.1%).

- Medication success rates were calculated in those with sustained response if the medication was started within 2 weeks of the period of improvement and was maintained during ≥ 75% of the improvement period.

Mood outcomes during follow-up:

- Well on study entry and sustained improvement: 18.3% (n=96)
- Much or very much improved for ≥ 6 months during follow-up: 37.1% (n=195)
- Poor responders: 49.6% (n=234)

Medication success rates for those not well on program entry (70% US, 30% Europe):

- Lithium 49.3%
- Carbamazepine 39.9%
- Divalproex 34.8%

Further analysis of lithium success rates: In the logistic regression model, neither lifetime history of RC nor ≥ 20 lifetime mood episodes were significant.

Lithium in Groundwater and Dementia

1. Danish nationwide, nested case-control study examined longitudinal and geographic data from drinking water measurements combined with time-specific data from all patients age 50-90 with a hospital contact and dementia Dx from 01/01/1970 - 12/31/2013, and 10 age- and sex-matched controls. Mean lithium exposure in drinking water since 1986 was estimated for all individuals. **Sample size:** 73,731 pts with dementia and 733,653 controls (median age 80.3 yrs; 60.7% female).

2. Lithium exposure was statistically significantly different between patients with a diagnosis of dementia (median 11.5 μg/L; interquartile range, 6.5-14.9 μg/L) and controls (median 12.2 μg/L; interquartile range, 7.3-16.0 μg/L; P < .001).

3. Compared with individuals exposed to low lithium levels (2.0 to 5.0 μg/L), the incidence rate ratio (IRR) of dementia was decreased in those exposed to > 15.0 μg/L: IRR = 0.83 (95% CI, 0.81-0.85; P < .001). Similar patterns were found with Alzheimer’s disease and vascular dementia as outcomes.

Normal Renal Parameters
NB: values may vary somewhat between labs, esp. urine osmolality

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

24-hr urine volume: up to 2000 mL

Creatinine Clearance:
- Men: 97 - 137 mL/min
- Women: 88 - 128 mL/min

Acute Mania: 1.0 - 1.5 mEq/L, but only one prospective randomized study (Stokes 1976) that examined dose and treatment response. Numerous studies used target levels or ranges, or maximum tolerated doses.

Acute Bipolar Depression: Same as maintenance dosing (0.6 - 1.0 mEq/L) but no dose response studies

Maintenance: In general, levels 0.7/0.8 - 1.0 mEq/L have lower rates of relapse based on seven studies of patients randomly assigned to different serum levels during long-term follow-up. No a priori way to determine who will do well at lower vs. higher levels.

## Demographic Factors Associated With Renal Insufficiency

<table>
<thead>
<tr>
<th></th>
<th>Univariate, odds ratio</th>
<th>Adjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.68</td>
<td>0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/ethnicity, white</td>
<td>1.63</td>
<td>1.53</td>
<td>&lt;0.001</td>
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<tr>
<td>Age (per decade)</td>
<td>1.80</td>
<td>1.55</td>
<td>&lt;0.001</td>
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<td>Charlson index (Log 10)</td>
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<td>1.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insurance, private</td>
<td>1.01</td>
<td>1.29</td>
<td>0.006</td>
</tr>
<tr>
<td>Lifetime hypertension</td>
<td>4.74</td>
<td>2.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lifetime smoking</td>
<td>1.79</td>
<td>1.27</td>
<td>0.01</td>
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<tr>
<td>Lifetime diabetes mellitus</td>
<td>3.16</td>
<td>1.17</td>
<td>0.166</td>
</tr>
<tr>
<td>Any schizophrenia/schizoaffective</td>
<td>1.72</td>
<td>1.63</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Comments:** Certain variables such as having a schizophrenia spectrum disorder may relate to the quality of general medical care received by these individuals (i.e., confounding by indication), since prior studies have not shown a signal based on that psychiatric Dx.
Consider when:

- 24-hr FIR > 3.5 liters
- Urine osm < 300 mOsm/kg (NDI)
- Patient complains and urine osm is subnormal (e.g. < 750 mosm/kg)

Starting dose 5 mg/day

- Do not use while on other K-sparing agents, ACE inhibitors or angiotensin receptor blockers, or with supplemental K⁺
- Effective in studies at doses up to 20 mg/day, with no significant change in lithium levels at doses up to 10 mg/day
- Monitor serum sodium due to sodium wasting and the potential impact it may have on lithium levels
Does Stage 4 or 5 CKD 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%

Retrospective study of 630 Swedes starting lithium Jan 1981 - Dec 2010 and with ≥ 10 years of cumulative exposure

- **Results:** In this sample with mean age of lithium initiation 46 years, 32% of those who had taken lithium for 10–29 years had evidence of CKD (eGFR < 60 ml/min) but only 5% were in the severe (stage 4) or very severe (stage 5) category

Current Monitoring Should Prevent Lithium-Related End-Stage Renal Disease (ESRD)

- Modern lithium monitoring guidelines were started in Sweden in 1980
- Swedish registry data on 3936 lithium-treated patients (as of Dec 2010) examined to locate 32 patients in whom lithium treatment was the sole or main contributing cause of ESRD
- No patient started on lithium after 1980 progressed to ESRD