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Rethinking Lithium

Jonathan M. Meyer MD, Stephen M. Stahl, MD – May 2024

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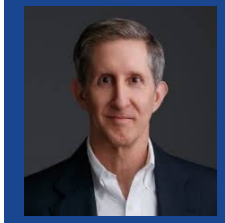

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DISCLOSURES

For all presenter disclosure information, see that submitted for this presentation.

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LEARNING OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Understand the limitations of antipsychotics for bipolar I maintenance, the reproductive harms of valproate, and how to use lithium during pregnancy and breastfeeding.
2. Appreciate the evidence supporting lithium's unique benefits on risk for completed suicide, its neuroprotective effects and the hypothesized mechanisms underlying these effects.
3. Understand lithium's renal journey, its ENaC affinity, polyuria pathophysiology, why polyuria is an early signal of lithium related renal dysfunction, and how to monitor for and manage polyuria.
4. Safely monitor lithium treatment, manage drug-drug interactions impacting lithium clearance and common non-renal adverse effects.

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LITHIUM REMAINS THE GOLD STANDARD FOR PATIENTS WITH A HISTORY OF MANIA

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The Place of Lithium in Treatment Guidelines Updated Since 2018

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	CANMAT/ ISBD 2018 [2]	WFSBP 2009–2018 [76–80]	RANCZP 2020 [81]	CINP 2017–2020 [82–84]	NICE 2020 [85]
Acute mania	1	3	1	2	1 *
Prophylaxis: any mood episode	1	1		1	1 *
Prophylaxis: mania	1	1	1	1	
Prophylaxis: depression	1	4		1	

* But not in primary care settings

Fountouloakis, KN, et al. Lithium treatment of Bipolar disorder in adults: A systematic review of randomized trials and meta-analyses . Eur Neuropsychopharmacology 2022; 54: 100–115.
Meyer JM, Stahl SM. **The Lithium Handbook – Stahl's Handbooks.** Cambridge University Press, 2023.

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The Scientific Literature Recognizes the Unique Value of Lithium: 70-year trend of references on lithium, mood disorders & neuroprotection

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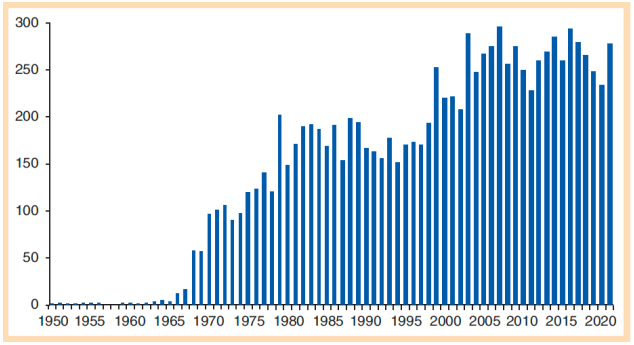

Meyer JM, Stahl SM. **The Lithium Handbook – Stahl's Handbooks.** Cambridge University Press, 2023.

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Prescription Practices Do Not Mirror the Robust Recommendations From Treatment Guidelines

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Figure 0.2 US trends 1997–2016 in different medication categories prescribed during outpatient visits for bipolar disorder

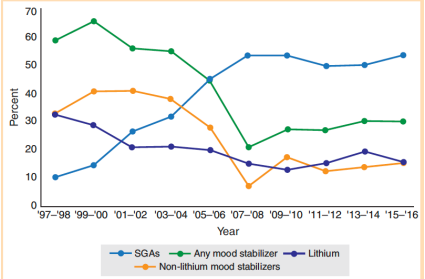
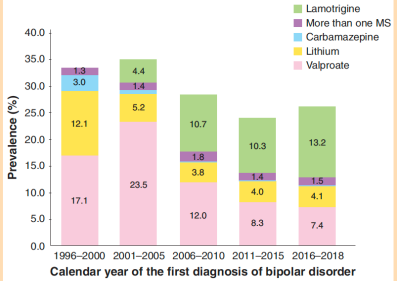


Figure 1.1 20-year trends in use of mood stabilizing (MS) medications among newly diagnosed Finnish BD patients [5]



Rhee TG, et al. 20-year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. Am J Psychiatry 2020; 177, 706–715.
Poranen J, et al. 20-year medication use trends in first-episode bipolar disorder. Acta Psychiatr Scand 2022; 146, 583–593.
Meyer JM, Stahl SM. **The Lithium Handbook – Stahl's Handbooks.** Cambridge University Press, 2023.

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DISPELLING THE MISCONCEPTIONS

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Malhi's list of 7 lithium-related myths:

1. Lithium is an old drug; it has nothing new to offer
2. Lithium seldom works
3. Lithium is not suitable first line
4. Lithium is complicated to prescribe and manage
5. Lithium is a dirty drug and difficult to tolerate
6. Lithium destroys thyroid function
7. Lithium ruins kidney function and eventuates in kidney failure

Malhi, GS, et al. Lithium mythology. Bipolar Disord 2021; 23, 7–10.

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RETHINKING THE USE OF SGA MONOTHERAPY FOR BD-1: PATIENTS WITH A HISTORY OF MANIA NEED MOOD STABILIZATION

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Antipsychotics and Mood Stabilizers Act Differently for Mania: They Are Not Equal

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While certain features of mania will improve after antipsychotic administration, **other untreated aspects can continue to drive positive psychotic symptoms, ongoing acts of impulsivity or mood instability**. This phenomenon was described by the Danish psychiatrist and lithium pioneer Mogens Schou in the 6th edition of his guide to lithium treatment:

"An experienced patient, who during previous manias had first tried a neuroleptic and then lithium, reported that during treatment with the former ***he felt as if the gas pedal and the brake were pressed down at the same time***. With lithium it was as if the ***ignition had been switched off***."

Meyer (2021) Approach to Bipolar Diathesis in Schizophrenia Spectrum Patients. In, "Management of Complex Treatment-Resistant Psychotic Disorders" (Cummings, M. A. and Stahl, S. M., eds.). Cambridge University Press, Cambridge, UK, pp. 42-50.
Schou, M. (2004). Lithium Treatment of Mood Disorders. 6th ed. Basel, Switzerland, S. Karger AG.

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Treatment Failure During the Maintenance Phase Following Hospitalization for Mania in BD-1 Patients

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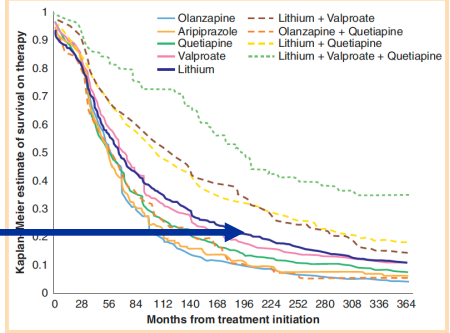
Comment:

- Patients with bipolar 1 disorder (BD-1) often require more than one agent for optimal control of both mood polarities
- **Among monotherapy options, lithium has the lowest risk of treatment failure**

Wingård L, et al. Monotherapy vs. combination therapy for post mania maintenance treatment: A population based cohort study. Eur Neuropsychopharmacol 2019;29:691-700.

Figure 1.4 Time to treatment failure after hospitalization for mania among various treatment options for BD-1 using lithium (dark blue line) as the comparator treatment [18]



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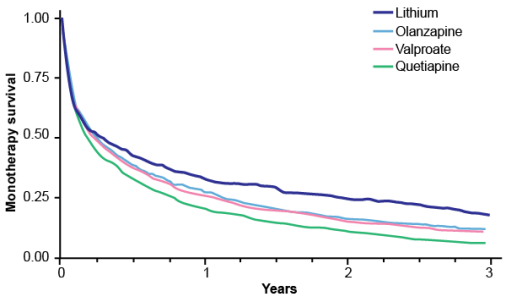
Monotherapy Treatment Failure During the Maintenance Phase Following Hospitalization for Mania in BD-1

- **Patients on SGA monotherapy had the highest rates of treatment failure**
- Patients on VPA monotherapy also fared worse than those on lithium monotherapy



Wingård L, et al. Monotherapy vs. combination therapy for post mania maintenance treatment: A population based cohort study. Eur Neuropsychopharmacol 2019;29:691-700.

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The Evidence Landscape for Treatment of Bipolar Disorder

	Acute mania	Bipolar depression	Bipolar maintenance	Suicidality	Neuroprotection
Lithium	+++	+/-	+++	+++	+++
VPA	+++	-	++	-	-
Carbamazepine	++	+/-	++	-	-
LTG	-	-	++	-	-
Topiramate	-	-	-	-	-
Gabapentin	-	-	-	-	-
Oxcarbazepine	+/-	-	-	-	-

VPA = valproic acid; LTG = lamotrigine

Malhi GS, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust NZ J Psych.* 2021;55(1):7-117.

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RETHINKING LITHIUM IN PREGNANCY AND LACTATION

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Dangers of Valproate in Women of Reproductive Potential

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EMA warning issued in 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2018
EMA/145600/2018

New measures to avoid valproate exposure in pregnancy endorsed

Member State representatives agree new restrictions and pregnancy prevention programme

The CMDh[1] has endorsed new measures to avoid exposure of babies to valproate medicines in the womb, because exposed babies are at high risk of malformations and developmental problems.

Valproate-containing medicines have been approved nationally in the EU to treat epilepsy and bipolar disorder and in some countries for prevention of migraine. The new measures include a ban on the use of such medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available.

Further, the medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme are met. The programme is designed to ensure that patients are made fully aware of the risks and the need to avoid becoming pregnant.

2023: UK Bans New VPA Starts for Men and Women < 55 years old

Medicines & Healthcare products Regulatory Agency

Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 16 Issue 5 December 2022

Advice for healthcare professionals:

- continue to follow the existing strict precautions, including that valproate should not be prescribed to female children or women of childbearing potential unless other treatments are ineffective or not tolerated and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme
- following a new safety review conducted in light of concerns that the current regulatory requirements for safe use are not being consistently followed, the Commission on Human Medicines (CHM) has advised that there should be greater scrutiny of the way valproate is prescribed and that further risk minimisation measures are required – in particular that 2 specialists should independently consider and document that there is no other effective or tolerated treatment for patients aged under 55 years
- consider all other suitable therapeutic options before newly prescribing valproate in patients younger than 55 years
- these new measures will be implemented over the coming months. In the meantime, GPs and pharmacists should continue to provide repeat prescriptions for valproate and dispensers should continue to ensure patients receive the patient card, a copy of the Patient Information Leaflet and packaging bearing pregnancy warnings
- **patients currently taking valproate must be advised not to stop taking it unless they are advised by a specialist to do so**

1. European Medicines Agency. (2018). "New measures to avoid valproate exposure in pregnancy endorsed (press release 3 March 2018)." Retrieved 1 January, 2022, from https://www.ema.europa.eu/en/documents/press-release/ new-measures-avoid-valproate-exposure-pregnancy-endorsed_en.pdf. 2. Freeman, M. P. (2022). Prescribing Guideline for Valproic Acid and Women of Reproductive Potential: Forget It Exists. *J Clin Psychiatry*, 83. 3. National Institute for Health and Care Excellence (2022). Medicines and Healthcare Products Regulatory Agency Drug Safety Update, Vol. 16 Issue 5, December 2022: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1124612/Dec-1122022-DSU-PDF.pdf.

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Dangers of VPA: High Rates of Fetal Valproate Syndrome

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1. **In utero exposure:** fetal valproate syndrome

   From the UK advisory, page 3: **"Valproate has a high teratogenic potential. Exposure of an unborn child to valproate in utero is associated with a high risk of congenital malformations (11%) and neurodevelopmental disorders (30–40%), which may lead to permanent disability."**

2. **Women:** *Polycystic ovary syndrome* and other menstrual abnormalities. Conclusion of 2016 comprehensive meta-analysis: "statistically significant differences between the VPA treated and non-VPA treated groups in PCOS (**OR 6.74;** 95% CI 1.66-27.32; P=0.00), menstrual disorder (**OR 1.81**; 95% CI 1.02-3.23; P=0.04), and hyperandrogenism (HA) (**OR 2.02**; 95% CI 1.11-3.65; P=0.02)."
3. **Males:** impact on fertility (based largely on animal studies, and appears reversible), ? intergenerational effects on germ line

Zhang L, et al. Reproductive and metabolic abnormalities in women taking valproate for bipolar disorder: a meta-analysis. Eur J Obstet Gynecol Reprod Biol 2016; 202(July): 26-31. Clayton-Smith J, et al. Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder - a consensus statement from the Eur Ref Network for Congenital Malformations and Intellectual Disability Orphanet Journal of Rare Diseases 2019; 14(1): 180-201
National Institute for Health and Care Excellence (2022). Medicines and Healthcare Products Regulatory Agency Drug Safety Update, Vol. 16 Issue 5, December 2022: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1124612/Dec-1122022-DSU-PDF.pdf.

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Lithium in Pregnancy: New Risk Estimates for CVM

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- **Pregnant BD spectrum patients need mood stability:** Women who discontinue a mood stabilizer during pregnancy have 2-fold higher recurrence risk for any mood episode, & the time spent ill during pregnancy is 5-fold greater.
  - **Managing eGFR changes during 2nd trimester:** Lithium levels decrease during pregnancy, and reach their lowest point in the 2nd trimester, 36% below baseline. Monitoring the level during each trimester can help prevent relapse due to subtherapeutic levels.
- **Risk of Ebstein's and other cardiovascular malformations (CVM) from 1st trimester lithium exposure is much lower than previously estimated:** The findings from a 2020 meta-analysis should support the decisions of women whose psychiatric health depends on continuous lithium use to not stop treatment during pregnancy, albeit with appropriate monitoring.
  - **The number needed to harm (NNH) for all CVM was 83 comparing lithium users and non-users with bipolar disorder. One would need to expose 83 BD individuals to lithium to see one additional CVM case compared to lithium non-using peers.**
  - **For women on doses > 900 mg/d, a rigorous US study provides an NNH of 39.**

Fornaro M, et al. (2020). Lithium exposure during pregnancy and the postpartum period: a systematic review and meta-analysis of safety and efficacy outcomes. *Am J Psychiatry*, 177, 76-92.
Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Lithium is Safe During Breastfeeding With Appropriate Monitoring

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- A 2022 paper provided the best longitudinal data from 30 breastfeeding dyads. This paper increased the world's literature by 77% (previous total was 39 dyads).
- **After the 4th week of life infant lithium levels were nearly undetectable.** During the first 4 weeks, if there is concern about lithium exposure (e.g. poor feeding), reduce the proportion of breastmilk to 75% or 50% and supplement with formula. **Cessation of breastfeeding is not typically necessary.**

	Infant lithium data				Maternal lithium data			
Infant age	Mean level ± SD (mEq/l)	Median level (mEq/l)	Range (mEq/l)	Missing (n)	Mean level ± SD (mEq/l)	Median level (mEq/l)	Range (mEq/l)	Missing (n)
< 2 weeks	0.19 ± 0.20	0.10	< 0.05 - 0.70	0	0.61 ± 0.24	0.70	0.10 - 0.90	1
2 wks - 1 mo	0.16 ± 0.30	0.08	< 0.05 - 1.20	0	0.59 ± 0.14	0.60	0.20 - 0.70	8
1 - 2 months	0.07 ± 0.0	0.06	< 0.05 - 0.20	1	0.73 ± 0.15	0.70	0.50 - 1.00	15
> 2 months	0.08 ± 0.0	0.07	< 0.05 - 0.20	4	0.62 ± 0.12	0.60	0.50 - 0.90	10

Suggested infant monitoring: eGFR, TSH, lithium level at week 4, 8, 12 and 24 (and then every 6 months unless maternal lithium exposure changes). The lithium level at time of delivery is reflective of peripartum exposure. Decisions about minimizing breastfeeding during the initial 7 days after birth should be driven by the infant's health (e.g. reactivity, hypotonia) and not the lithium level. Consider a lithium level on day 7 to document that infant exposure has decreased as expected.

Heinonen E, et al. Lithium use during breastfeeding was safe in healthy full-term infants under strict monitoring. *Acta Paediatr* 2022; 111; 1891-1898.
Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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RETHINKING THE EVIDENCE BASE: LITHIUM'S UNIQUE EFFECTS ON SUICIDALITY AND NEUROPROTECTION

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Mechanisms of Action - Lithium

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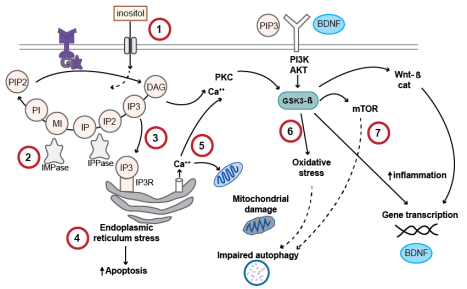
Lithium has multiple intracellular actions, but primarily targets the inositol pathway and the enzyme GSK3-β, and these have downstream effects. **You can be a very successful clinician without memorizing these pathways....!**

1. Inhibition of inositol reuptake
2. Depletion of intracellular inositol triphosphate (IP_3)
3. Decreased IP_3 levels minimize stimulation of endoplasmic reticulum (E calcium (Ca^{++}) release and downstream processes that induce mitochondrial damage
4. Impact on IP_3 levels also mitigates impaired stress related apoptosis regulation
5. Direct impact on Ca^{++} release from ER also lessens stimulation of protei kinase C (PKC) and its promotion of GSK3-β activity
6. **Direct inhibition of GSK3-β activity, with the net result being less oxidative stress and impaired autophagy**
   - Destabilizes the Akt/βArr/PP2A signaling complex: This prevents Akt from being inactivated, and results in potent GSK3β inactivation
7. Direct inhibition of GSK3-β activity also promotes neurotrophic, neuroprotective and antioxidant gene expression



Puglisi-Allegra S, et al. Translational evidence for lithium-induced brain plasticity and neuroprotection in the treatment of neuropsychiatric disorders. *Transl Psychiatry* 2021; 11: 366.
Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

SUICIDALITY AND BIPOLAR DISORDER: FACTS

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- **BD patients are 20–30 times more likely to die by suicide compared with the general population**
- 30%–50% of adults with BD have a lifetime history of suicide attempts, with an estimated 15%–20% of affected people dying by suicide
- Suicide attempts and deaths are more likely to occur in people who have depressive or mixed symptoms
- Evidence suggests that patients with bipolar II disorder may have higher suicide rates than those with bipolar I

McIntyre RS, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841–1856. Dong M, et al. Prevalence of suicide attempts in bipolar disorder: a systematic review and meta-analysis of observational studies. *Epidemiol Psychiatr Sci*. 2019;29:e63. Meyer JM, et al. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press; 2023.

LITHIUM REDUCES SUICIDAL EVENTS 5-FOLD

	Studies (n)	Risk ratio	RR 95% CI	*p*
1. All two-armed studies	31	4.91	3.82–6.31	< 0.0001
2. Omitting Goodwin et al. (2003)[a]	30	5.34	4.27–6.68	< 0.0001
3. Open clinical studies	26	3.41	2.61–4.46	< 0.0001
4. Randomized controlled trials	5	1.76	1.65–1.88	0.001
5. Suicides only	24	4.86	3.36–7.02	< 0.0001
6. Attempts only	17	4.98	3.56–6.96	< 0.0001
7. Bipolar disorder	14	5.34	3.59–7.93	< 0.0001
8. Major affective disorders (unipolar MDD, schizoaffective disorder)	17	4.66	3.43–6.33	< 0.0001
9. Quality score ≥ 50%	16	3.92	2.94–5.23	< 0.0001
10. Quality score < 50%	15	5.56	3.98–7.76	< 0.0001

[a] Results after the data from Goodwin et al. (2003) were omitted indicated that this very large study did not exert a misleading influence on the overall findings.

Method: Meta-analysis of 45 studies involving 85,229 person-years of risk-exposure during treatment with lithium for an average of 18 months. Studies excluded if 0 events. (31/45 papers met criteria for analysis.)

Comments:

- All of the RCTs had zero events in the lithium arm and were of much shorter duration than the open-label studies.
- Exposure times in studies rated as having higher quality (including RCTs) were 5.5 times shorter than than in the open-label clinical studies (1.41 ± 1.09 years vs. 7.77 ± 6.54 years). **Therefore, it is hard to argue that the effect of lithium on suicidality is demonstrable for exposures shorter than those seen in higher quality studies (i.e. the effect may not be instantaneous).**

Baldessarini R, et al. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disorders 2006; 8:625-39.

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LITHIUM'S SUPERIORITY TO VPA FOR SUICIDALITY

Method: within patient study in 51,535 Swedish BD patients

1. **Suicide event rate:** decreased 14% during 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). **Analyses for lithium plus VPA yielded no substantial difference from lithium alone**
2. **Lithium discontinuation: increased suicidal behavior** within 30 days of lithium discontinuation (HR 1.33, 95% CI 1.09-1.61)
3. **Lithium effective in substance use:** The majority of suicidal events occurred in those with comorbid SUD (7976 events in 15,927 pts). Lithium also reduced events in this group (**HR 0.84**, 95% CI 0.75-0.94)

Risk of Suicide-Related Events With Lithium or VPA in 51,535 Swedish BD Adults (2005–13) From An Analysis of 10,403 Events in 4405 Subjects

	Within-Individual Analysis[a]		Between-Individual Analysis[b]	
Medication Status	Hazard Ratio[c]	95%CI	Hazard Ratio[c]	95%CI
Lithium				
On for less than 30 days	0.71	0.58–0.88	0.70	0.60–0.82
On for more than 30 days	0.84	0.75–0.94	0.78	0.70–0.87
Off for less than 30 days	1.33	1.09–1.61	1.37	1.21–1.56
Valproate				
On for less than 30 days	1.00	0.78–1.29	1.07	0.88–1.30
On for more than 30 days	0.97	0.84–1.12	0.97	0.86–1.09
Off for less than 30 days	1.26	0.95–1.68	1.34	1.11–1.62

Conclusions: ***For valproate, there was no protective effect for suicide related events in the Swedish study, 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.

Song J, et al. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. *Am J Psychiatry*. 2017;174:795-802.

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LITHIUM REDUCES SUICIDAL BEHAVIOR MORE EFFECTIVELY THAN VPA, OLANZAPINE OR QUETIAPINE

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Methods

- 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 monotherapy.**
- The PS model was based on factors decided *a priori* to affect MD prescribing choice (sex, age, year, race/ethnicity, medical disease (CV, hypertension, CKD, thyroid, liver, DM type 2, seizure), EtOH use (by severity), illicit drug use, smoking status (by severity), BMI (grouped as < 25, 25-30, or > 30 kg/m^2), 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.

Hayes JF, et al. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: A UK population-based electronic health records study. JAMA Psychiatry 2016; 73:630-7.

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LITHIUM REDUCES SUICIDAL BEHAVIOR MORE EFFECTIVELY THAN VPA, OLANZAPINE OR QUETIAPINE

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Self-harm rate hazard ratio comparisons *versus lithium* after propensity score adjustment and matching:

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

Unintentional injury hazard ratio comparisons *versus lithium* after propensity score adjustment and matching:

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

Hayes JF, et al. Self-harm, unintentional injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment: A UK population-based electronic health records study. JAMA Psychiatry 2016; 73:630-7.

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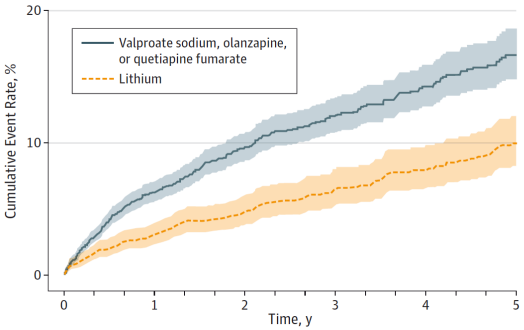
Figure 2. Cumulative Self-harm Rate in Patients Prescribed Lithium vs Valproate, Olanzapine, or Quetiapine



No. at risk						
Valproate, olanzapine, or quetiapine	4523	2482	1561	1026	708	493
Lithium	2148	1458	1066	804	649	509

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Lithium's Superiority to VPA for Neuroprotection

1. **Study of 41,931 US BD pts age ≥ 50 years old** from a Medicaid database of 44M individuals (2001-2004)
2. **Inclusion:** BD 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.
4. **Results:** There were 66,258 person-years of follow-up (**mean 19 months**). 1538 patients (3.7%) were newly diagnosed with dementia during the follow-up period (2.32 cases per 100 patient-years).

- **301-365 days of lithium exposure significantly reduced dementia risk (HR = 0.77**, 95% CI 0.60-0.99).
- No association was observed for shorter lithium exposure (HR = 1.04, 95% CI 0.83–1.31 for 61–300 days; HR = 1.07, 95% CI 0.67–1.71 for 1–60 days) *or for any exposure to anticonvulsants (e.g. VPA)*

Gerhard T, et al. Lithium treatment and risk for dementia in adults with bipolar disorder: population-based cohort study. *British Journal of Psychiatry* 2015; 207:46-51.

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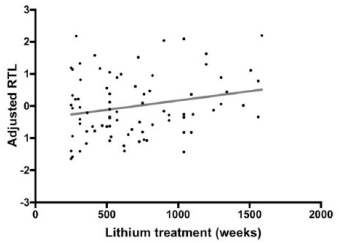
Lithium and Neuroprotection: Hypotheses

1. Neuroprotective effects seen in numerous animal disease models,[1] and in a human study of MCI patients without BD.[2] Lithium increases gray matter volume in healthy humans and in those with bipolar disorder.[3]
2. **GSK3-β Inhibition**: Lithium inhibits glycogen synthase kinase (GSK) 3-β, an enzyme implicated in neurotrophic response, autophagy, oxidative stress, inflammation and mitochondrial function.[1]
3. **Telomerase Inhibition:** Telomeres are stretches of nucleotide repeats at the ends of chromosomes. These DNA elements are sacrificed to prevent the loss of core DNA each time a cell divides. When a critical telomere length is reached, a cell loses the ability to divide.[4]

Association between treatment duration and relative telomere length (RTL) adjusted for age, sex, BMI, genetic risk and current lithium use) in chronic lifetime lithium users



1. Morris G, Berk M. The putative use of lithium in Alzheimer's Disease. *Curr Alzheimer Res* 2016;13:853-61.
2. Forlenza OV, et al. Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial. Br J Psychiatry 2019;215:668-74.
3. Benedetti F, et al. Lithium and GSK3-beta promoter gene variants influence white matter microstructure in bipolar disorder. *Neuropsychopharm* 2013; 38:313-27.
4. Couts F, et al. The polygenic nature of telomere length and the anti-ageing properties of lithium. *Neuropsychopharm* 2019; 44:757–765.

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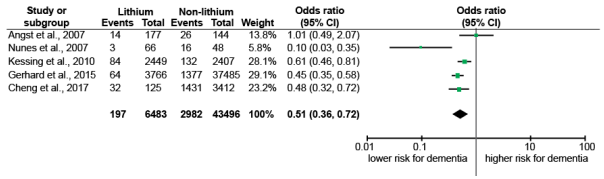
Bipolar Disorder, Dementia Risk and Lithium

2020 review and meta-analysis of dementia risk in bipolar disorder patients and the effect of lithium. 10 studies (4 cohort, 6 case–control design) (N=6859 BD; 487,966 controls) were included of which 5 had data on lithium (N=6483 lithium; 43,496 non-lithium). For the cohort studies, follow-up ranged from 3 to 17 years.

Results:

1. Bipolar disorder increases the risk of dementia 3-fold (**OR 2.96,** 95% CI 2.09–4.18, p < 0.001).
   - Every new episode leading to psychiatric admission increased the rate by 6% for BD patients (95% CI: 3–10)
2. **Lithium decreases dementia risk in BD patients by half** (**OR: 0.51,** 95% CI: 0.36–0.72, p < 0.0001)



Velosa J, et al. Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. *Acta Psychiatr Scand* 2020; 6: 510-521.

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IT'S NOT ALWAYS LITHIUM - BIPOLAR DISORDER IS ASSOCIATED WITH CHRONIC KIDNEY DISEASE

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eGFR and Albuminuria Stages

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- eGFR < 60 ml/min/1.73 m^2 for 3 months is 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.**

eGFR categories (units in ml/min/m^2)		Albuminuria categories A1 < 30 mg/g (normal to mildly increased)	A2 30–300 mg/g (moderately increased)	A3 > 300 mg/g (severely increased)
G1	Normal or high	≥ 90			
G2	Mildly decreased	60–89			
G3a	Mildly to moderately decreased	45–59			
G3b	Moderately to severely decreased	30–44			
G4	Severely decreased	15–29			
G5	Kidney failure	< 15			

- **Green = low risk** (if no other markers of kidney disease and no CKD)
- **Yellow = moderately increased risk**
- **Orange = high risk**
- **Red = very high risk**

Chen TK, et al. Chronic kidney disease diagnosis and management - a review. JAMA 2019; 322(13):1294-1304.

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Bipolar Disorder and the Risk of CKD: Analyzing Confounding Bias

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Rationale: Since bipolar patients may have comorbid conditions (e.g. hypertension, DM, metabolic syndrome, smoking) or receive less than adequate general medical care, one way to examine this issue is to look at a bipolar population who receives anticonvulsants, and compare the rates of renal dysfunction between the two groups.

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 diagnosis of CKD (by ICD-10 codes)
- End-stage CKD, defined as irreversible end-stage CKD with either dialysis or transplantation

Kessing LV, et al. Use of lithium and anticonvulsants and the rate of chronic kidney disease a nationwide population-based study. JAMA Psychiatry 2015; 72(12):1182-91.

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Bipolar Disorder Is Associated With Nearly 3-Fold Higher CKD Risk Than Seen in the General Population

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	Definite CKD	Possible CKD	End-Stage CKD
Cohort 1 - General Population	0.80%	1.0%	0.2%
(n)	(14,727)	(18,762)	(3407)
Cohort 2 - Bipolar Disorder Only	**2.6%**	**3.0%**	**0.6%**
(n)	(278)	(319)	(62)

Findings: Independent of lithium use, having a bipolar spectrum disorder diagnosis was associated with 3 times higher rates of CKD and end-stage CKD.

Kessing LV, et al. Use of lithium and anticonvulsants and the rate of chronic kidney disease a nationwide population-based study. JAMA Psychiatry 2015; 72(12):1182-91.

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BIPOLAR DISORDER IS ASSOCIATED WITH INCREASED CKD RISK WITH LITHIUM OR ANTICONVULSANTS

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Kessing LV, et al. Use of lithium and anticonvulsants and the rate of chronic kidney disease a nationwide population-based study. JAMA Psychiatry 2015; 72(12):1182-91.

Table 2. Hazard Ratios of CKD for 10 591 Patients With a Main Diagnosis of a Single Manic Episode or Bipolar Disorder in Cohort 2[a]

Variable	Definite CKD (n = 278) HR (95% CI)	*P* Value[b]	Possible CKD (n = 319) HR (95% CI)	*P* Value[b]	End-Stage CKD (n = 62) HR (95% CI)	*P* Value[b]
Lithium prescriptions, No.						
0	1 [Reference]		1 [Reference]		1 [Reference]	
1-2	0.89 (0.39-2.06)		1.26 (0.65-2.43)		3.24 (1.19-8.86)	
3-9	1.40 (0.84-2.33)		1.24 (0.76-2.01)		2.86 (1.25-6.51)	
10-19	1.11 (0.66-1.88)	<.001	1.31 (0.83-2.07)	<.001	1.82 (0.75-4.42)	.30
20-29	1.53 (0.92-2.53)		1.60 (1.01-2.55)		3.24 (1.50-6.98)	
30-39	2.03 (1.26-3.28)		1.82 (1.15-2.89)		0.93 (0.27-3.19)	
40-59	2.24 (1.50-3.35)		2.07 (1.42-3.03)		1.33 (0.55-3.23)	
≥60	2.54 (1.81-3.57)		2.48 (1.80-3.42)		0.32 (0.09-1.11)	
Anticonvulsant prescriptions, No.						
0	1 [Reference]		1 [Reference]		1 [Reference]	
1-2	1.23 (0.76-1.99)		1.11 (0.70-1.76)		0 (0.00-Infinity)	
3-9	1.74 (1.16-2.61)		1.71 (1.18-2.49)		1.14 (0.43-3.06)	
10-19	1.70 (1.08-2.68)	<.001	1.71 (1.13-2.59)	<.001	1.74 (0.69-4.37)	.002
20-29	1.50 (0.86-2.61)		1.51 (0.91-2.51)		3.00 (1.24-7.23)	
30-39	2.58 (1.57-4.24)		2.39 (1.49-3.83)		3.23 (1.26-8.27)	
40-59	2.28 (1.43-3.64)		2.24 (1.45-3.45)		2.64 (1.07-6.49)	
≥60	2.30 (1.53-3.44)		1.97 (1.34-2.90)		2.06 (0.82-5.16)	

Lithium

Anticonvulsants

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What Is the Independent Effect of Lithium on eGFR

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Study: Comparison of eGFR changes among adults with mood disorders started on **monotherapy with** lithium (n=305), quetiapine (n=526), olanzapine (n=241) or VPA (n=48)

a. **Method:** Comparative data on new adult starts to one of the 4 meds in Scotland 2000-11 with ≥ 6 months exposure and no prior use of any of the 4 meds. Excluded were those with eGFR < 30 ml/min within 12 months of starting the new med, h/o renal transplant, prior ICD-10 Dx of glomerular or tubular disease or CKD, or any psychotic disorder.

b. **Demographics:** Group mean baseline age was 40.0-43.7 yrs (range 18-64), female gender 48%-65%, and median drug exposure was 42.3 months (lithium), 29.1 months (quet), 38.4 months (olanz), 46.7 months (VPA) [range 6 to 106-147 months). Mean baseline eGFR: lithium 110.9 ml/min, comparators: 101.4 ml/min.

c. **Results: After adjustment for age, baseline eGFR, medical comorbidities, episodes of lithium level > 0.8 mEq/l, and use of ACEIs, NSAIDs and β-blockers, the mean annual eGFR change was 1.0 ml/min (lithium) vs. 0.4 ml/min (comparator), a difference that was not significant. That attributable to lithium alone was 0.24 ml/min per year.**

Clos S, Rauchhaus P, Severn A, et al. Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study. *Lancet Psychiatry*. 2015;2:1075-83.

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IT'S NOT ALWAYS LITHIUM – IT'S HOW IT IS PRESCRIBED

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Large Case-Control Study on Risk For Renal Insufficiency (RI) in Lithium Treated Patients

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Method

- New England EHR database, adults age ≥ 18 with at least one lithium prescription between 2006-13 based on e-prescribing data. Renal insufficiency (RI) was defined as: eGFR < 60 ml/min or by ICD-9 code.
- Lithium-treated patients with RI (**n=1445**) were matched 1:3 with lithium-exposed patients without RI (**n= 4306**)

Aims

- 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).
- To develop and validate a risk stratification tool.

Castro VM, et al. Stratifying risk for renal insufficiency among lithium-treated patients: an electronic health record study. *Neuropsychopharmacology* 2016; 41:1138-43

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Treatment Related Factors Associated With Renal Insufficiency

	Univariate, odds ratio	Adjusted for clinical model, odds ratio	Fully adjusted for clinical model plus other treatments			
			Odds ratio	*p*-value	[95% Conf. interval]	
Once-daily dosing	0.86	0.79	0.80	0.003	0.69	0.93
Extended release (vs immediate/citrate)	0.90	1.09	1.13	0.164	0.95	1.36
Concomitant first-generation antipsychotic	1.55	1.40	1.48	0.004	1.14	1.94
Concomitant second-generation antipsychotic	0.67	0.87	0.95	0.472	0.81	1.10
Comcomitant SSRI/SNRI	0.73	0.67	0.68	<0.001	0.58	0.80

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.

Castro VM, et al. Stratifying risk for renal insufficiency among lithium-treated patients: an electronic health record study. *Neuropsychopharmacology* 2016; 41:1138-43

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Outpatient Lithium Levels and Renal Insufficiency Risk

Maximum level analysis: 285 cases & 299 controls had at least one **outpatient** level > 1.2 mEq/L prior to their first recorded RI Dx.

- In adjusted regression models, just one level > 1.2 mEq/L was associated with RI risk with **OR 1.72 (95% CI 1.38-2.14).**

Mean outpatient level analysis (excluding values within 90 days of the RI diagnosis): In fully adjusted models using 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) **(The sweet spot for BD maintenance !!)**
- 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) **(Never !!)**

Comments:

a. In ***outpatients*** excessively high levels contribute to risk for renal dysfunction.

b. Once acutely manic 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.

Castro VM, et al. Stratifying risk for renal insufficiency among lithium-treated patients: an electronic health record study. *Neuropsychopharmacology* 2016; 41:1138-43

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Knowing Kinetics Can Prevent Dosing Errors

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Time Since Last Dose	10 hrs	12 hrs	14 hrs
Level	1.28	1.20	1.12

Comments: Once daily lithium should never be qam or qnoon as the levels obtained the next morning will be 18 hr or 24 hr trough values **and** uninterpretable.

	QD	BID	TID
Amdisen [1]	1.37	1.07	1.00
Swartz [2]	0.90	0.70	--
Greil [3]	1.04	0.81	--

Comments: BID dosing distorts the level obtained the next morning, as this will be a 24 hr trough value for half of the dose. **When a BID dose is consolidated to QHS dosing, the a.m. trough value will increase by 28%.** Many patients on BID doses are simply overexposed to lithium (one possible risk for RI). QHS only dosing also allows more time for lithium to be cleared from collecting duct cells....

1. Amdisen A. Serum level monitoring and clinical pharmacokinetics of lithium. Clin Pharmacokinet 1977;2:73-92. 2. Swartz CM. Correction of lithium levels for dose and blood sampling times. J Clin Psychiatry 1987;48:60-4. 3. Greil W. [Pharmacokinetics and toxicology of lithium]. Bibl Psychiatr 1981:69-103.

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Target Levels

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Indication	Level Range	Rationale
Acute mania	1.00 - 1.20 mEq/l	• Single levels > 1.20 mEq/l are associated with increased risk of renal insufficiency • Patients with inadequate mania control at a level of 1.20 mEq/l despite concurrent use of an antipsychotic will typically need divalproex added to obtain optimal mood control.
BD-1 or SAD-BT maintenance	0.60 - 0.80 mEq/l (Response & tolerability may dictate a range of 0.40 - 0.60 mEq/l, or a range of 0.80 - 1.00 mEq/l).	• Compelling evidence that many individuals remain stable in this range and with improved short term and long term tolerability compared to higher levels. • Maintenance levels should not exceed 1.00 mEq/l to avert long-term renal adverse effects. • Individuals > age 50 often have higher brain lithium levels than younger patients, and thus may respond to and better tolerate lithium when peripheral levels are in the lower range.
BD-2	Same as BD-1, but consider the lower end of the range	• Limited data, but control of hypomania/mixed episodes may be possible in the lower end of the serum level range for BD-2 patients who need mood stabilization.
Unipolar MDD adjunctive use	0.40 - 0.60 mEq/l	• It's the level range best studied, and is included in many consensus recommendations. Levels < 0.4 mEq/l appear less effective.

If a higher than expected level is obtained, confirm that it is a 12h level and see if patient took a dose just prior. If asymptomatic and the level < 2.00 mEq/l, hold one dose and repeat the next a.m. Send to ER if level ≥ 2.00 mEq/l or the patient has significant CNS SEs.

BID dosing: avoid if possible, otherwise do the math !

- **Principle:** If BID dosing is converted to a QHS schedule the 12h trough level will be 28% higher (though on the same total daily dose)
- The usual 12h trough maintenance level on BID dosing therefore should be no higher than 0.62 mEq/l, equivalent to 0.80 mEq/l from single QHS dosing. (The max maintenance level on BID dosing should be no higher than 0.78 mEq/l, equal to 1.00 mEq/l from single QHS dosing.)
- For acute mania, the BID maximal level is 0.94 mEq/l (comparable to 1.20 mEq/l for QHS dosing).

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Lithium: Facts & Peripheral Kinetics

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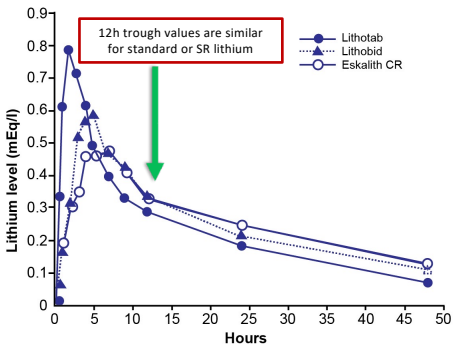
1. **Preparations: carbonate** [capsules & tablets 150, 300, 450 and 600 mg], **citrate** [8 mEq/5 ml = to 300 mg lithium carbonate) (and on the web - orotate)
2. **Equivalence:** 300 mg lithium carbonate = 8 mEq = 56 mg of elemental lithium
3. **Peripheral Kinetics**
   a. **Peripheral T_{Max}** - standard 1-3h; sustained release 3-6h
   b. **Peripheral $T_{1/2}$** - 20-24h at steady state
   c. **Food:** does not alter bioavailability but slows proximal absorption & lessens upper GI SE (nausea, cramping)
   d. **Dosing:** Always single QHS dosing, with levels obtained as 12h trough values
   - Single daily dosing incurs 20% lower long-term risk of renal dysfunction than BID dosing



Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Lithium: CNS Kinetics and Comments About Preparations

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1. **CNS T_{Max}** - delayed approximately 3h from the serum T_{Max}
2. **CNS $T_{1/2}$** - 28-48h at steady state - **there is no efficacy advantage from BID dosing !**
3. **Brain-to-serum (BTS) ratio:** Steady state brain levels correlate with serum levels and 12h post-dose brain levels are 50% lower than serum levels. Factors influencing the BTS ratio:
   a. **Dosing schedule:** Single dosing associated with higher BTS ratio than BID: 0.61 ± 0.12 vs. 0.37 ± 0.07
   b. **Age:** The BTS ratio is highly correlated in younger patients, but older patients may experience higher brain levels for any given peripheral level and thus may experience higher rates of CNS AEs.

Why use a sustained release form?

Answer. Lithium is rapidly absorbed in the upper GI tract (jejunum and ileum). Slowing this absorption can help mitigate nausea. For patients with diarrhea on an SR form, the ion is being delivered too late (in the colon) - go back to standard lithium.

Komoroski RA, et al. In vivo ^{7}Li nuclear magnetic resonance study of lithium pharmacokinetics and chemical shift imaging in psychiatric patients. Psychiatry Res 1993;50:67-76. Plenge P, et al. 24-hour lithium concentration in human brain studied by Li-7 magnetic resonance spectroscopy. Biol Psychiatry 1994;36:511-6.

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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HOW LITHIUM MOVES THROUGH THE KIDNEY AND CAUSES RENAL DYSFUNCTION

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How Lithium Moves Through the Kidney

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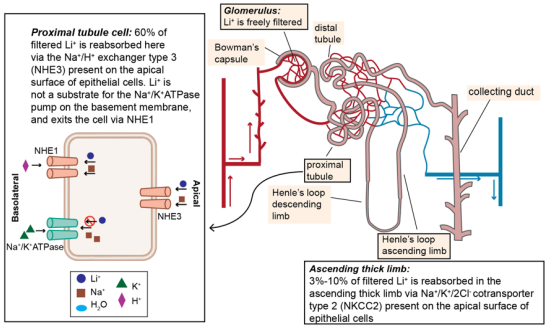
Principles:

1. Lithium is filtered like sodium and competes for glomerular reabsorption
   - Proximal (i.e. glomerular) pathology is manifested as proteinuria. Lithium only rarely induces this problem with only 36 reported cases of nephrotic syndrome,
   - Hypertension, DM are the primary causes of glomerular pathology and proteinuria
2. Medications that alter renal blood flow or deplete sodium are the primary cause of lithium toxicity.
   - Illnesses that result in low sodium levels (e.g. diarrhea with volume replacement using water and not an electrolyte solution) can also induce high lithium levels



Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: Unravelling the complex pathophysiological threads of the lightest metal. Nephrology (Carlton) 2018;23:897-903.Łukawska E, et al. Lithium toxicity and the kidney with special focus on nephrotic syndrome associated with the acute kidney injury - A case-based systematic analysis. J Appl Toxicol 2021; 41(12): 1896-1909
Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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How Lithium Causes Polyuria: It's All About ENaC

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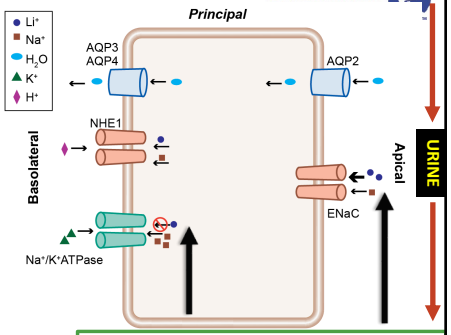
Principles:

1. 20% of reabsorption occurs in the collecting duct **principal cells** via the epithelial sodium channel (ENaC)
2. Lithium has 1.6-fold higher affinity for ENaC than does sodium, but lithium exits these cells relatively slowly resulting in intracellular accumulation.
   - Lithium is a poor substrate for the Na^+/K^+-ATPase pump and leaves slowly via the the Na^+/H^+-1 (NHE1) exchanger
3. Lithium's initial effect on renal function relates to inhibition of cellular processes in principal cells causing:
   - Downregulation of water absorbing aquaporin 2 (AQP2) channel expression and membrane trafficking
   - Vasopressin insensitivity

The clinical result is impaired urine concentrating ability and the complaint of polyuria ! (The canary in the coal mine.)



Lithium is the uninvited party guest: it rushes past sodium at the door, it won't leave by the usual exit (the Na^+/K^+-ATPase pump), and inside the cell it wreaks havoc on 2nd messenger systems.

Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: Unravelling the complex pathophysiological threads of the lightest metal. Nephrology (Carlton) 2018;23:897-903.Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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The Importance of Detecting Polyuria: It's The Earliest Signal of Lithium Related Renal Dysfunction

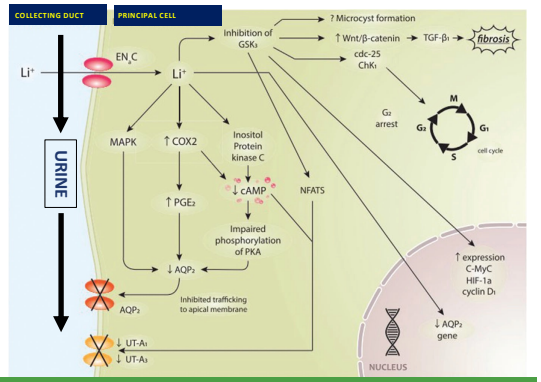
Actions at principal cells are the primary cause of renal dysfunction

1. **Early effects from accumulation in principal cells:** Lithium's actions at MAPK, protein kinase C, and COX2 decrease AQP2 expression. Lithium limits the ability of AQP2 to be trafficked and inserted into the apical membrane resulting by inhibiting GSK3-β and decreasing cAMP effects on urea transporters (UT-A).

   Net result: decreased water absorption and polyuria. [1,2]

2. **Longer term effects from accumulation in principal cells: GSK3-β** inhibition may induce the formation of microcysts, and ultimately lead to fibrosis and chronic tubulointerstitial changes through the upregulation of TGF-1β. [1,2]

   Net result: decrease in the number of principal cells and tubular atrophy [1,2]



Clinical insight: How do I stop my house from burning (principal cell loss and tubular atrophy)? **Pay attention to the smoke**. Polyuria from lithium's early effects within principal cells is that signal.

Davis J, et al. Lithium and nephrotoxicity: Unravelling the complex pathophysiological threads of the lightest metal. Nephrology 2018;23:897-903. Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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MONITORING FOR POLYURIA AND OTHER ASPECTS OF RENAL FUNCTION

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Lithium Related Renal Monitoring: The Tools

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1. **eGFR:** Measures intrinsic renal function from a blood specimen. The modern eGFR formula calculates this from creatine and cystatin C.
2. **24h Fluid Intake Record (FIR):** Total fluid intake over 24h. A good proxy for urine output and one which the patient themself can track.
   - **Method:** Ask the patient to record fluid intake for two days (48h) and average the result.
3. **Early morning urine osmolality (EMUO):** Urine is maximally concentrated in the AM (normal EMUO ≥ 850 mOsm/kg). Dilute AM urine is a proxy for the extent of nephrogenic diabetes insipidus (NDI).
   - **Method:** Give the patient the urine cup, ask them to use it the 1st time they urinate upon waking. The specimen is stable at room temp for 5 days and can be dropped at the lab when convenient.
   - **Comment:** Although a 24-hour urine collection is the gold standard, it is cumbersome for patients and a test not easily repeated if one wants to track the response to polyuria treatment.
4. **Albumin-to-creatinine ratio (ACR):** Used for those with baseline eGFR < 90 ml/min **or CKD** risk factors to define proteinuria due to CKD related risks unrelated to lithium.
   - **Method:** Best results obtained from EMUO specimen. Helpful to define extent of proteinuria due to CKD related risks prior to and during lithium treatment.
5. **Talk to your patient:** Ask at each visit about increased frequency of urination! Polyuria/polydipsia is the 3rd leading somatic adverse effect leading to lithium discontinuation (9%) behind diarrhea (13%) and tremor (11%).

Öhlund L, et al. Reasons for lithium discontinuation in men and women with bipolar disorder - a retrospective cohort study BMC Psychiatry 2018 BMC Psych 2018; 18: 37-46. Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Lithium Related Renal Monitoring: Initial

Parameter	6 weeks	3 months	12 weeks	6 months
eGFR (baseline eGFR ≥ 60 ml/min)	✅	✅		✅
eGFR (baseline eGFR 45 - 59 ml/min)	✅	✅	✅	✅
24h FIR	✅	✅		✅
EMUO	✅	✅		✅
ACR		✅		✅

Notes:

- **eGFR:** After 6 months the monitoring frequency depends on CKD stage
- **24h FIR:** Values > 3500 ml/d are grossly abnormal, 2000-3500 ml/d may indicate partial NDI
- **EMUO:** Should also be added following a new complaint of polyuria/polydipsia. Values < 850 mOsm/kg are abnormal as early morning urine should be maximally concentrated.
- **ACR:** At 3 months and 6 months for those with baseline eGFR < 90 ml/min **or** risk factors for renal dysfunction. After 6 months the monitoring frequency depends on the ACR stage.

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Lithium Related Renal Monitoring: Ongoing

a. **Routine 6 month monitoring during established lithium therapy:**
   i. Review medical history for renal dysfunction risk factors and use of nephrotoxic medications
   ii. eGFR (along with lithium level, TSH, serum calcium)
   iii. 24h FIR: Ask the patient to record fluid intake for two days (48 hours) and average the result
   iv. EMUO: For those with polyuria complaints, on stable amiloride treatment, or for patients whose most recent EMUO value is ≤ 850 mOsm/kg as verified by a repeat specimen
   v. ACR: For those with eGFR < 90 ml/min **or** risk factors for renal dysfunction as noted in 1a above

b. **Increase frequency of labs to every 3 months during established lithium therapy when one of the following are present: (higher risk patients)**
   i. eGFR value: When values are < 60 ml/min
   ii. eGFR trends: Initial evidence of a decline in eGFR > 2 ml/min over 6 months or > 4 ml/min over 12 months as verified by a repeat specimen
   iii. EMUO: For increased or new complaints of polyuria, when titrating amiloride (or adjunctive acetazolamide) to manage polyuria, or for urine osmolality values < 300 mOsm/kg
   iv. ACR: If ACR has progressed from stage A1 to A2 as verified by a repeat specimen

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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MANAGING POLYURIA AND CHANGES IN RENAL FUNCTION (EGFR)

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Using EMUO and the 24h FIR to Track Polyuria

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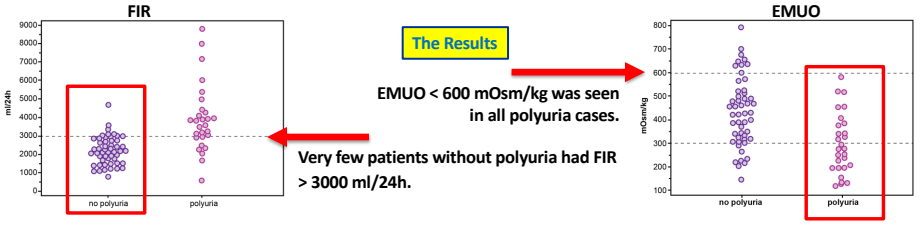
Study: 79 lithium-treated outpatients received comprehensive screening including questionnaires on polyuria, polydipsia, and nocturia; 24-hour urine collection; early morning urine osmolality (EMUO); and 24-hour fluid intake recollection (FIR).
(Polyuria definition: urine output > 3000 ml/24h)

Expected values: EMUO: Urine is maximally concentrated in the morning. EMUO is ≥ 850 mOsm/kg.
FIR: Most individuals consume on average 2000 ml/24 hours



Kinahan JC, et al. Diagnostic accuracy of tests for polyuria in lithium-treated patients. J Clin Psychopharm 2015; 35: 434-441
Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Treating Lithium Related Polyuria

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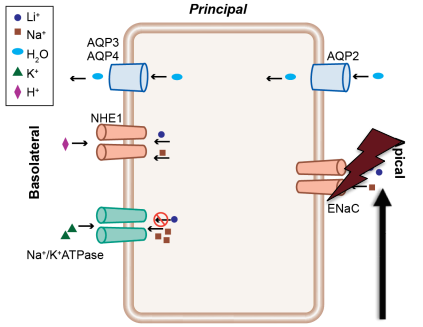
- ✓ **Amiloride, an ENaC antagonist. (Note:** Amiloride should not be combined with ACEIs, ARBs, spironolactone or triamterene due to risk of hyperkalemia.).
  - **Amiloride Dosing:** 5 mg qam x 7 days then increase to 5 mg BID. (Maximum dose 10 mg PO BID)
  - Repeat EMUO and 24h FIR in 6 weeks to allow lithium effects on collecting duct principal cells to slowly dissipate.
- ✓ **Treatment goal:** No patient complaints of polyuria, EMUO > 600 mOsm/kg and 24h FIR < 2500 ml.
- – **When amiloride is not enough:** Use the carbonic anhydrase inhibitor **acetazolamide** adjunctively. (**Note:** Acetazolamide decreases lithium levels 31% - adjust lithium dosing based on level).
  - **Acetazolamide dosing:** 250 mg PO BID initially. Allow 2 weeks before rechecking 24h FIR and EMUO and increasing to 750 mg/d. (Maximum daily dose: 500 mg BID.)



Amiloride to the rescue: as an ENaC antagonist it prevents lithium entry into collecting duct principal cells

Kortenoeven ML, Li Y, Shaw S, et al. Amiloride blocks lithium entry through the sodium channel thereby attenuating the resultant nephrogenic diabetes insipidus. Kidney Int 2009;76:44-53.Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Managing eGFR Declines

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Principle: recent studies indicate that when dosed once daily with recommended 12h trough levels the renal effects of lithium are more modest than previously estimated. Much of the CKD risk relates to medical comorbidities.

- – **Increase renal/level monitoring to q 3 months:**
  - CKD stage G3a (45-59 ml/min)
  - if there is a decline in eGFR > 2 ml/min over 6 months or > 4 ml/min over 12 months as verified by a repeat specimen
- – **Reassess need for lithium:** As eGFR approaches stage G3b CKD (eGFR 30-44 ml/min), re-evaluate the compelling need to remain on lithium.
  - Considerations: can the patient negotiate more frequent laboratory monitoring, was there failure of non-lithium therapies (especially suicidality), patient preference for staying on lithium.

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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STARTING AND MONITORING LITHIUM

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Baseline Work-Up (Note: Most of these are part of SGA monitoring)

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Measure	Rationale	Response to Abnormal Results
History	Personal or family Hx of CKD or risk factors, use of nephrotoxic medications or medications having kinetic interactions with lithium.	• Medical comorbidity and CKD risk factors are common in patients with SMI. Their presence does not disqualify a patient from a lithium trial.
Weight, body mass index (BMI)	Lithium has modest weight gain, but it will be additive with that from other psychotropics (SGAs, VPA).	• Establishes baseline.
Blood pressure	Rule out untreated hypertension, a CKD risk factor.	• Refer for treatment. Not a reason to delay lithium, but must follow-up if a medication that interacts with lithium is added.
Thyroid stimulating hormone (TSH)	Baseline is necessary due to lithium's effect on thyroid function.	• Refer for treatment. Hypothyroidism not a reason to delay lithium, but patient will need follow-up to adjust L-thyroxine dose. • Endocrinology consultation (even if informal) is helpful for undiagnosed hyperthyroidism to determine work-up.
Chemistry panel	Rule out undiagnosed electrolyte disturbances, document serum calcium, and check eGFR. **There is no absolute minimum eGFR to start lithium, but 60 ml/min is a reasonable threshold.**	• Appropriate work-up depending on the electrolyte abnormality. • Baseline eGFR needed to determine the monitoring frequency.
Pregnancy test	For women of reproductive age.	• Rule out undetected pregnancy.
Urine albumin-to-creatinine ratio (ACR)	**Indication:** early morning specimen for ACR if eGFR < 90 ml/min or CKD risk factors present to detect baseline glomerular disease.	• Stages A2 (30 - 300 mg/g) or A3 (> 300 mg/g) should be referred to nephrology for consultation prior to starting lithium.
ECG	**Indication:** > 40 years old, especially with cardiac risk factors, to rule out untreated conduction abnormalities or other cardiac disease. **Strongly consider:** H/o arrhythmia, other cardiac disease, recurrent syncope or near syncopal episodes, family h/o sudden death before the age of 45 or Brugada syndrome.	• Cardiology consultation for abnormal findings, or when the patient has a history of arrhythmia, other cardiac disease, recurrent syncope or near syncopal episodes, or family history of sudden death or Brugada syndrome.

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Baseline Work-Up: Optional Items

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Measure	Rationale	Response to Abnormal Results
Early morning urine osmolality (EMUO)	Not necessary at baseline, but EMUO encouraged among older patients (age > 50 years) due to age related declines in urine osmolality.	• Establishes a baseline urine osmolality to help track lithium related changes.
CBC with differential	Absolute neutrophil count (ANC) to define the patient's baseline, as lithium increases the ANC due to its effects on granulocyte colony stimulating factor (G-CSF) production.	• Appropriate work-up depending on the abnormality found (e.g. differentiating low ANC from medications such as divalproex/valproate, or due to benign neutropenia).
A1C	Rule out untreated diabetes mellitus (DM) or prediabetes, both of which are significant CKD risk factors.	• A1C values ≥ 6.5% are diagnostic of diabetes. In those with known DM, values > 7.0% represent less than ideal control and need to be addressed. Undiagnosed or undertreated DM should be addressed, but need not delay lithium treatment.
Lipid panel	Rule out untreated dyslipidemia, a significant CKD risk factor.	• Significant abnormalities must be addressed, but need not delay lithium treatment.

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Ongoing Nonrenal Lithium Related Monitoring

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Parameter	Comments
Vitals signs	• Weight at every visit with BMI calculated, BP every 6 months
ECG	• A follow-up should be obtained once lithium is a steady state after initial titration (e.g. week 12) only in patients who required an ECG upon lithium initiation. • An annual ECG may be required by local protocol or if there are pre-existing abnormalities. • An annual ECG is not recommended by most treatment guidelines for other patients.
Serum calcium and TSH	• Every 6 months. • An increase in the frequency or the need to add additional laboratory measures (e.g. ionized calcium, parathyroid hormone, T3, T4, free T4 index) will be dictated by the presence of abnormalities.
Lithium level: new starts	• A 12h trough one week after any dosage change or following the introduction or removal of a medication having kinetic interactions with lithium. • Through week 24 (6 months) the level should be obtained with the eGFR.
Lithium level: ongoing treatment	• 12h trough level should be obtained with the eGFR, and the frequency dictated by the eGFR. • For patients with low eGFR values, this may necessitate levels every 6 weeks. • If maintenance levels are in the range of 0.80-1.00 mEq/l consider increasing the frequency of levels to every 3 months to minimize the occurrence of supratherapeutic levels that might incur risk for renal toxicity.

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Starting Lithium: Gradual Titration Method

1. **Advantages:** unlikely to incur tolerability issues, unlikely to have supratherapeutic level.
2. **Disadvantages:** prolongs the time to therapeutic serum levels.
3. **Optimal situation:** initiation in outpatients with modest symptoms where a delay in reaching therapeutic levels is not critical, and when establishing rapport by minimizing adverse effects is important.

When to obtain an initial level. Always at least 5 days after a dose change, but there is no perfect answer with respect to the dose at which the initial level is drawn! The answer depends on many factors:

1. A patient's ability to go to the lab (and their tolerance for repeated phlebotomy).
2. Baseline eGFR and presence of medications that kinetically interact with lithium clearance.
3. The target serum lithium level (e.g. low, typical or high).
4. **Typical dose thresholds:**
   - 600 mg: pts with low baseline eGFR, pts on meds expected to raise levels, or when target level is 0.4 – 0.6 mEq/l
   - 900 mg: pts with high baseline eGFR, pts not on meds expected to raise levels, or when target level is 0.6 – 1.00 mEq/l

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Starting Lithium: 600 mg Test Dose Method

1. **Advantages - 1:** eliminates guesswork by taking into account all variables impacting lithium clearance (age, eGFR, concurrent meds, etc.). **The 24 h level after a single 600 mg dose** predicts the maintenance dose needed for a level 0.60 – 1.20 mEq/l, with an R^2 of 0.97 with that obtained at steady state.
2. **Advantages – 2:** Avoids use of complicated predictive formulas that may not exactly capture a specific patient's lithium clearance.
3. **Disadvantages:** need to get a level at exactly 24 h after the 600 mg test dose.
4. **Optimal situation:** initiation in manic inpatients to avoid delays in reaching therapeutic levels due to titration based guesses.

24 h lithium level mEq/l	Cooper's suggested dose	Multiple daily dosing converted to QHS only
< 0.05	1200 mg TID	(See note below)[2]
0.05–0.09	900 mg TID	2100 mg
0.10–0.14	600 mg TID	1350 mg
0.15–0.19	300 mg QID	900 mg
0.20–0.23	300 mg TID	750 mg
0.24–0.30	300 mg BID	450 mg
> 0.30	300 mg BID[3]	Avoid lithium[3]

BID = twice per day; TID = thrice per day; QID = 4 times per day

Cooper TB, Simpson GM. The 24-Hour Lithium Level as a Prognosticator of Dosage Requirements: A 2-Year Follow-Up Study. Am J Psychiatry 1976; 33(4): 440-443.
Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Starting Lithium: 30 mg/kg Loading Method

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1. **Advantages:** hastens the time to steady state by using a weight based formula to load lithium.
2. **Disadvantages:** for obese women the standard dose (30 mg/kg) tended to generate supratherapeutic levels. Also, the QHS dose after the load is a judgment call based on eGFR & the 12-hour lithium level that morning.
3. **Optimal situation:** initiation in manic inpatients to avoid delays in reaching therapeutic levels
4. **The method:** PharmDs at LA County-USC Med Ctr developed a 30 mg/kg formula to achieve 12 h levels of 0.9 - 1.1 mEq/L. Critical to their approach was to administer lithium in **3 divided doses of ~ 10 mg/kg each** (**4 pm, 6 pm and 8 pm**), and use **LithoBid to minimize GI side effects for the loading procedure.**

Demographics: 20 M/18 F inpts, mean age: 36.2 ± 2.95 yrs, mean weight 70.1 ± 3.50 kg, CrCl: 46-128 ml/min.
Female loading dose range: 1200 - 2400 mg. Male loading dose range: 1800 - 3000 mg.

Results: No dropouts, and no adverse effects (nausea, diarrhea or other GI distress, neuromuscular or CNS effects) during the loading procedure or in the 12 hours afterwards.

i. Males 12-hour levels range: 0.58 - 1.10 mEq/L. Mean Error: 0.16 ± 0.09 mEq/L
ii. Females 12-hour levels range: 0.45 - 1.40 mEq/L. Mean Error: 0.28 ± 0.14 mEq/L.
iii. 3 of the 4 with levels beyond that predicted by the formula (1.28 - 1.40 mEq/L) were obese women.

Conclusions: Patients can be safely loaded with SR lithium at 30 mg/kg in 3 divided doses.

Kook KA, et al. Accuracy and safety of a priori lithium loading J Clin Psychiatry 1985; 46(2) : 49-51. Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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MANAGING LITHIUM-RELATED ADVERSE EFFECTS AND DRUG INTERACTIONS

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Lithium Related Drug Interactions

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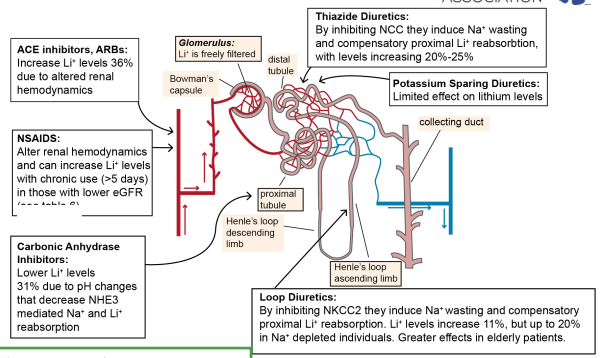
1. Most drug interactions are well known. **You can manage these!** When starting a med that increases lithium levels, reduce the lithium dose by the appropriate amount and recheck the level in a week.
2. The only ACE inhibitor never to use with lithium is **lisinopril because it is 100% renally cleared**.
3. Transient NSAID use (≤ 5 day) with eGFR > 75 ml/min and baseline levels < 0.80 mEq/l unlikely to be clinically significant.
   - Extended or chronic NSAID use with high baseline levels (≥ 0.80 mEq/l), eGFR < 75 ml/min or in any patient receiving another interacting medication: decrease current lithium dose by 25%, and check levels after 1 week, 3 weeks, 6 weeks and 12 weeks.



An odd interaction: Sodium-glucose cotransporter 2 (SGLT-2) inhibitors used for diabetes reduces lithium levels 63%. Check lithium level after 72 hours and adjust dosage. Recheck level in 1 week.

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Common Nonrenal Adverse Effects

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- **Tremor:** managed initially by propranolol, with primidone or level reduction possible options
  - **Other CNS complaints** (e.g. cognitive slowing, emotional blunting) require consideration of all causes (e.g. depressed mood, other medication effects) before deciding on a course of action. Modest level reduction can be considered if other causes have been ruled out.
- **ECG changes:** Common benign findings reflect the chronicity of lithium exposure and accumulation in myocytes, and do not represent a source of sudden cardiac death risk. These include PR interval prolongation, T-wave changes and development of U-waves. **These are not a reason to discontinue lithium.** Rare patients with sinus node dysfunction may require treatment interruption until pacemaker placement.
- **Skin/hair:** Ask at every visit about skin changes (e.g. acneiform eruptions) and hair loss to detect these problems early and before the patient decides to stop lithium.
  - **Hair loss:** Topical 5% minoxidil (all genders). Can use 2% if scalp irritation.
  - **Acne:** Start with OTC benzoyl peroxide 2%-10% BID. Some may require the addition of topical retinoids. For more severe cases oral antibiotics or hormonal therapy may be needed and are best prescribed by a dermatologist. For other skin eruptions: depends on issue.
- **Thyroid and parathyroid dysfunction:**
  - **Hypothyroidism:** The annual incidence of new onset hypothyroidism during lithium treatment is 1.5%, but may be 3-fold higher in women. Treated with L-thyroxine – never a reason to stop lithium. Patients may have less depression recurrence with TSH values closer to the midpoint of the therapeutic range (2.4 mIU/l).
  - **Hyperparathyroidism:** May require surgery, but cinacalcet is now an option in lieu of surgery for some patients.

Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023.

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Summary

- Lithium remains the gold standard mood stabilizer for any patient with a history of mania
  - SGA monotherapy is often inadequate for those with a history of mania
  - Lithium also has unique neuroprotective and anti-suicide properties
  - Provide women of childbearing potential with the latest data on lithium use in the 1st trimester, and during breastfeeding. VPA is not an option for women of childbearing potential.
- Renal impact is minimized by once nightly dosing with maintenance levels in the range of 0.60 - 0.80 mEq/l, but never higher than 1.00 mEq/l
  - Monitor renal parameters: eGFR, ACR, EMUO
- Adjust dosing and levels for kinetic interactions
- Use EMUO and the 24h FIR to monitor polyuria complaints
  - Treat polyuria with amiloride, and, if necessary acetazolamide

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THANK YOU!

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