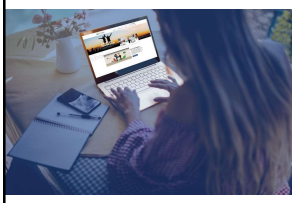
Welcome



Clozapine & LAI Virtual Forum

November 1, 2023 | 4:00 – 5:00 PM ET

The Clozapine & LAI Virtual Forum is a peer-to-peer, interactive dialogue between psychiatrists, nurse practitioners, and other prescribing clinicians. It is informal, no registration required — just join our Zoom call and share your challenges and questions on the month's trending topic around either clozapine or LAIs.

TODAY'S TOPIC:
Demystifying Lithium's Renal Effects

1

MODERATORS

Robert Cotes, MD

SMI Adviser Physician Expert; Emory University

Dr. Robert Cotes, MD, is an Associate Professor at Emory University School of Medicine in the Department of Psychiatry and Behavioral Sciences. He has interest in clozapine, characterizing persistent symptoms of schizophrenia, understanding cardiometabolic side effects of antipsychotic medications, and first episode psychosis.

Donna Rolin, PhD, APRN

SMI Adviser Nursing Expert; University of Texas, Austin

Dr. Donna Rolin is Clinical Associate Professor and the Director of the Psychiatric Mental Health Nurse Practitioner program at the University of Texas with 23 years of experience in psychiatric nursing, including inpatient, community, forensic, and older adult settings.

Jonathan M. Meyer, MD

SMI Adviser Physician Expert; University of California, San Diego

Dr. Jonathan M. Meyer, MD, is a Voluntary Clinical Professor of Psychiatry at the University of California, San Diego School of Medicine. He has broad interests in psychopharmacology, especially for medications used to treat schizophrenia and bipolar disorder. Dr. Meyer has published books on the use of clozapine, lithium and also how to use plasma antipsychotic levels to optimize schizophrenia treatment.

Megan Ehret, PharmD, MS, BCPP

SMI Adviser Pharmacy Consultant, University of Maryland

Dr. Megan Ehret is a Professor at University of Maryland School of Pharmacy in the Department of Practice, Sciences, and Health Outcomes Research and is Co-Director of the Mental Health Program. She is a Past-President of the American Association of Psychiatric Pharmacists. Her current interests include psychotropic medication adherence and the incorporation of the psychiatric pharmacist in practice.

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Faculty Disclosures

- **Dr. Meyer:** Advisor—Alkermes, Axsome, BioXcel, Cerevel, ITCI, Karuna, Neurocrine, Otsuka America, Relmada, Sumitomo, Teva; Speaker's Bureau—AbbVie, Alkermes, Axsome, ITCI, Neurocrine, Noven, and Teva

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Learning Objectives

- Upon completion participants will understand lithium's renal journey, and appreciate how the use of modest outpatient 12h trough serum levels and once daily lithium dosing lessens lithium's renal impact.
- Upon completion participants will appreciate the importance of polyuria as the first sign of lithium related renal dysfunction, the pathophysiology of polyuria, newer methods for tracking polyuria, and managing polyuria with amiloride.

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What's Happening in the World of Bipolar Disorder Treatment?

5

Dangers of Valproate in Women of Reproductive Potential

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**

European Medicines Agency. New measures to avoid valproate exposure in pregnancy endorsed. March 23, 2018. Accessed January 1, 2022. https://www.ema.europa.eu/en/documents/press-release/new-measures-avoid-valproate-exposure-pregnancy-endorsed_en.pdf. Freeman MP. *J Clin Psychiatry*. 2022;83(6):22ed. Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Latest advice for medicines users. GOV.UK. December 5, 2022. Accessed June 2023. 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 Valproate: The Concerns

1. **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)."

2. **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."**

3. **Males:** Impact on fertility (based largely on animal studies, and appears reversible)

Zhang L, et al. *Eur J Obstet Gynecol Reprod Biol.* 2016;202:26-31. Clayton-Smith J, et al. *Orphanet J Rare Dis.* 2019;14(1):180. Medicines and Healthcare products Regulatory Agency. Drug Safety Update: Latest advice for medicines users. GOV.UK. December 5, 2022. Accessed June 2023. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1124612/Dec-2022-DSU-PDF.pdf.

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Lithium Kinetics

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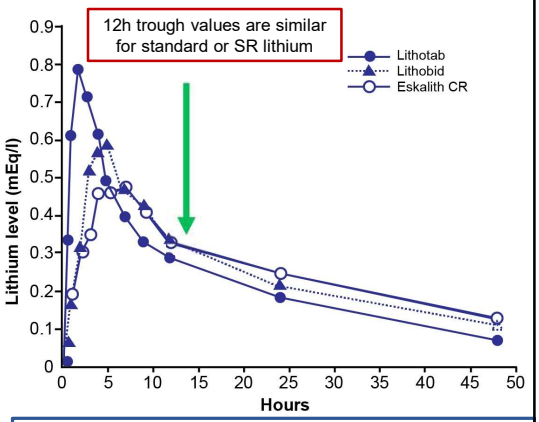
Lithium: Facts and Peripheral Kinetics

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
      - The CNS $T_{1/2}$ is 28-48h at steady state: There is no efficacy advantage from BID dosing



Why use a sustained release form?

Answer. Lithium is rapidly absorbed in the upper GI tract (jejunum and ileum). Slowing absorption can 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.

- SE = side effect; QHS = every night at bedtime; CNS = central nervous system.
- Meyer JM, et al. *The Lithium Handbook – Stahl's Handbooks*. Cambridge University Press; 2023.

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Knowing Kinetics Can Prevent Dosing Errors

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 18h or 24h values **and** uninterpretable.

	QD	**BID**	**TID**
Amdisen	1.37	1.07	1.00
Swartz	0.90	0.70	--
Greil	1.04	0.81	--

Comments: BID dosing distorts the level obtained the next morning, as this will be a 24h 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....

qam = every morning; qnoon = every day at noon; QHS = every night at bedtime.

Amdisen A. Serum level monitoring and clinical pharmacokinetics of lithium. *Clin Pharmacokinet*. 1977;2(2):73-92. Swartz CM. Correction of lithium levels for dose and blood sampling times. *J Clin Psychiatry*. 1987;48(2):60-64. Greil W. Pharmakokinetik und Toxikologie des Lithiums [Pharmacokinetics and toxicology of lithium]. *Bibl Psychiatr*. 1981;(161):69-103.

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Lithium's Renal Journey

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SAMHSA Substance Abuse and Mental Health Services Administration

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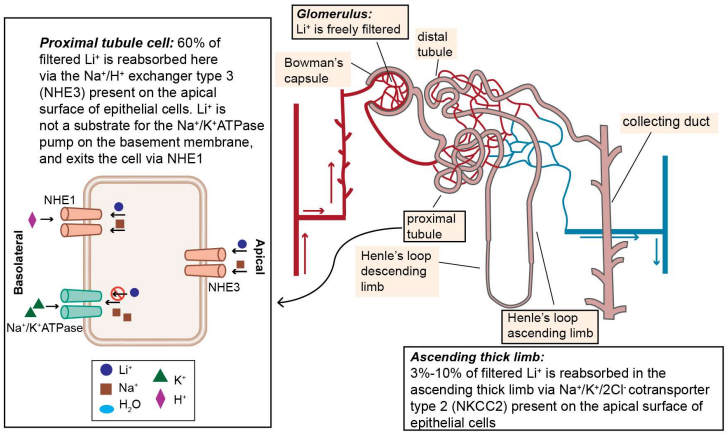
How Lithium Moves through the Kidney

Principles

1. As an ion lithium is filtered like sodium and competes for reabsorption proximally
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



NHE1 = Na^+/H^+ exchanger type 1; NHE3 = Na^+/H^+ exchanger type 3; NKCC2 = $Na^+/K^+/2Cl^-$ cotransporter type 2.

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

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SAMHSA Substance Abuse and Mental Health Services Administration

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Lithium-Related Renal Effects:
What It Does and Does Not Do

What Can Occur Due to Lithium

- **Impact on eGFR:** Can occur, especially with multiple daily dosing or high maintenance levels
  - **Be mindful that medical comorbidity may be contributing as much or more than the use of lithium**
- **Polyuria:** Also a known adverse effect, with greater risk from multiple daily dosing

What Is Not Due to Lithium

- **Proteinuria:** The loss of protein in the urine (measured using the urine albumin-to-creatinine ratio (ACR)) reflects glomerular pathology, a common sequela of hypertension, metabolic syndrome/type 2 diabetes mellitus
  - In a comprehensive 2021 review, full-blown nephrotic syndrome (defined as proteinuria > 3.5 g/24 hr/1.73 m^2 with hypoalbuminemia, edema, and hyperlipidemia) had been reported in only 36 cases where lithium was deemed the primary etiology. **Comment:** The reason to monitor ACR in those with CKD risks is to identify a preexisting problem that will typically be blamed on lithium

ACR = albumin-to-creatinine ratio.

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, et al. *The Lithium Handbook – Stahl's Handbooks*. Cambridge University Press; 2023.

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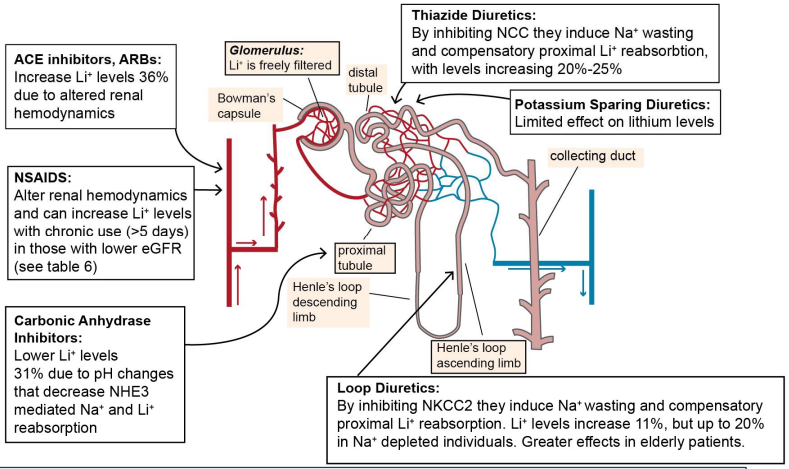
Lithium-Related Drug Interactions

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.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; NSAID = non-steroidal anti-inflammatory drug; eGFR = estimated glomerular filtration rate; NCC = thiazide-sensitive Na^+-Cl^- cotransporter. Meyer JM, et al. *The Lithium Handbook – Stahl's Handbooks*. Cambridge University Press; 2023.

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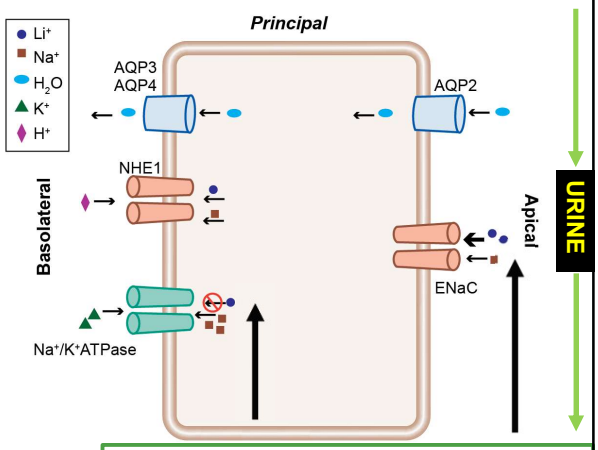
How Lithium Causes Polyuria: It's All About ENaC

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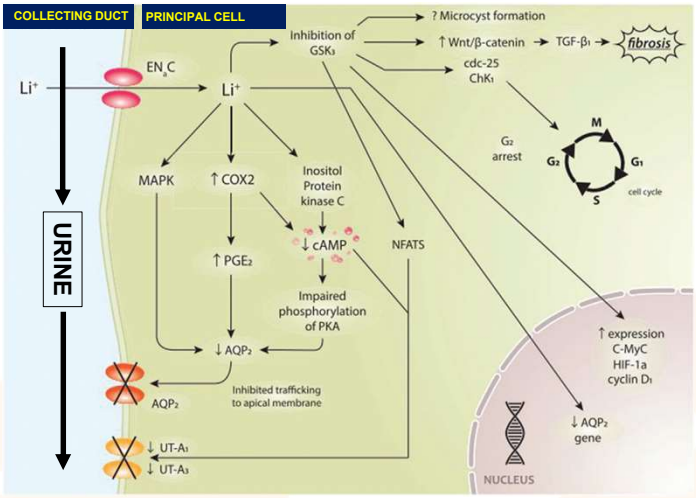
The Importance of Detecting Polyuria:
It's the Earliest Signal of Lithium-Related Renal Dysfunction

Principles

1. **Actions at 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.

2. **GSK3-β** inhibition may induce the formation of microcysts, and ultimately lead to fibrosis and chronic tubulointerstitial changes through the upregulation of TGF-1β.



Clinical insight: How do I stop my house from burning (death of principal cells)? Pay attention to the smell of smoke. Polyuria from lithium's actions at principal cells is that signal.

Davis J, et al. *Nephrology (Carlton)*. 2018;23(10):897-903. Meyer JM, Stahl SM. The Lithium Handbook – Stahl's Handbooks. Cambridge University Press, 2023. Wall SM. *Kidney Res Clin Pract*. 2017;36(4):305-317.

It's Not Always Lithium – Bipolar Disorder Is Associated with Chronic Kidney Disease

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Terminology of Chronic Kidney Disease

- Individuals with eGFR < 60 ml/min/1.73 m^2 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 or stage of CKD is preferred**

Staging of CKD by eGFR:

Stage	eGFR (ml/min)
1. Normal	≥ 90
2. Mild	60-89
3a. Moderate	45-59
3b. Moderate	30-44
4. Severe	15-29
5. Failure	< 15

CKD = chronic kidney disease.
Chen TK, et al. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA*. 2019;322(13):1294-1304.

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eGFR and Albuminuria Stages

eGFR categories (units in ml/min/m²)			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

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

DM = diabetes mellitus.

Kessing LV, et al. Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study [published correction appears in JAMA Psychiatry. 2016 Feb;73(2):179]. *JAMA Psychiatry*. 2015;72(12):1182-1191.

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Bipolar Disorder is Associated with Nearly 3-Fold Higher CKD Risk than That in the General Population

	Definite CKD	Possible CKD	End-Stage CKD
Cohort 1 - General Population (n)	0.80% (14,727)	1.0% (18,762)	0.2% (3407)
Cohort 2 - Bipolar Disorder Only (n)	**2.6%** (278)	**3.0%** (319)	**0.6%** (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 [published correction appears in JAMA Psychiatry. 2016 Feb;73(2):179]. *JAMA Psychiatry*. 2015;72(12):1182-1191.

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Bipolar Disorder Is Associated with Increased CKD Risk with Lithium or Anticonvulsants

Hazard Ratios of CKD for 10591 Patients With a Main Diagnosis of a Single Manic Episode or Bipolar Disorder in Cohort 2

	Definite CKD (n = 278)		Possible CKD (n = 319)		End-Stage CKD (n = 62)	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Lithium prescriptions, No.						
0	1 [Reference]	<.001	1 [Reference]	<.001	1 [Reference]	.30
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)		1.31 (0.83-2.07)		1.82 (0.75-4.42)	
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]	<.001	1 [Reference]	<.001	1 [Reference]	.002
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)		1.71 (1.13-2.59)		1.74 (0.69-4.37)	
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)	

Kessing LV, et al. Use of Lithium and Anticonvulsants and the Rate of Chronic Kidney Disease: A Nationwide Population-Based Study [published correction appears in JAMA Psychiatry. 2016 Feb;73(2):179]. *JAMA Psychiatry*. 2015;72(12):1182-1191.

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What is the Independent Effect of Lithium on eGFR?

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 adjustments 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**

h/o = history of; ICD-10 = International Classification of Diseases, Tenth Revision; ACEIs = angiotensin-converting enzyme inhibitors.

Clos S, et al. Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study [published correction appears in Lancet Psychiatry. 2015 Dec;2(12):1056]. *Lancet Psychiatry*. 2015;2(12):1075-1083.

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It's Not Always Lithium – It's How It is Prescribed

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Largest Study on Risk for Renal Insufficiency (RI) In Lithium-Treated Patients

Method

- New England EHR database, adults age ≥ 18 with at least one lithium prescription 2006-2013 based on e-prescribing data. 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(4):1138-1143.

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Demographic Factors Associated with Renal Insufficiency

	Univariate, odds ratio	Adjusted			
		Odds ratio	*p*-value	[95% Conf. interval]	
Sex, male	0.68	0.57	<0.001	0.48	0.67
Race/ethnicity, white	1.63	1.53	<0.001	1.21	1.94
Age (per decade)	1.80	1.55	<0.001	1.45	1.65
Charlson index (Log 10)	2.68	1.46	<0.001	1.31	1.64
Insurance, private	1.01	1.29	0.006	1.08	1.53
Lifetime hypertension	4.74	2.62	<0.001	2.18	3.16
Lifetime smoking	1.79	1.27	0.01	1.06	1.53
Lifetime diabetes mellitus	3.16	1.17	0.166	0.94	1.46
Any schizophrenia/schizoaffective	1.72	1.63	<0.001	1.31	2.03

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 diagnosis.

Castro VM, et al. Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study. *Neuropsychopharmacology*. 2016;41(4):1138-1143.

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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(4):1138-1143.

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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, the presence of 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 for outpatients!!)**

Comments

a. In 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

Castro VM, et al. Stratifying Risk for Renal Insufficiency Among Lithium-Treated Patients: An Electronic Health Record Study. *Neuropsychopharmacology*. 2016;41(4):1138-1143.

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Target Levels

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)

BD-1 = bipolar 1 disorder; SAD-BT = schizoaffective disorder, bipolar type; BD-2 = bipolar 2 disorder.

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

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Renal Monitoring

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Lithium-Related Renal Monitoring: The Tools

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 as recorded by the patient. A good proxy for urine output and one which the patient themself can track
   - **Method:** Ask the patient to record fluid intake for two separate days (48h) and average the result
3. **Early morning urine osmolality (EMUO):** Urine is maximally concentrated in the AM. 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
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. **Talking to your patient: Ask at each visit about increased frequency of urination!** Polyuria or polydipsia is the 3rd leading somatic adverse effect leading to lithium discontinuation (9%) behind diarrhea (13%) and tremor (11%)

NDI = nephrogenic diabetes insipidus.

Meyer JM, et al. *The Lithium Handbook – Stahl's Handbooks*. Cambridge University Press; 2023.
Öhlund L, et al. Reasons for lithium discontinuation in men and women with bipolar disorder: a retrospective cohort study [published correction appears in BMC Psychiatry. 2018 Oct 3;18(1):322]. *BMC Psychiatry*. 2018;18(1):37.

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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 (albumin-to-creatinine ratio)		☑		☑

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 grossly 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, et al. *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

1. Review medical history for renal dysfunction risk factors and use of nephrotoxic medications
2. eGFR (along with lithium level, TSH, serum calcium)
3. 24h FIR: Ask the patient to record fluid intake for two days (48 hours) and average the result
4. EMUO: For those with polyuria complaints, on stable amiloride treatment, or whose most recent EMUO value is ≤ 850 mOsm/kg as verified by a repeat specimen
5. 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)

1. eGFR value: When values are < 60 ml/min
2. 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
3. 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
4. ACR: If ACR has progressed from stage A1 to A2 as verified by a repeat specimen

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

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Managing Lithium - Related Adverse Effects

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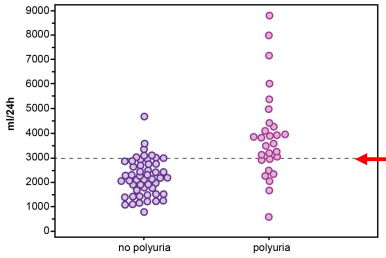
Using Early Morning Urine Osmolality (EMUO) and the 24h Fluid Intake Record (FIR) to Track Polyuria

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 record (FIR). **(Polyuria definition: Urine output > 3000 ml/24h)**

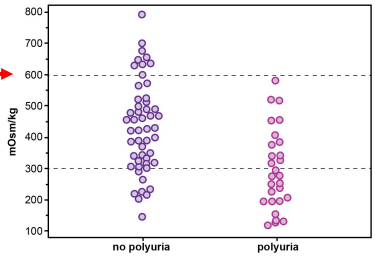
Expected values: EMUO: Urine is maximally concentrated in the morning. EMUO is ≥ 850 mOsm/kg
FIR: Most individuals consume on average 2000 ml/24 hours



Results

EMUO < 600 mOsm/kg was seen in all polyuria cases

Very few patients with polyuria had FIR > 3000 ml/24h



Kinahan JC, et al. Diagnostic Accuracy of Tests for Polyuria in Lithium-Treated Patients. *J Clin Psychopharmacol*. 2015;35(4):434-441.
Meyer JM, et al. *The Lithium Handbook – Stahl's Handbooks*. Cambridge University Press; 2023.

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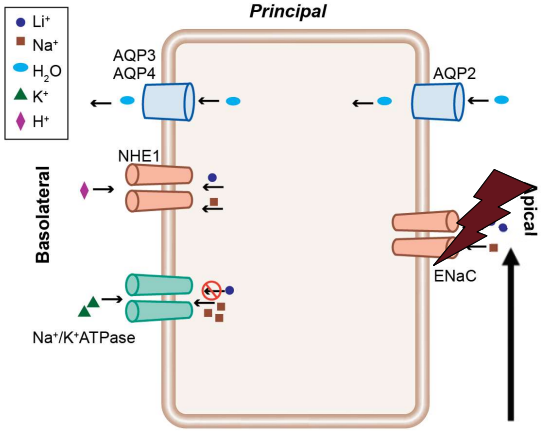
Treating Lithium Related Polyuria

- ✓ **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

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

G3a = subdivision of CKD stage G3; G3b = subdivision of CKD stage G3.
Meyer JM, et al. *The Lithium Handbook – Stahl's Handbooks*. Cambridge University Press; 2023.

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Practical Take-Aways

- ✓ Lithium remains the gold standard mood stabilizer for any patient with a history of mania
- ✓ Using lithium once daily QHS and keeping the 12h levels modest are evidence-based measures to limit the renal adverse effects
- ✓ Polyuria represents the early signal of lithium-related renal effects. Track it with 24h FIR and EMUO and treat it with **amiloride** (an ENaC antagonist)

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Questions?

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LAI Topic

December 3, 2023 @4-4:45pm ET

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- www.smiadviser.org/cloz_lai_signup

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