Association of Lithium Use and a Higher Serum Concentration of Lithium With the Risk of Declining Renal Function in Older Adults: A Population-Based Cohort Study

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ABSTRACT

Objective: Lithium is an important mood disorder treatment; however, the renal risks of its use in older adults are unclear. We wished to determine in older adults (1) whether lithium is associated with increased risk of renal decline compared to valproate and (2) whether this association differs with higher vs lower baseline serum lithium concentrations.

Method: We conducted a population-based cohort study using linked health care databases (Ontario, Canada). The cohort consisted of older adults (mean age 71 years) accrued 2007–2015; 3,113 lithium users were propensity-score matched 1:1 to 3,113 valproate users. Users with higher (> 0.7 mmol/L) or lower concentration of serum lithium were further examined. The primary outcome was ≥ 30% loss in estimated glomerular filtration rate from baseline.

Results: Matched lithium users and valproate users demonstrated similar indicators of baseline health over a median (maximum) follow-up of 3.1 (8.3) years. Lithium was associated with increased risk of renal function loss compared to valproate (674/3,113 [21.7%] vs 584/3,113 [18.8%]; 6.5 vs 5.7 events per 100 person years; hazard ratio = 1.14 [95% CI = 1.02–1.27]). When baseline serum lithium concentrations were > 0.7 mmol/L, the risk of renal decline compared to valproate use was 1.26 (95% CI = 1.06–1.49); when baseline lithium concentrations were ≤ 0.7 mmol/L, the risk was 1.06 (95% CI = 0.92–1.22).

Conclusion: In older adults, lithium use is associated with a statistically significant increased risk of renal decline compared to valproate use, although the decline is less than previously reported. Further studies should confirm whether this effect is primarily in patients with higher serum lithium concentrations.

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Lithium remains the gold-standard treatment in bipolar disorder,[1] with up to 30%–40% of patients responding preferentially to this medication.[2,3] Lithium is also an important therapeutic for treatment-resistant depression, which affects up to 60% of older adults with unipolar depression.[4] Clinical trials are now exploring potential neuroprotective effects of lithium in dementia[5] and stroke.[6]

With over 50% of patients treated for bipolar disorder and depression expected to be over the age of 60 by 2030,[7] and 35%–45% of older adults having pre-morbid moderate chronic kidney disease (CKD),[8] the renal safety of lithium is an important consideration. CKD is a serious condition with notable morbidity and mortality.[9] CKD can also sometimes necessitate lithium discontinuation, which often leads to relapse of the mood disorder.[10] Recent large epidemiologic studies including both geriatric and adult patients have reported a 1.5- to 2.5-fold higher risk of incident CKD among lithium users.[11,12] Fears of increased renal disease have contributed to the low North American rates of prescribing lithium in bipolar disorder: < 8%–15% vs 30%–50% in parts of Europe.[13,14] However, the link between lithium and a long-term decline in kidney function remains somewhat controversial, particularly in younger adult patients, with some studies finding no association.[15,16] Most studies in the field have not focused on geriatric patients and have had limited geriatric sample sizes (often n < 50–100).[17] It is difficult to extrapolate the findings of studies of younger adults, since older adults often have premorbid renal decline, multiple cardiovascular comorbidities, and concurrent pharmacotherapies (eg, diuretics, anti-inflammatories) that may affect risk.[18] Clinical trials are very difficult to conduct in older lithium users, with only one 9-week randomized controlled trial (RCT) of lithium vs valproate in late-life mania (n = 224)[19] and one small 2-year lithium discontinuation RCT in late-life unipolar depression (n = 12).[20] Similarly, in this field of lithium and kidney disease, there have been only 2 geriatric population-based studies[21,22] and few mixed-aged adult studies,[11,12,15,16,23] which have been limited by the use of nonpsychiatric comparator groups who differ in important baseline characteristics from lithium users, limited methods to control for confounding, and laboratory data being available for only a minority of reports.[11,16] All of this together makes it difficult for older

Clinical Points

- This study investigated whether the use of lithium, a first-line mood disorder treatment, is associated with renal decline in older adults, a question that remains controversial.
- Relative to valproic acid, lithium use was associated with an increase in the risk of renal decline 6.5 vs 5.7 events per 100 person years; hazard ratio = 1.14 (95% CI = 1.02–1.27). In patients with lithium levels > 0.7 mmol/L, the risk compared to valproic acid use was 1.26 (95% CI = 1.06–1.49); the corresponding number when the baseline lithium concentration was ≤ 0.7 mmol/L was 1.06 (95% CI = 0.92–1.22).
- The findings suggest that lithium use is associated with an increase in the risk of renal decline in older adults.

people with these psychiatric conditions and their providers to appreciate the safety of lithium.

A recent population-based analysis specifically examining older adults also found a 1.76 times higher risk of incident CKD with lithium compared to valproate use.[22] Studies that identified a higher risk of lithium-associated CKD were usually conducted in samples where family physicians and psychiatrists in the community were the main lithium prescribers,where less than half the patients had regular follow-up measurements of lithium and kidney function, and where elevated lithium levels are frequently encountered.[24–27] This contrasts with studies in academic centers where more conservative lithium levels are used and where monitoring closely followed guidelines: longer-term effects of lithium on CKD/renal decline were not usually observed.[18] Even though laboratory reference ranges for lithium are 0.6–1.2 mmol/L (1 mmol/L of lithium = 1 mEq/L), recent older-age expert consensus guidelines recommend lithium levels 0.4–0.8 mmol/L for ages 60–79 and levels 0.4–0.7 mmol/L for ages ≥ 80.[28] It remains unknown whether the potential association between lithium and renal function decline is mostly due to unsafe lithium prescribing and monitoring practices, for example using lithium levels > 0.7 mmol/L in geriatric patients,[28] continuing lithium use after baseline CKD has been diagnosed,[29,30] and infrequent monitoring of serum lithium levels and renal function.

We aimed to compare the incidence of clinically important renal decline (> 30% decline in serum creatinine from baseline) in lithium users compared to valproate users. We also were interested in whether lithium levels > 0.7 mmol/L were associated with an increased risk of renal decline in older adults. We also explored whether baseline CKD affected the association between lithium use and the incidence of renal decline.

METHODS

Design and Setting

We performed a population-based cohort study of residents in the province of Ontario, Canada, aged ≥ 66 years who had 2 prescriptions of either lithium or valproate between January 1, 2007, and September 30, 2015. In Ontario, residents have universal health insurance coverage for hospital and medically necessary physician services. In addition, people aged ≥ 65 years obtain outpatient prescription drug coverage from the Ontario Drug Benefit program.

The use of data in this study was approved under section 45 of Ontario's Personal Health Information Protection Act, which does not require research ethics board approval or informed consent from participants. Reporting for this study followed the REporting of studies Conducted using Observational Routinely collected health Data for pharmacoepidemiology guidelines (Supplementary Table 1).

Data Sources

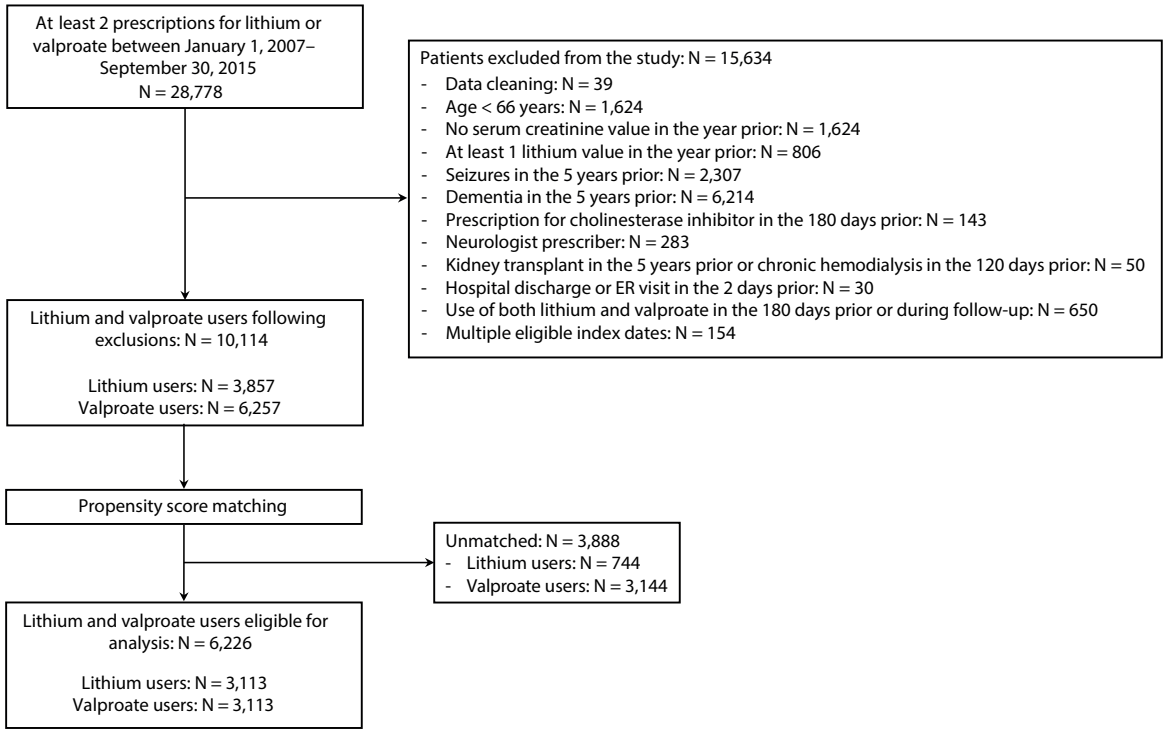
Data from multiple linked administrative health care databases stored at Institute for Clinical and Evaluative Sciences (ICES) were used. The datasets were linked using unique encoded identifiers and analyzed at ICES. The Ontario Health Insurance Plan (OHIP) database includes claims for inpatient and outpatient physician services and was used to ascertain covariate information and outpatient laboratory tests. The ICES Physician Database contains physician related information such as birth date, education, and specializations. Outpatient serum creatinine and lithium level values were provided by the Ontario Laboratory Information System. Using serum creatinine, we calculated the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation.[31] The remaining datasets are described in Supplementary Appendix 1. Previous studies have used these databases to study medication use and associated health care use and outcomes.[32–34]

Patient Cohort

The index date was the time of the second filled prescription of lithium or valproate. After the index date, individuals were followed as long as their medications were being continuously refilled; we required that the second prescription be filled within 1.5 times the days supplied of the initial prescription (ie, second prescription within 45 days if the initial prescription had 30 days supplied). Requiring 2 filled prescriptions allowed the assessment of continuous use. Patients were censored if they died or reached the end of the maximum follow-up period (September 30, 2015).

In our cohort, the index date was defined as the beginning of follow-up. We included older adults aged ≥ 66 using lithium or valproate who had at least 1 serum creatinine value in the prior year. For lithium users to be included, they needed to have at least 1 lithium value in the year preceding the index date. We searched for patients with either (1) ≥ 2 prescriptions of lithium or (2) ≥ 2 prescriptions of valproate between January 1, 2007, and September 30, 2015. This time window was used to maximize (1) the number of eligible patients and (2) adequate follow-up for outcomes. Figure 1 outlines how the cohort was selected, while drug

Figure 1. Study Flowchart: Cohort Selection



Abbreviation: ER = emergency room.

identification numbers for lithium and valproate can be found in Supplementary Table 2.

Before matching, we excluded < 0.16% of patients from both lithium and valproate cohorts (n = 39) who had invalid identifying information (age, sex, or identifier), were non-Ontario residents, or died on/before the index date. Patients with the following criteria were also excluded: evidence of dementia or seizure ≤ 5 years before the index date or prescriptions by a neurologist (to exclude situations where valproate was used for these conditions); evidence of cholinesterase inhibitor use (also characterizes dementia); serious prior renal disease (kidney transplant ≤ 5 years preceding the index date or dialysis in the 120 days prior to index date); being discharged from hospital or visiting an emergency department on the index date or within 2 days prior; having a pre-index (overtly toxic) lithium level > 1.2 mmol/L; and concurrent prescriptions of both lithium and valproate, to ensure mutually exclusive groups. Patients entered the cohort only once, at the time of their first eligible prescription.

Valproate users were chosen as a comparator group for lithium users because (1) lithium and valproate are prescribed for similar indications, (2) users both have high rates of relevant physical comorbidities compared to the general population (eg, hypertension, diabetes mellitus),[35] and (3) valproate use has not been associated with renal problems after controlling for potential confounders.[22]

Baseline comorbidities were assessed using *International Classification of Diseases*, 10th revision (*ICD-10*) and 9th revision (*ICD-9*) codes, Ontario Mental Health Reporting System, and OHIP physician diagnostic and fee codes in the 5 years preceding the index date (Supplementary Appendix 2). Similarly, medication use was assessed in the 120 days prior to index date, while health care use (physician visits and diagnostic/screening tests) was examined in the previous year.

Exposures

Our primary exposure was lithium use. These were compared to the reference group, valproate users. We then did a subgroup analysis of lithium users by baseline serum lithium levels (1) > 0.7 mmol/L and (2) ≤ 0.7 mmol/L, comparing them with valproate users. Lithium levels were based on the most recent value in the 365 days prior to the index date and needed to be ≤ 1.2 mmol/L. The use of lithium levels ≤ 0.7 mmol/L was based on the International Society for Bipolar Disorders (ISBD) consensus recommendations for geriatric lithium prescribing.[28]

Our exploratory modifier was CKD at baseline, defined as an eGFR < 60 mL/min/1.73 m^2.

Renal Outcomes

Our primary outcome was clinically important renal decline—30% or greater decrease in eGFR from baseline, a well-validated measure strongly and consistently associated with the risk of end-stage renal disease, dialysis, and mortality.[36] eGFR was calculated from serum creatinine using the CKD-EPI equation.[31] Baseline creatinine levels

were based on the 365 days preceding the index date, taking the most recent value. Follow-up creatinine levels were assessed during follow-up: eg, for the primary outcome, we looked for any event of eGFR during follow-up, where eGFR had decreased by ≥ 30%.

Our exploratory outcomes were evidence of (1) a 2-fold or greater increase of serum creatinine (any serum creatinine during follow-up ≥ 2 times the baseline creatinine) and (2) dialysis or kidney transplant over the course of follow-up.

Statistical Analysis

In order to control for systematic differences in the lithium and valproate groups, we used propensity score matching. Baseline characteristics were reported as percentages for categorical variables and mean (SD) or median (interquartile range; IQR) for continuous variables. Multivariable logistic regression was performed using the 62 baseline characteristics selected for their potential influence on outcomes or segregation of patients between lithium and valproate groups (Supplementary Table 3). Lithium users were matched 1:1 with valproate users using greedy matching without replacement, within 0.2 standard deviations of the logit of the propensity score and baseline CKD status. Standardized differences were used to identify any differences in baseline characteristics between lithium and valproate groups. Standardized differences calculate differences between group means relative to the pooled standard deviation, with differences > 10% considered significant.[37]

We compared renal outcomes between lithium users and valproate users. We also used Kaplan-Meier curves to examine the probability of experiencing the outcome over time. We then performed exploratory subgroup analyses comparing (1) lithium levels > 0.7 mmol/L and (2) lithium levels ≤ 0.7 mmol/L groups to valproate users (reference group) for our primary outcome (≥ 30% decrease in eGFR from baseline). We did additional exploratory subgroup analyses examining the potential effect of CKD at baseline (eGFR < 60 mL/min/1.73 m^2) on our primary outcome. For the 2 subgroup analyses, we assessed for statistically significant interactions between our primary association (lithium use vs valproate use and renal outcome) and the subgroup (lithium levels > 0.7 mmol/L vs. ≤ 0.7 mmol/L, CKD at baseline vs not, respectively). Rates were reported as per 1,000 person-years, as well as n (%) during follow-up. Time to the first event of each outcome, respectively, was compared between lithium and valproate users using hazard ratios (HRs), generated from Cox proportional hazards regression models, accounting for matched pairs. For each patient, we

Table 1. Selected Baseline Characteristics of Valproate Users and Lithium Users After Propensity Score Matching (n = 6,226)[a]

Characteristic	Valproate (N = 3,113)	Lithium (N = 3,113)	Standardized Difference[b]
Demographics			
Age at cohort entry, y			
Mean (± SD)	70.96 (5.95)	70.96 (6.02)	0%
Median (IQR)	69 (66–74)	69 (66–74)	
Sex, female	1,832 (58.8)	1,834 (58.9)	0%
Rural location[c]	442 (14.2)	447 (14.4)	1%
Long term care	135 (4.3)	144 (4.6)	1%
Prescriber information			
General practitioner	1,670 (53.6)	1,712 (55.0)	3%
Psychiatrist	1,097 (35.2)	1,053 (33.8)	3%
Other	346 (11.1)	348 (11.2)	0%
Comorbidities[d]			
Charlson Comorbidity Index, mean (± SD)	0.37 (0.94)	0.37 (0.99)	0%
Bipolar disorder	2,104 (67.6)	2,072 (66.6)	2%
Coronary artery disease	534 (17.2)	525 (16.9)	1%
Diabetes mellitus	538 (17.3)	531 (17.1)	1%
Nephrogenic diabetes insipidus	44 (1.4)	45 (1.4)	0%
Hypertension	1,610 (51.7)	1,612 (51.8)	0%
Lithium toxicity	9 (0.3)	14 (0.4)	2%
Schizophrenia or other psychotic disorders	1,024 (32.9)	1,009 (32.4)	1%
Unipolar depression/ and or anxiety	1,224 (39.3)	1,200 (38.5)	2%
Concurrent medication use[e]			
Loop diuretics	216 (6.9)	214 (6.9)	0%
ACE inhibitors	728 (23.4)	722 (23.2)	0%
Angiotensin II blockers	388 (12.5)	400 (12.8)	1%
COX-2 inhibitors	112 (3.6)	99 (3.2)	2%
Other diuretics	257 (8.3)	268 (8.6)	1%
Potassium-sparing diuretics	79 (2.5)	83 (2.7)	1%
Typical antipsychotics	186 (6.0)	187 (6.0)	0%
Atypical antipsychotics	1,243 (39.9)	1,185 (38.1)	4%
SSRIs	1,060 (34.1)	1,053 (33.8)	1%
Anticonvulsants	294 (9.4)	310 (10.0)	2%
Antidepressants	872 (28.0)	883 (28.4)	1%
Benzodiazepines	1,011 (32.5)	999 (32.1)	1%
NSAIDs (excluding ASA)	337 (10.8)	337 (10.8)	0%
No. of health care contacts, mean (± SD)[f,g]			
Primary health care visits	10.99 (11.17)	10.73 (10.46)	2%
Nephrologist visits	0.16 (0.75)	0.15 (1.08)	1%
Psychiatrist visits	5.79 (13.10)	5.70 (13.43)	1%
Hospitalizations	0.21 (0.59)	0.20 (0.62)	2%
Emergency department visits	0.95 (1.82)	0.91 (1.79)	2%
Laboratory measurements[h]			
eGFR			
≥ 60 mL/min/1.73 m^2	2,261 (72.6)	2,261 (72.6)	0%
< 60 mL/min/1.73 m^2	852 (27.4)	852 (27.4)	0%
Serum lithium			
> 0.7 mmol/L		1,218 (39.1)	
≤ 0.7 mmol/L		1,895 (60.9)	

[a]Data shown as n (%) unless otherwise noted.
[b]Standardized differences were used to compare valproate users to lithium users. Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of difference between groups with respect to a pooled standard deviation. A standardized difference > 10% is considered a meaningful difference between groups. In this study, standardized differences were calculated using valproate users as the referent.
[c]Rural defined as residing in a location with a population of ≤ 10,000 individuals.
[d]Comorbidities in the 5 years prior to the index date were considered.
[e]Concurrent medication use in the 120 days prior to index date were considered.
[f]Health care contacts in the 365 days prior to index date were considered.
[g]Health care utilization in the 365 days prior to index date were considered.
[h]Laboratory measurements in the 365 days prior to index date were considered.
Abbreviations: ACE = angiotensin-converting enzyme, ASA = acetylsalicylic acid, CNS = central nervous system, COX = cyclo-oxygenase, CT = computed tomography, eGFR = estimated glomerular filtration rate, IQR = interquartile range, NSAID = nonsteroidal anti-inflammatory drug, PSA = prostate-specific antigen, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor.

looked ahead from index date and censored for end of data availability or death. Analyses were performed using SAS version 9.4 (SAS Institute; Cary, North Carolina; 2011) at ICES Western (London, Ontario, Canada).

RESULTS

After inclusion and exclusion criteria were applied, a total of 3,857 lithium users and 6,257 valproate users were identified. Prior to matching, data were complete, with 2 exceptions: 0.4% and 10% of patients' data were missing regarding income quintile and prescriber specialty, respectively. We were able to match 3,113 lithium users to 3,113 valproate users. The mean age of the matched cohort was 71.0 (± 6.0) years, and 59.0% were female. Lithium users had baseline lithium levels with a mean of 0.63 (± 0.26) mmol/L and a median of 0.63 mmol/L (IQR, 0.43–0.82). At baseline, the mean eGFR was similar between matched lithium and valproate users: 70.87 (± 17.41) and 70.63 (± 18.84) mL/min/1.73 m^2, respectively. Matched lithium and valproate users were similar for important baseline characteristics, such as psychiatric diagnosis, use of other psychiatric medications, and level of severity/chronicity (eg, number of hospitalizations in the 5 years prior to the index date) (Table 1).

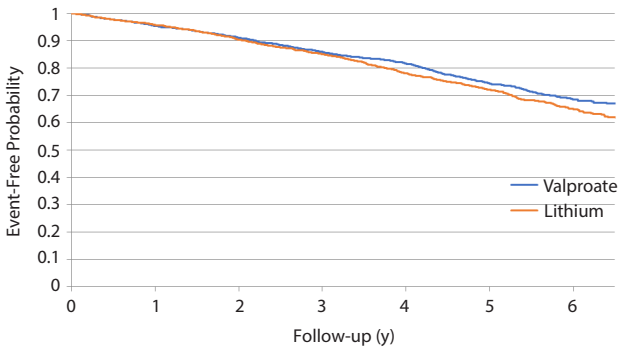
The median duration of continuous medication usage during follow-up was 1.54 (IQR, 0.48–3.56) and 1.46 (IQR, 0.42–3.45) years in lithium and valproate users, respectively. Lithium and valproate users were followed for a median (IQR) of 3.0 (1.4–5.2) and 3.1 (1.5–5.2) years, respectively. We did not censor for medication discontinuation or switching. During follow-up, 1,844 lithium users (47.8%) and 2,861 valproate users (45.7%) discontinued the study drug. Only a small fraction of patients switched to alternate study drug during follow-up: 193 lithium users (5%) and 70 (1.1%) valproate users.

Lithium use was associated with an increased risk of renal decline compared to valproate use (HR = 1.14 [95% CI = 1.02–1.27]) over a median follow-up of 3.1 years (IQR, 1.4–5.2) years (maximum 8.3 years) (Figure 2). Other outcomes are described in Table 2.

We found that lithium levels > 0.7 mmol/L were associated with an increased risk of renal decline compared to valproate use (HR = 1.26 [95% CI = 1.06–1.49], $P = .0091$), whereas this was not the case when lithium levels ≤ 0.7 mmol/L were compared to valproate use (HR = 1.06 [95% CI = 0.92–1.22], $P = .40$, P value for interaction .14) (Table 3). The mean and median lithium levels for patients with levels ≤ 0.7 mmol/L vs levels > 0.7 mmol/L were mean (SD) 0.46 (± 0.16) vs 0.90 (± 0.13) mmol/L and median (IQR) 0.48 (0.33–0.60) vs 0.87 (0.78–0.99) mmol/L.

CKD at baseline (eGFR < 60 mL/min/1.73 m^2) was not associated with greater subsequent decreases in renal function during follow-up (HR = 0.85 [95% CI = 0.71–1.02], $P = .08$). In contrast, patients who *did not* have CKD at baseline had a higher risk (HR = 1.34 [95% CI = 1.17–1.54], $P < .0001$) (Table 3). Baseline CKD did significantly interact with our observed association between lithium use and renal outcome: patients who did not have CKD at baseline had a significantly higher risk of declined renal function (P value for interaction .0001).

Figure 2. Time-to-Event Data: Point at Which Patients Were First Noticed to Have a ≥ 30% Decrease in Renal Function (eGFR)



Abbreviation: eGFR = estimated glomerular filtration rate.

DISCUSSION

In this large longitudinal study of older lithium users, we found that lithium was associated with a 14% increased risk of clinically important ≥ 30% decrease in renal function compared to valproate users, over an average follow-up of 3.05 years. These estimates are more modest than previous studies with similar follow-up duration, which have suggested a 1.5–2.5 times increased risk of CKD and/or renal decline in older lithium users.[11,12,22] These discrepancies may be due in

Table 2. Renal Outcomes With Older Lithium and Valproate Users

	Lithium (n = 3,113)	Valproate (Reference Group; n = 3,113)	HR (95% CI)	*P* Value
Primary Outcome				
Evidence of a 30% or greater decrease of eGFR from baseline	21.7% (n = 674) 6.47/100 person years	18.8% (n = 584) 5.68/100 person years	1.14 (1.02–1.27)	.017
Secondary Outcomes				
Evidence of a 2-fold or greater increase of serum creatinine	4.5% (n = 139) 1.20/100 person years	4.4% (n = 137) 1.21/100 person years	0.99 (0.78–1.25)	.91
Evidence of dialysis or kidney transplant	0.4% (n = 13) 0.11/100 person years	0.4% (n = 11) 0.10/100 person years	1.14 (0.51–2.53)	.75

Abbreviations: CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio.

Table 3. Renal Outcome (Evidence of ≥ 30% eGFR Decrease From Baseline) in Older Lithium and Valproate Users Stratified by Baseline Lithium and CKD Values

Subgroup	Exposure	n	Total Person Year Follow-Up	Hazard Ratio (95% CI)	*P* Value	Interaction *P* Value
Baseline lithium ≤ 0.7 mmol/L	Lithium	374	6,239	1.06 (0.92–1.22)	.40	.14
	Valproate	361	6,371	1.0 (reference)		
Baseline lithium > 0.7 mmol/L	Lithium	300	4,171	1.26 (1.06–1.49)	.01	
	Valproate	223	3,916	1.0 (reference)		
Baseline no CKD	Lithium	456	7,585	1.34 (1.17–1.54)	< .0001	.0001
	Valproate	342	7,598	1.0 (reference)		
Baseline CKD	Lithium	218	2,825	0.85 (0.71–1.02)	.08	
	Valproate	242	2,689	1.0 (reference)		

Abbreviations: CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate.

large part to our use of a valproate-using control group with propensity-score matching to control for many important covariates. Much of the renal risk in lithium patients is likely attributable to physical health comorbidities such as hypertension and diabetes, which should be monitored and managed in primary care.[38] Since nephrologists can be more difficult to access, the National Institute for Health and Care Excellence (NICE) CKD guidelines recommend referral if eGFR is < 30 mL/min/1.73 m^2 and/or there is a steep decline in renal function (eg, 5 points in 1 year, or 10 points in 5 years).[39] Nonetheless, this study continues to describe a substantial association between lithium use and clinically important decreases in renal function, although perhaps a smaller association than previously reported.

Of interest, in our secondary analysis, we explored whether lithium levels > 0.7 mmol/L may be associated with subsequent risk of renal decline (HR = 1.26 [95% CI = 1.06–1.49]), whereas this was not observed when patients had baseline serum lithium level ≤ 0.7 mmol/L (HR = 1.06 [95% CI = 0.92–1.22]). While the interaction term was negative (*P* = .14), this was quite likely because the secondary analysis was underpowered. This suggests that lower levels may be helpful at mitigating the risk of lithium renal toxicity and that future studies should focus on determining empirically what levels are safest for use in the elderly.

To the best of our knowledge, this is the first large-scale examination of the specific association between lithium levels and renal outcomes. The previous literature, consisting mostly of relatively small clinical samples, had found associations of toxic lithium levels with acute kidney injury (AKI) (eg, lithium levels > 1.0 mmol/L associated with eGFR reductions at 3-month follow-up),[40] but no consistent association between lithium levels and chronic renal outcomes.[17,23,41] In many jurisdictions, laboratory test centers use a serum lithium level target range of 0.6–1.2 mmol/L based on the initial treatment trials of lithium in the 1960s–1980s,[42,43] with geriatric-specific lithium levels not being reported. Recent expert consensus guidelines recommend lower lithium levels (0.4–0.8 mmol/L for ages 60–79 and levels 0.4–0.7 mmol/L for ages ≥ 80[28]) in order to minimize toxicity, while having clinical effectiveness in older age bipolar disorder and late-life depression.[3,44] Along similar lines, our study also suggests the use of lithium levels ≤ 0.7 mmol/L in older adults with bipolar disorder, depression, and other disorders to lower the risk of progressive renal decline. Our findings also reinforce the need for increased monitoring of lithium levels and eGFR in older adults. This is especially important because (1) psychiatrists still often do not use eGFR, even though it is more precise than creatinine for measuring renal function[45]; (2) AKI can commonly lead to lithium level elevations in older age, which in our study is associated with worse renal outcomes; and (3) internationally only < 25%–30% of older adult lithium users[25–27,46] meet NICE and ISBD guidelines to screen for lithium levels and renal function every 3 months.[24,44]

With renal decline being one of the main reasons to discontinue lithium,[47] prescribing a dose that results in lithium levels ≤ 0.7 mmol/L could help patients remain safely on this agent.[3,44] In turn, this could prevent psychiatric relapse due to lithium discontinuation, which occurs in > 33%–50% of unipolar depression patients and is more common in bipolar disorder patients.[10] Whether ≤ 0.7 mmol/L is enough for psychiatric stability is an important clinical question: In the recent GERI-BD trial, the only RCT to date in older age bipolar disorder, lithium's head-to-head utility was confirmed vs valproate for mania/hypomania, with mean maximum lithium level of 0.76 mmol/L.[48] On the other hand, lithium levels of even 0.3–0.6 mmol/L have been helpful for geriatric bipolar depression and maintenance.[1,28] It appears that the neuroprotective effects of lithium appear optimal, even at 0.25–0.5 mmol/L, to prevent cognitive impairment[49] and have antisuicide effects,[50] with lithium levels ≥ 0.8 mmol/L having the risk of neurotoxicity.[51] In summary, psychiatric stability and neuroprotective effects with lithium are likely observed at < 0.7 mmol/L for most older adults. Some patients, especially those with mania, may need higher dosing on a case-by-case basis with close monitoring. Further research could assess whether changing laboratory recommendations for geriatric lithium levels to ≤ 0.7 mmol/L and the use of centralized monitoring systems (eg, clinical decision support system) could prevent psychiatric relapse while preventing progressive renal dysfunction in lithium users.[25]

Interestingly, patients with baseline CKD (eGFR < 60) were at lower risk of having further renal decline during follow-up. There are several potential explanations. Patients

with CKD may be more closely monitored by their physicians for lithium levels and renal function, allowing more appropriately timed changes. Physicians caring for patients with CKD may target more conservative lithium levels (eg, < 0.7 mmol/L). This finding may also be due to selection bias—perhaps clinicians prescribe lithium preferentially in patients whose CKD is more stable. Although we found that patients with CKD may have a lower risk of progressive renal decline while on lithium, prescribing clinicians should be cautious: previous studies have been mixed, with some demonstrating that continuation of lithium in patients with CKD may be associated with worse renal outcomes in lithium users, while other studies did not find this.[17,29,52] Future studies could conduct similar analyses with a more stringent CKD definition (eg, baseline eGFR < 45 mL/min/1.73 m^2) and also explore whether the frequency of lithium level monitoring affects renal outcomes.

Strengths and Limitations

This study had many strengths. It was 5 times larger than previous analyses using older lithium users,[11,12,22] which permitted for propensity-score matching to control for many important covariates not previously controlled for. As well, in contrast to past reports, this study included laboratory measures of renal function. It was also the first study to examine the effects of serum lithium levels, as well as baseline CKD on renal outcomes.

There were also some limitations. First, we were unable to account for practice pattern variations in the timing/frequency that physicians ordered renal function and lithium level laboratory tests. These tests could have been performed systematically, but we are unable to determine based on available data. Second, despite our use of a propensity score, there was also the possibility of residual confounding. Finally, we were unable to assess for certain clinical characteristics that may have affected kidney function (eg, acute kidney injury episodes).

CONCLUSIONS

In older adults, lithium use is associated with a statistically significant, but modest, increased risk of progressive renal decline. Specifically, lithium levels > 0.7 mmol/L are associated with the highest renal risk. Accordingly, in older adults with bipolar disorder or depression, targeting lithium levels ≤ 0.7 mmol/L may be a strategy to lower the risk of decreased renal function associated with this agent. Doing so may permit many patients to remain safely on lithium and prevent psychiatric relapse.[10] An interesting future direction, if ever feasible in an even larger older lithium user sample, could be the following: to use a receiver operating curve analysis to identify the serum lithium level at which CKD risk begins to elevate. Further research could also assess whether changing laboratory recommendations for geriatric lithium levels to ≤ 0.7 mmol/L and the use of centralized monitoring/warning systems could still be effective psychiatrically, while preventing renal disease in lithium users.[25]

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Supplementary material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Association of Lithium Use and a Higher Serum Concentration of Lithium With the Risk of Declining Renal Function in Older Adults: A Population-Based Cohort Study

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List of Supplementary Material for the article

Disclaimer

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Supplementary Table 1: REporting of studies Conducted using Observational Routinely-collected Data Pharmaco-Epidemiology (RECORD-PE)

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
Title and abstract				
1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. 1.2: If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	—	1-3
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	7-8
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	8
Methods				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	9
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and	—	—	9

Supplementary Table 1: REporting of studies Conducted using Observational Routinely-collected Data Pharmaco-Epidemiology (RECORD-PE)

	data collection.			
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs.	10-11 Figure 1
Variables				
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1.a: Describe how the drug exposuredefinition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for\ selecting a particular time window should be provided. The extent ofpotential left truncation or left censoring should be specified.	10-13

Supplementary Table 1: REporting of studies Conducted using Observational Routinely-collected Data Pharmaco-Epidemiology (RECORD-PE)

			7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	
Data sources/measurement				
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	9-10
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	12
Study size				
10	Explain how the study size was arrived at.	—	—	Figure 1
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	13-14
Statistical methods				
	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examinesubgroups and interactions. (c) Explain how missing data were addressed.	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	14

Supplementary Table 1: REporting of studies Conducted using Observational Routinely-collected Data Pharmaco-Epidemiology (RECORD-PE)

	(d) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.			
Data access and cleaning methods				
12	—	12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. 12.2: Authors should provide information on the data cleaning methods used in the study.	—	13-14
Linkage				
12	—	12.3: State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	—	9
Results				
Participants				
13	(a) Report the numbers of individuals at eachstage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	14 Figure 1
Descriptive data				

Supplementary Table 1: REporting of studies Conducted using Observational Routinely-collected Data Pharmaco-Epidemiology (RECORD-PE)

14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).	—	—	14-15 Table 1 19-20
Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.	—	—	15 Table 2
Main results				
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	—	—	16 Table 2
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	16
Discussion				
Key results				
18	Summarise key results with reference to study objectives.	—	—	16-17

Supplementary Table 1: REporting of studies Conducted using Observational Routinely-collected Data Pharmaco-Epidemiology (RECORD-PE)

Limitations				
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	18
Interpretation				
20	Give a cautious overall interpretation of results considering objectives, limitations,multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant.	16-18
Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	17-18
Other information				
Funding				
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	—	—	19-20
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such asthe study protocol, raw data, or programming code.	—	20

RECORD=reporting of studies conducted using observational routinely collected data; RECORD-PE=RECORD for pharmacoepidemiological research; STROBE=strengthening the reporting of observational studies in epidemiology. *REFERENCE: Langan SM, Schmidt S, Wing K, Ehrenstein V, Nicholls S, Filion K, Klungel O, Petersen I, Sorensen H, Guttmann A, Harron K, Hemkens L, Moher D, Schneeweiss S, Smeeth L, Sturkenboom M, von Elm E, Wang S, Benchimol EI. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement for Pharmacoepidemiology (RECORD-PE).*BMJ* 2018; 363: k3532.

Supplemental Table 2: Study Drugs From The Ontario Drug Benefit (ODB) Database

Drug Name	Drug Identification Numbers
Lithium	
Lithium Carbonate	"00024406", "00236683", "00328782", "00328790", "00404365", "00406775", "00461733", "00464635", "00590665", "02011239", "02013231", "02216132", "02216140", "02216159", "02231397", "02231398", "02231399", "02237006", "02237007", "02237008", "02237441", "02237442", "02237443", "02242837", "02242838", "02266695", "02304511", "02304538", "02311356", "02311364", "09852255", "09857532", "09857540", "09991107", "66123909", "80000218"
Lithium Citrate	"02074834"
Lithium Gluconate	"00765724"
Valproate	
Divalproex	"02239517", "02239518", "02239519"
Divalproex Sodium	"00596418", "00596426", "00596434", "02239698", "02239699", "02239700", "02239701", "02239702", "02239703", "02244138", "02244139", "02244140", "02265133", "02265141", "02265168"
Valproic Acid	"02100630", "02140047", "02140055", "02140063", "02184648", "02217414", "02229628", "02230768", "02231489", "02236807", "02237830", "02238042", "02238048", "02238370", "02239713", "02239714"
Valproic Acid Sodium	"00443832", "00443840", "00507989"

Supplemental Table 3: Variables included in the propensity score model

Variables included in the propensity score model	
Demographics	Age, sex, year of cohort entry, long-term care residence, income quintile, rural/urban location
Comorbidities	Charlson comorbidity score, acute kidney injury, alcoholism, angina, atrial fibrillation/flutter. bipolar disorder, chronic liver disease, chronic lung disease, congestive heart failure, coronary artery disease, diabetes,nephrogenic diabetes insipidus,heart valve replacement, hypertension, lithium toxicity, obesity, Parkinson's disease, peripheral vascular disease, prostatic hyperplasia, prostatitis, schizophrenia or other psychotic disorders, haemorrhagic stroke, ischemic stroke, transient ischemic attack, unipolar depression/ and or anxiety
Medications	Loop diuretics, ACE inhibitors, angiotensin II blockers, COX-2 inhibitors, , other diuretics, potassium- sparing diuretics, typical antipsychotics, anticonvulsants, atypical antipsychotics, SSRIs, acetylsalicylic acid, antibiotics, anticoagulants, anticonvulsants, antidepressants,antineoplastics, anti-Parkinson's drugs,antiplatelets, baclofen and combinations, benzodiazepines, CNS stimulants, digoxin, glucose test strip, inhalers (combined acetylcholine, beta-agonist, corticosteroid), migraine therapies, narcotics, NSAIDs, overactive bladder medication, statins, warfarin
Health care use	Visits to general practitioner, visits to cardiologist, visit to geriatrician, visits to nephrologist, visits to OB/GYN, visits to ophthalmologist, visits to psychiatrist, visits to urologist, number of hospitalizations, number of emergency department visits, at home physician service, bone mineral test, cardiac catheterization, cardiac stress test, carotid endarterectomy, carotid ultrasound, cataract surgery, cervical cancer screening, chest x-ray, cholesterol test, colorectal cancer screening, CT (abdomen, extremities, head, neck, pelvis, spine, thorax), cystoscopy, echocardiography, EEG, flu shot, hearing test, holter monitoring, mammography, PSA test, pulmonary function test, transurethral resection of the prostate, TSH test, urine culture test
Other	Prescriber specialty, number of unique DINs, number of unique drug names, OLIS catchement area, baseline eGFR category, baseline serum lithium category

Abbreviations: ACE, angiotensin converting enzyme; COX,cyclo-oxygenase; , SSRI, selective serotonin reuptake inhibitors; CNS, central nervous system; NSAID, nonsteroidal-anti-inflammatory drug; eGFR, estimated glomerular filtration rate

Appendix 1: Description of Data Sources

Database	Description
Canadian Institute for Health Information's Discharge Abstract Database/ Same Day Surgery	Database contains diagnostic and procedural information for all hospitalizations.
ICES Physician Database	Database contains physician related information such as birth date, sex, education, and specializations.
Local Health Integration Network	Database contains population and hospital volume information for each of the 14 different geographic areas of the province.
National Ambulatory Care Reporting System	Database contains information on hospital and community based ambulatory care visits.
Ontario Drug Benefits	Database contains highly accurate records of all dispensed outpatient prescriptions covered through the Ontario Drug Benefits program.
Ontario Health Insurance Plan	Database includes diagnostic information, and health claims for inpatient and outpatient services.
Ontario Laboratories Information System	Database contains laboratory test orders and results from hospitals, community labs, and public health labs.
Ontario Mental Health Reporting System	Database contains *adult* inpatient mental health information.
Registered Persons Database	Database contains information on patient demographics including sex, birth and death dates.

Appendix 2: Codes used in the study to identify baseline comorbid conditions

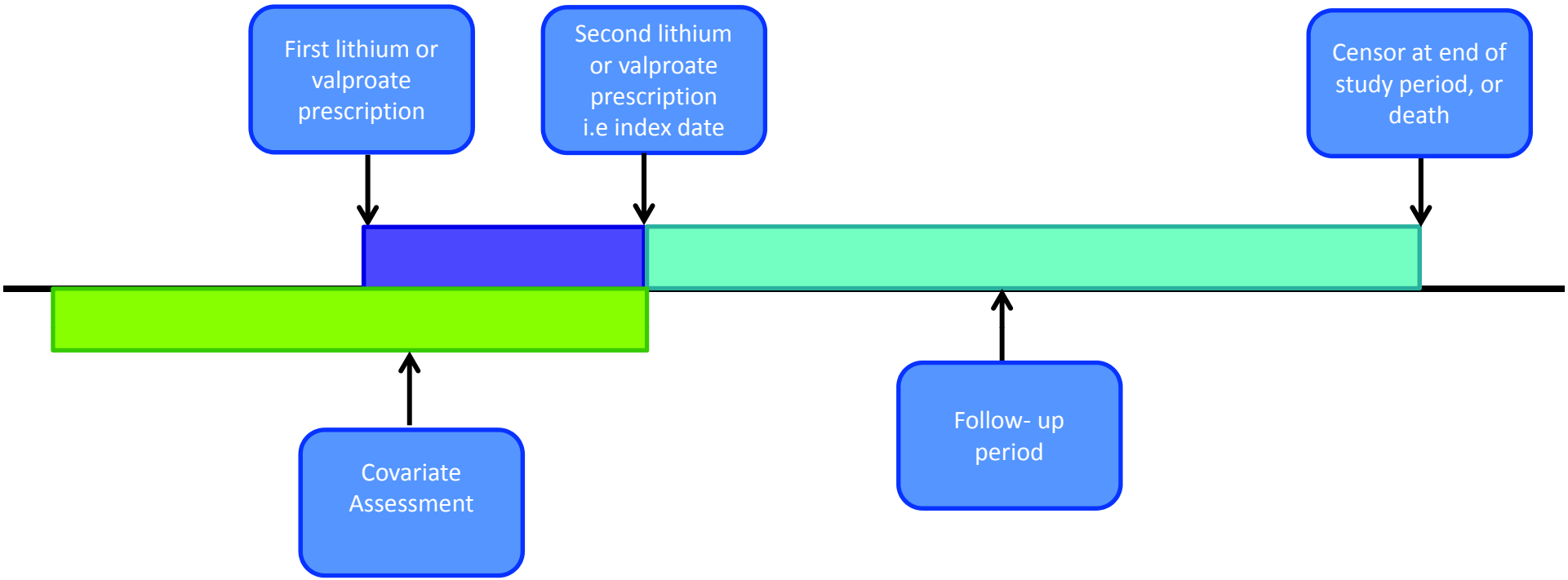
Acute Kidney Injury		
CIHI-DAD	ICD-9	"584"
	ICD-10	"N17"
Alcoholism		
CIHI-DAD	ICD-9	"303", "3050"
	ICD-10	"E24", "E512", "F10", "G312", "G621", "G721", "I426", "K292", "K70", "K860", "T510", "X45", "X65", "Y15", "Y573", "Z502", "Z714", "Z721"
OHIP	Diagnostic code	"303"
Angina		
CIHI-DAD	ICD-9	"413"
	ICD-10	"I20", "I23"
OHIP	Diagnostic code	"413"
Atrial Fibrillation/flutter		
CIHI-DAD	ICD-9	"4273"
	ICD-10	"I48"
Bipolar Disorder		
CIHI-DAD	ICD-9	"2960", "2961", "2964", "2965", "2966", "2967", "2968"
	ICD-10	"F300", "F301", "F302", "F308", "F309", "F310", "F311", "F312", "F313", "F314", "F315", "F316", "F317", "F318", "F319"
OHIP	Diagnostic code	"296"
	Feecode	"Q020"
OMHRS	DSM-IV	"29600", "29601", "29602", "29603", "29604", "29605", "29606", "29640", "29641", "29642", "29643", "29644", "29645", "29646", "29650", "29651", "29652", "29653", "29654", "29655", "29656", "29660", "29661", "29662", "29663", "29664", "29665", "29666", "29670", "29680", "29689"
Cancer		
CIHI-DAD	ICD-9	"150", "154", "155", "157", "162", "174", "175", "185", "203", "204", "205", "206", "207", "208"
	ICD-10	"971", "980", "982", "984", "985", "986", "987", "988", "989", "990", "991", "993", "C15", "C18", "C19", "C20", "C22", "C25", "C34", "C50", "C56", "C61", "C82", "C83", "C85", "C91", "C92", "C93", "C94", "C95", "D00", "D05"
OHIP	Diagnostic code	"203", "204", "205", "206", "207", "208", "150", "154", "155", "157", "162", "174", "175", "183", "185"
Chronic Liver Disease		
CIHI-DAD	ICD-9	"4561", "4562", "070", "5722", "5723", "5724", "5728", "573", "7824", "V026", "2750", "2751", "7891", "7895", "571"
	ICD-10	"B16", "B17", "B18", "B19", "I85", "R17", "R18", "R160", "R162", "B942", "Z225", "E831", "E830", "K70", "K713", "K714", "K715", "K717", "K721", "K729", "K73", "K74", "K753", "K754", "K758", "K759", "K76", "K77"
OHIP	Diagnostic code	"571", "573", "070"

	Feecode	"Z551", "Z554"
Chronic Lung Disease		
CIHI-DAD	ICD-9	"491", "492", "493", "494", "495", "496", "500", "501", "502", "503", "504", "505", "5064", "5069", "5081", "515", "516", "517", "5185", "5188", "5198", "5199", "4168", "4169"
	ICD-10	"I272", "I278", "I279", "J40", "J41", "J42", "J43","J44", "J45", "J47", "J60", "J61", "J62", "J63", "J64", "J65", "J66", "J67", "J68", "J701", "J703", "J704", "J708", "J709", "J82", "J84", "J92", "J941", "J949", "J953", "J961", "J969", "J984", "J988", "J989", "J99"
OHIP	Diagnostic code	"491", "492", "493", "494", "496", "501", "502", "515", "518", "519"
	Feecode	"J889", "J689"
Congestive heart failure		
CIHI-DAD	ICD-9	"425", "5184", "514", "428"
	ICD-10	"I500", "I501", "I509", "I255", "J81"
	CCP	"4961", "4962", "4963", "4964"
	CCI	"1HP53", "1HP55", "1HZ53GRFR", "1HZ53LAFR", "1HZ53SYFR"
OHIP	Diagnostic code	"428"
	Feecode	"R701", "R702", "Z429"
Coronary Artery Disease		
CIHI-DAD	ICD-9	"412", "410", "411"
	ICD-10	"I21", "I22", "Z955", "T822"
	CCP	"1IJ50", "1IJ76"
	CCI	"4801", "4802", "4803", "4804", "4805", "481", "482", "483"
OHIP	Diagnostic code	"410", "412"
	Feecode	"R741", "R742", "R743", "G298", "E646", "E651", "E652", "E654", "E655", "Z434", "Z448"
Nephritic Diabetes Insipidus		
CIHI-DAD	ICD-9	"5881 ","7884“, "2760”
	ICD-10	"N251 ","R35” , "E870”
Lithium Toxicity		
CIHI-DAD	ICD-9	"9698", "9859"
	ICD-10	"T438", "T439", "T568", "T569"
Obesity		
CIHI-DAD	ICD-9	"2780"
	ICD-10	"E660", "E661", "E662", "E668", "E669"
OHIP	Diagnostic code	"278"
Parkinson’s Disease		
CIHI-DAD	ICD-9	"332"
	ICD-10	"G20", "F023"
OHIP	Diagnostic code	"332"
Peripheral Vascular Disease		
CIHI-DAD	ICD-9	"4402", "4408", "4409", "5571", "4439", "444"
	ICD-10	"I700", "I702", "I708", "I709", "I731", "I738", "I739", "K551"
	CCP	"5125", "5129", "5014", "5016", "5018", "5028", "5038", "5126",

		"5159"
	CCI	"1KA76", "1KA50", "1KE76", "1KG26", "1KG50", "1KG57", "1KG76MI", "1KG87", "1IA87LA", "1IB87LA", "1IC87LA", "1ID87", "1KA87LA", "1KE57"
OHIP	Feecode	"R787", "R780", "R797", "R804", "R809", "R875", "R815", "R936", "R783", "R784","R785", "E626", "R814", "R786", "R937", "R860", "R861", "R855", "R856", "R933", "R934", "R791", "E672", "R794", "R813", "R867", "E649"
Prostatic hyperplasia		
CIHI-DAD	ICD-9	"600"
	ICD-10	"N40"
OHIP	Diagnostic code	"600"
Prostatitis		
CIHI-DAD	ICD-9	"6010", "6011", "6012"
	ICD-10	"N410", "N411", "N412"
OHIP	Diagnostic code	"601"
Schizophrenia or other psychotic disorders		
CIHI-DAD	ICD-9	"2950", "2951", "2952", "2953", "2954", "2955", "2956", "2957", "2958", "2959", "2970", "2971", "2972", "2973", "2978", "2979", "2980", "2981", "2983", "2984", "2988", "2989"
	ICD-10	"F060", "F062", "F105", "F107", "F115", "F117", "F125", "F127", "F135", "F137", "F145", "F147", "F155", "F157", "F165", "F167", "F175", "F177", "F185", "F187", "F195", "F197", "F200", "F201", "F202", "F203", "F204", "F205", "F206", "F208", "F209", "F220", "F228", "F229", "F230", "F231", "F232", "F233", "F238", "F239", "F24", "F250", "F251", "F252", "F258", "F259", "F28", "F29"
OHIP	Diagnostic code	"291", "292", "295", "297", "298"
	Feecode	"Q021"
OMHRS	DSM-IV	"29130", "29150", "29211", "29212", "29381", "29382", "29510", "29520", "29530", "29540", "29560", "29570", "29590", "29710", "29730", "29880", "29890"
Haemorrhagic stroke		
CIHI-DAD	ICD-9	"430", "431"
	ICD-10	"I600", "I601", "I602", "I603", "I604", "I605", "I606", "I607", "I609", "I61"
Ischemic stroke		
CIHI-DAD	ICD-9	"436", "4340", "4341", "4349", "3623"
	ICD-10	"I630", "I631", "I632", "I633", "I634", "I635", "I638", "I639", "I64", "H341"
Transient Ischemic Attack		
CIHI-DAD	ICD-9	"435"
	ICD-10	"G450", "G451", "G452", "G453", "G458", "G459", "H340"
Unipolar depression and/ or anxiety		
CIHI-DAD	ICD-9	"2962", "2963", "3000", "3002", "3003", "3004", "3091", "311"
	ICD-10	"F063", "F064", "F320", "F321", "F322", "F323", "F328", "F329",

		"F330", "F331", "F332", "F333", "F334", "F338", "F339", "F341", "F400", "F401", "F402", "F408", "F409", "F410", "F411", "F412", "F413", "F418", "F419", "F420", "F421", "F422", "F428", "F429", "F430", "F431"
OHIP	Diagnostic code	"311"
OMHRS	DSM-IV	"29189", "29284", "29289", "29383", "29384", "29620", "29621", "29622", "29623", "29624", "29625", "29626", "29630", "29631", "29632", "29633", "29634", "29635", "29636", "30000", "30001", "30002", "30021", "30022", "30023", "30029", "30030", "30040", "30113"

CIHI-DAD: Canadian Institutes for Health Information's Discharge Abstract Database
CCP: Canadian Classification of Procedures
CCI: Canadian Classification of Interventions
OHIP: Ontario Health Insurance Plan



1.5x the days supplied of the 1st prescription

- 5 year look back period for comorbidities
- 120 days look back period for baseline medication
- 1 year look back period for health care contact, health care utilization and baseline laboratory measurements

Follow up period
- Minimum 1 day
- Maximum 10.25 years

Supplementary Figure 1: Study timeline for a patient