CME Background
Articles are selected for credit designation based on an assessment of the educational needs of CME participants, with the purpose of providing readers with a curriculum of CME articles on a variety of topics throughout each volume. Activities are planned using a process that links identified needs with desired results.

To obtain credit, read the article, correctly answer the questions in the Posttest, and complete the Evaluation. A $5 processing fee will apply.

CME Objective
After studying this article, you should be able to:

- Provide serum lithium monitoring that is consistent with international standards

Accreditation Statement
The CME Institute of Physicians Postgraduate Press, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation
The CME Institute of Physicians Postgraduate Press, Inc., designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Note: The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 1 hour of Category I credit for completing this program.

Release, Expiration, and Review Dates
This educational activity was published in November 2018 and is eligible for *AMA PRA Category 1 Credit*™ through December 31, 2020. The latest review of this material was November 2018.

Financial Disclosure
All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Marlene P. Freeman, MD, Editor in Chief, has received research funding from JayMac and Sage, has been a member of the Independent Data Safety and Monitoring Committee for Janssen, has been medical editor for the *Global Organization for EPA and DHA Omega-3s* newsletter, and, as a Massachusetts General Hospital (MGH) employee, works with the MGH National Pregnancy Registry, which is sponsored by Alkermes, Otsuka, Actavis, and Sunovion, and works with the MGH Clinical Trials Network and Institute, which receives research funding from multiple pharmaceutical companies and the National Institute of Mental Health. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears at the end of the article.**

Blood Lithium Monitoring Practices in a Population-Based Sample of Older Adults

Soham Rej, MD, MSc[a,*]; Nathan Herrmann, MD[b]; Andrea Gruneir, PhD[c,d,e]; Racquel Jandoc, MSc[e]; Eric McArthur, MSc[e]; Stephanie Dixon, PhD[e]; and Amit X. Garg, MD, PhD[e]

ABSTRACT

Objective: Lithium is an effective treatment for mood disorders, but lithium level and renal monitoring every 3 months is recommended in older patients treated with lithium to prevent serious adverse events. This study examined lithium monitoring practices in a large geriatric cohort.

Methods: This population-based cohort study (N = 11,006) used linked health care administrative databases. Older lithium users (n = 5,503; mean age = 70.6 years) in Ontario, Canada, enrolled between April 1, 2002, and March 31, 2014, were propensity score matched 1:1 to valproate users (n = 5,503). The frequency with which serum lithium levels were monitored and renal and endocrine laboratory testing was done during a 1-year follow-up period was examined.

Results: The baseline characteristics of the 2 groups were similar. At least 1 serum lithium concentration recorded within 90, 180, and 365 days of follow-up was present in 24.1%, 42.4%, and 66.8% of lithium users, respectively. Corresponding numbers for serum creatinine were 29.6%, 50.4%, and 75.4%, respectively. While serum creatinine monitoring (hazard ratio [HR] = 1.19; 95% CI, 1.12–1.27; $P < .001$), thyroid-stimulating hormone monitoring (HR = 1.47; 95% CI, 1.37–1.58; $P < .001$), and calcium testing (HR = 1.15; 95% CI, 1.02–1.29; $P = .018$) were statistically higher in lithium compared to valproate users, absolute differences between groups were not clinically meaningful.

Conclusions: In a geriatric Canadian community sample, lithium monitoring was infrequent and inconsistent with international standards that call for screening of lithium levels and renal function every 3 months.

J Clin Psychiatry 2018;79(6):17m12095

To cite: Rej S, Herrmann N, Gruneir A, et al. Blood lithium monitoring practices in a population-based sample of older adults. *J Clin Psychiatry*. 2018;79(6):17m12095.

To share: https://doi.org/10.4088/JCP.17m12095

[a]Department of Psychiatry, Lady Davis Institute/Jewish General Hospital, McGill University, Montreal, Québec, Canada

[b]Department of Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

[c]Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada

[d]Department of Family Medicine, University of Alberta, Edmonton, Alberta, Canada

[e]Institute for Clinical Evaluative Sciences, London, Ontario, Canada

**Corresponding author:* Soham Rej, MD, MSc, Department of Psychiatry, Lady Davis Institute/Jewish General Hospital, McGill University, 4333 Cote-Ste-Catherine, Rm 144, Montreal, Québec, Canada, H3T 1E4 (soham.rej@mcgill.ca).

Clinical Points

- In a Canadian community setting, serum lithium monitoring is not consistent with international standards that call for screening of lithium levels and renal function every 3 months in older adults.
- Rates of testing for serum creatinine, thyroid-stimulating hormone, and calcium levels were statistically higher in the lithium-treated group compared to the valproate-treated group, but the differences did not appear to be clinically meaningful.
- The findings in this sample suggest that clinicians are not necessarily performing additional monitoring in older lithium users.

Lithium remains an essential medication for bipolar disorder and treatment-resistant depression.[1] However, there has been concern about adverse effects of lithium on the functioning of a variety of organ systems, including endocrine and renal function.[2–4] In recent studies, lithium was independently associated with an almost 2-fold higher risk of chronic kidney disease in older mental health service users in the community,[2,5] although this finding remains controversial.[6] Similar associations have been found for lithium use and a higher risk of acute kidney injury,[7] as well as thyroid disease[4] and hypercalcemia.[8] Lithium has a narrow therapeutic range, so laboratory monitoring is essential; poor monitoring has been associated with acute and chronic lithium level elevations and a higher incidence of most lithium-associated adverse effects.[9] These findings suggest that monitoring is critical to the safe usage of lithium.

Poor laboratory monitoring may contribute to lithium-related adverse events in community settings, where monitoring may be less regimented.[10,11] Guidelines from the International Society for Bipolar Disorders (ISBD), Canadian Network for Mood and Anxiety Treatments (CANMAT), and the UK National Institute for Clinical Excellence (NICE) recommend that lithium users undergo lithium level and serum creatinine tests at least every 3–6 months[1,12,13] and ideally every 3 months in older adults.[12,14] Similarly, international guidelines recommend that thyroid and calcium testing be performed every 6–12 months.[1,12,13] Despite guidelines, lithium monitoring has been poor in different parts of world, with less than 25% of patients in UK and New Zealand population-based studies receiving lithium monitoring ≥ 4 times a year.[13,15,16]

Lithium monitoring has not been assessed in older lithium-treated individuals receiving routine health care in a large population-based cohort, even though these individuals are most vulnerable for lithium-associated adverse effects and may benefit from more frequent monitoring.[10] To understand how much more monitoring occurs beyond routine testing, it would be useful to assess serum monitoring in lithium users compared to users of another drug such as valproic acid, which is also used for mental illness and does not require renal, thyroid, or calcium monitoring,[5] as well as to control statistically for potential confounders that may affect monitoring frequency. However, such research has not previously been done. We conducted this study to address these gaps in knowledge.

Aims of the Study

The aims of our study were to characterize the frequency of relevant laboratory monitoring in a province-wide cohort of older lithium users, specifically (1) lithium level and renal laboratory monitoring and (2) thyroid and calcium monitoring. We compared these monitoring rates to assess whether they differ from those of valproate users, who are similar but do not require renal, thyroid, or calcium monitoring.

MATERIALS AND METHODS

Design and Setting

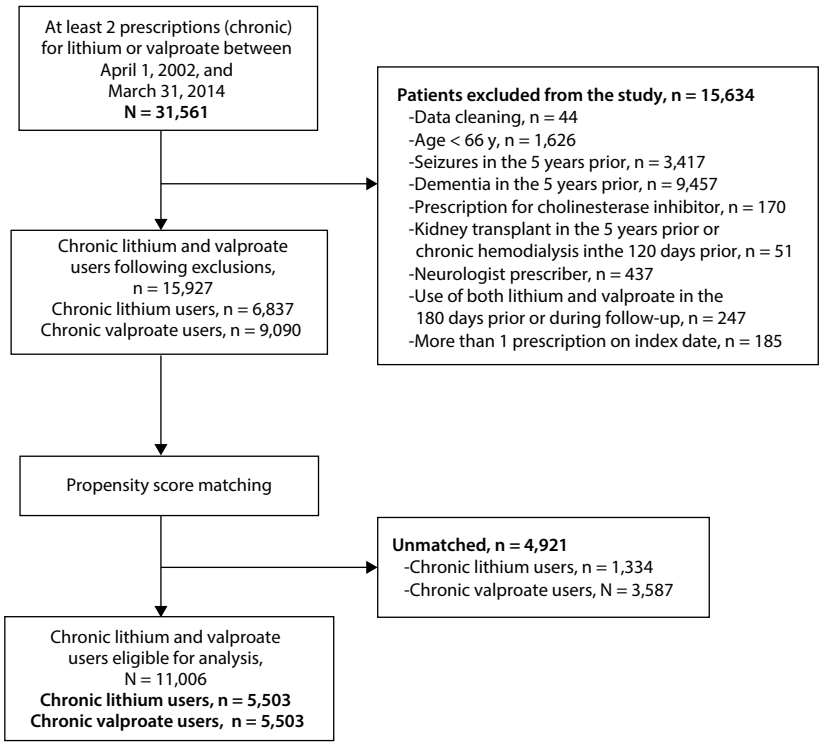
We conducted a population-based cohort study examining adults aged 66 years and older residing in the province of Ontario, Canada, who initiated treatment with either lithium or valproate between April 1, 2002, and March 31, 2014. All Ontario residents receive hospital care and physician services paid for by the Ontario Health Insurance Plan (OHIP), and those aged 65 years and older receive outpatient prescription drug coverage from the Ontario Drug Benefit program (ODB).

We conducted this study at the Institute for Clinical Evaluative Sciences (ICES) according to a prespecified protocol approved by the Research Ethics Board at Sunnybrook Health Sciences Centre (Toronto, Ontario). Participant informed consent was not required for this study. The reporting of this study followed guidelines for observational studies (Supplementary Table 1).

Data Sources

We obtained health care data from multiple linked administrative databases housed at ICES. Data sets were linked using unique, encoded identifiers derived from health card numbers, and patient-level data were analyzed at ICES. Vital statistics were obtained from the Registered Persons Database, which contains demographic data on all Ontario residents with a valid health card. Prescription data were obtained from the ODB database, which contains highly accurate records of all outpatient prescriptions (error rate < 1%) dispensed to patients aged 65 years and older. Diagnostic and procedural information on all hospital admissions and emergency department visits were obtained from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database and CIHI National Ambulatory Care Reporting System database. The OHIP database includes claims for inpatient and outpatient physician services and was used to ascertain covariate information and outpatient laboratory test results. The ICES Physician Database reports prescriber and specialist referral data. For a small proportion of the cohort, outpatient serum creatinine values were provided by a large commercial laboratory in the year before cohort entry, and we determined kidney function in this subpopulation using these data to estimate

Figure 1. Flow Diagram of Cohort Selection



glomerular filtration rate. Previous studies[17–19] have used these databases to study medication use and associated health care use and outcomes.

Patients: Lithium Users and Propensity Score Matched Valproate Comparators

Our cohort included patients aged ≥ 66 years in Ontario who were chronic users of either lithium or valproate (study drug identification numbers outlined in Supplementary Table 2). A flow diagram for cohort selection can be found in Figure 1. We searched for any use of lithium or valproate between April 1, 2002, and March 31, 2014. For a patient to be considered a "chronic user," we required a second prescription fill within 1.5 times the number of days supplied with the initial prescription (ie, second prescription within 45 days if the initial prescription had 30 days supplied). In the less likely case that a patient received a short lithium prescription (eg, 15 days) and 1 refill, such a person would still be included as a chronic lithium user; however, if they stopped getting lithium prescriptions after the second prescription, we would have stopped their follow-up at that point as well. We then deemed the date of the second prescription fill the index date (start time for follow-up in the cohort). After the index date, we followed individuals as long as they were continuously refilling the medications. Thus, there would be no instances when a patient stopped the drug shortly after index, but then was examined for the entire year of follow-up; such a patient's follow-up time would have been censored at medication stop. Patients were censored when there was no prescription refill claim within a set period of time relative to the prescription fill immediately prior (1.5 times the number of days supplied). Chronic lithium users were compared to a cohort of chronic valproate users with similar baseline indicators of health. Valproate was chosen as the comparator because (1) compared to the general population, lithium and valproate users both have high rates of physical health comorbidity[20] and low medication/monitoring adherence[21;] and (2) it allowed us to observe whether monitoring was more frequent in lithium users relative to a mental illness cohort exposed to a medication (valproate) that does not specifically require renal, thyroid, or calcium monitoring.

Before matching, we excluded a small proportion of patients from both cohorts due to data issues (less than 0.2%, n = 44) who had invalid identifiers (age, sex, or invalid health card number); were non-Ontario residents; or who had a date of death on or before the index date. We also excluded patients with the following criteria: those aged less than 66 years on the index date, to ensure complete medication history; those with evidence of seizure or dementia in the 5 years prior to index date; those with prescriptions dispensed by a neurologist (because valproate is sometimes prescribed for seizure and behavioral symptoms of dementia, whereas we wished to capture valproate users with mental illness); those with evidence of cholinesterase inhibitor use (also characterizes dementia); those with evidence of a kidney transplant in the 5 years prior to index date; those with

Table 1. Baseline Characteristics Before and After Propensity Score Matching (n = 11,006)[a]

	Before Propensity Score Matching			After Propensity Score Matching		
Variable	Valproate	Lithium	Standardized Difference, %[b]	Valproate	Lithium	Standardized Difference, %[b]
Total patients	9,090	6,837	…	5,503	5,503	…
Demographics						
Age at cohort entry, y						
Mean ± SD	71.49 ± 6.49	70.64 ± 5.83	14	70.59 ± 5.84	70.66 ± 5.93	1
Median (IQR)	69 (66–75)	68 (66–74)	…	68 (66–74)	68 (66–74)	…
66–69	4,798 (52.8)	3,921 (57.3)	9	3,194 (58.0)	3,178 (57.8)	0
70–74	1,788 (19.7)	1,316 (19.2)	1	1,069 (19.4)	1,030 (18.7)	2
75–79	1,258 (13.8)	920 (13.5)	1	710 (12.9)	727 (13.2)	1
80–84	762 (8.4)	465 (6.8)	6	357 (6.5)	379 (6.9)	2
85–89	352 (3.9)	164 (2.4)	9	123 (2.2)	142 (2.6)	3
90+	132 (1.5)	51 (0.7)	8	50 (0.9)	47 (0.9)	0
Sex						
Female	5,275 (58.0)	4,047 (59.2)	2	3,266 (59.3)	3,231 (58.7)	1
Male	3,815 (42.0)	2,790 (40.8)	2	2,237 (40.7)	2,272 (41.3)	1
Long-term care	891 (9.8)	266 (3.9)	24	267 (4.9)	258 (4.7)	1
Neighborhood income quintile						
1 (lowest)	2,221 (24.4)	1,456 (21.3)	7	1,275 (23.2)	1,226 (22.3)	2
2	1,820 (20.0)	1,350 (19.7)	1	1,101 (20.0)	1,087 (19.8)	1
3	1,739 (19.1)	1,280 (18.7)	1	1,040 (18.9)	1,071 (19.5)	2
4	1,586 (17.4)	1,281 (18.7)	3	995 (18.1)	999 (18.2)	0
5 (highest)	1,680 (18.5)	1,462 (21.4)	7	1,092 (19.8)	1,120 (20.4)	1
Prescriber Information						
General practitioner	5,396 (59.4)	3,469 (50.7)	18	2,932 (53.3)	2,937 (53.4)	0
Psychiatrist	2,007 (22.1)	2,162 (31.6)	22	1,611 (29.3)	1,596 (29.0)	1
Other	323 (3.5)	103 (1.5)	13	960 (17.4)	970 (17.6)	1
Comorbidities (3-year look back)						
Charlson Comorbidity Index						
0	7,893 (86.8)	6,375 (93.2)	21	5,090 (92.5)	5,081 (92.3)	1
1	502 (5.5)	248 (3.6)	9	211 (3.8)	223 (4.1)	2
2	320 (3.5)	126 (1.8)	11	127 (2.3)	116 (2.1)	1
3+	375 (4.1)	88 (1.3)	17	75 (1.4)	83 (1.5)	1
Medication Use (120-day look back)						
Loop diuretics	1,128 (12.4)	387 (5.7)	24	372 (6.8)	374 (6.8)	0
ACE inhibitors	2,626 (28.9)	1,460 (21.4)	17	1,287 (23.4)	1,288 (23.4)	0
Angiotensin II blockers	982 (10.8)	528 (7.7)	11	498 (9.0)	475 (8.6)	1
COX-2 inhibitors	439 (4.8)	322 (4.7)	0	269 (4.9)	263 (4.8%)	0
Other diuretics	1,207 (13.3)	553 (8.1)	17	517 (9.4)	511 (9.3)	0
Antibiotics	2,441 (26.9)	1,422 (20.8)	14	1,228 (22.3)	1,241 (22.6)	1
Anticonvulsants	1,296 (14.3)	404 (5.9)	28	349 (6.3)	390 (7.1)	3
Antidepressants	2,061 (22.7)	1,905 (27.9)	12	1,397 (25.4)	1,421 (25.8)	1
Health Care Use (365-day look back)						
Primary health care visits						
Mean ± SD	13.86 ± 14.47	11.21 ± 11.07	21	11.77 ± 11.8	11.72 ± 11.49	0
Median (IQR)	10 (5–17)	8 (4–14)	…	9 (5–15)	9 (5–15)	…
Nephrologist visits						
Mean ± SD	0.15 ± 0.93	0.09 ± 0.93	6	0.12 ± 0.69	0.11 ± 1.02	1
Median (IQR)	0 (0–0)	0 (0–0)	…	0 (0–0)	0 (0–0)	…
Neurologist visits						
Mean ± SD	0.53 ± 2.04	0.21 ± 1.38	18	0.26 ± 1.05	0.23 ± 1.2	3
Median (IQR)	0 (0–0)	0 (0–0)	…	0 (0–0)	0 (0–0)	…
Psychiatrist visits						
Mean ± SD	4.55 ± 11.87	6.83 ± 16.72	16	6.14 ± 13.68	5.96 ± 14.85	1
Median (IQR)	0 (0–4)	1 (0–6)	–	0 (0–6)	0 (0–5)	–
Hospitalizations						
Mean ± SD	0.37 ± 0.83	0.25 ± 0.66	16	0.27 ± 0.68	0.26 ± 0.69	1
Median (IQR)	0 (0–0)	0 (0–0)	–	0 (0–0)	0 (0–0)	–
Emergency department visits						
Mean ± SD	0.78 ± 2.08	0.6 ± 1.45	10	0.64 ± 1.19	0.63 ± 1.55	1
Median (IQR)	0 (0–1)	0 (0–1)	–	0 (0–1)	0 (0–1)	–

[a]Values are shown as n (%) unless otherwise noted.
[b]Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference between the groups.[22] In this study, standardized differences were calculated using valproate users as the referent.
Abbreviations: ACE = angiotensin-converting enzyme, COX-2 = cyclooxygenase 2, IQR = interquartile range.

Table 2. Blood Test Monitoring in Lithium and Valproate Recipients

Test and User Group	Incidence Rate per 1,000 Person-Years	Cumulative Incidence (%) of at Least 1 Test in the Period			Hazard Ratio	
		90 Days	180 Days	365 Days	HR (95% CI)	*P* Value
Serum lithium level						
Lithium	1,103	24.1	42.4	66.8	NA	NA
Serum creatinine						
Lithium	1,404	29.6	50.4	75.4	1.19 (1.12 to 1.27)	<.0001
Valproate	1,215	26.2	45.5	70.3	1.00 (referent)	
TSH						
Lithium	1,392	22.6	40.1	64.1	1.47 (1.37 to 1.58)	<.0001
Valproate	1,031	16.8	30.8	52.2	1.00 (referent)	
Calcium						
Lithium	142	3.5	6.9	13.3	1.15 (1.02 to 1.29)	.0183
Valproate	119	2.9	5.8	11.2	1.00 (referent)	

Abbreviations: HR = hazard ratio, NA = not applicable, TSH = thyroid-stimulating hormone.

evidence of dialysis in the 120 days prior to index date, as these treatments dramatically influence renal blood monitoring; and those with evidence of prescriptions for more than 1 study drug, to ensure mutually exclusive groups. Patients could enter the cohort only once, so for patients with multiple eligible prescriptions, we restricted to the first eligible prescription.

We used propensity score matching to eliminate systematic differences in the measured baseline characteristics of the lithium and valproate groups. Multivariable logistic regression was performed with 35 baseline characteristics selected for their potential influence on outcomes or segregation of patients between groups (listed in Supplementary Table 3). Chronic lithium users were matched 1:1 with chronic valproate users using greedy matching without replacement, within 0.2 standard deviations of the logit of the propensity score. We used standardized differences to assess differences in baseline characteristics between lithium and valproate users. Standardized differences describe differences between group means relative to the pooled standard deviation, with differences greater than 10% considered significant.[22]

Codes from the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (*ICD-10*) and 9th revision (*ICD-9*), were used to assess baseline comorbidities in the 5 years prior to the index date (Supplementary Table 4). Medication use was assessed in the 120 days before index date, and health care use, including physician visits and diagnostic and screening tests, was examined in the previous year.

Outcomes

The primary outcomes of our study were outpatient laboratory tests identified in OHIP for serum lithium levels, creatinine, thyroid-stimulating hormone (TSH), and calcium concentrations within 1 year following the index date. The outpatient physician billing codes used to identify laboratory tests are presented in Supplementary Table 5. Frequency of serum lithium laboratory testing was examined in lithium users only; the frequency of the remaining serum laboratory tests and rates of continuous medication use was compared between chronic lithium and valproate users.

Statistical Analysis

We compared the frequency of outpatient laboratory testing between propensity score matched lithium and valproate users. Rates were reported per 1,000 person-years. To ascertain whether laboratory testing followed international guidelines, we also examined the cumulative incidence of a test at 90 days, 180 days, and 365 days following the index date, with cumulative incidences estimated using the "exponential equation."[23] Time to first laboratory test monitoring after index prescription was compared between lithium and valproate users using hazard ratios (HRs), generated from Cox proportional hazard regression models, accounting for matched pairs. Analyses were conducted with SAS version 9.4 (SAS Institute, Cary, North Carolina, 2011) at the ICES Western facility (London, Ontario, Canada).

RESULTS

A total of 5,503 lithium users were matched 1:1 to 5,503 valproate users. In the overall sample (N = 11,006), the mean (SD) age of patients was 70.6 (5.9) years, and 59.0% of patients (n = 6,497) were female. After propensity score matching, lithium and valproate users did not differ with respect to their measured baseline characteristics (standardized difference < 10%). Patients' baseline characteristics are described in Table 1 and Supplementary Table 6.

Lithium level monitoring was infrequent in lithium users at 90, 180, and 365 days of follow-up (24.1%, 42.4%, and 66.8%, respectively) (Table 2) in light of international guidelines to monitor every 3 months.[12,14] Monitoring rates for serum creatinine were statistically higher in lithium compared to valproate users at 90, 180, and 365 days (lithium vs valproate: 29.6% vs 26.2%, 50.4% vs 45.5%, and 75.4% vs 70.3%, respectively; HR = 1.19; 95% CI, 1.12–1.27; $P < .001$). Similarly, at 90, 180, and 365 days, TSH and calcium annual testing rates were statistically higher in lithium users compared to valproate users: 22.6%, 40.1%, and 64.1%, respectively, vs 16.8%, 30.8%, and 52.2% for TSH (HR = 1.47; 95% CI, 1.37–1.58; $P < .001$) and 3.5%, 6.9%, and 13.3%, respectively, vs 2.9%, 5.8%, and 11.2% for calcium levels (HR = 1.15; 95% CI, 1.02–1.29; $P = .018$).

DISCUSSION

In our province-wide sample of older lithium users, lithium level and serum creatinine monitoring was relatively infrequent: only 24.1% and 29.6% of lithium users met international standards from the ISBD and NICE guidelines to ideally screen for lithium levels and renal function, respectively, every 3 months in older adults.[12,14] While the serum creatinine monitoring rates at 90-, 180-, and 365-day follow-up were statistically higher in lithium compared to valproate users, these differences were not clinically meaningful, even though valproate is not associated with renal disease.[5] Annual monitoring rates for TSH and calcium levels were also statistically different in lithium and valproate patients in our sample of 11,006 patients, but these differences may not have necessarily been clinically important. Even though the international guidelines and a recent, important 2014 Health Canada safety advisory recommend annual calcium testing in lithium-treated patients (http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/37903a-eng.php), only 13.3% of lithium-treated patients in this Canadian sample were tested for serum calcium within 1 year, compared to 11.2% of valproate-treated patients. These initial observations from a Canadian provincial sample suggest that (1) lithium monitoring among older adults may not be meeting current international standards[1,12,13] and (2) the monitoring that is taking place may reflect routine laboratory monitoring for older adults (eg, as primary screening or for other medical comorbidities) rather than monitoring specifically for lithium safety.

We suspect a number of physician and patient factors act as barriers to adhering to recommended blood monitoring. It is likely that primary care physicians and many psychiatrists may not necessarily be familiar with lithium monitoring given the decreasing use of this important therapy, as mentioned previously. Monitoring can be a burden on patients since it requires scheduling, taking time for the appointment (and often long waits), and arranging transportation (which may not be trivial for individuals with mobility limitations or who live in remote settings). Patients may also not be aware of why regular monitoring is being recommended. Older lithium users often have significant cognitive, physical, and mental health issues that make it even more difficult to remember, commit to, and arrange for blood monitoring, with caregiver support often inadequate or overwhelmed.[14]

Our findings are in keeping with those of previous reports in younger adults and mixed-aged lithium samples in the United Kingdom and New Zealand.[13,15,16] Lithium level and renal monitoring rates of 4 times/year, approaching the NICE and ISBD guideline recommendations (every 3 months), were similarly < 25%. Our study included novel elements: a larger sample size, calcium and thyroid monitoring frequencies, and a propensity score matched comparator group of patients with mental illness. These elements allowed us to clinically interpret that monitoring rates in lithium users were different, though perhaps not in a clinically meaningful way, compared to valproate users who did not require specific monitoring for renal, thyroid, or calcium disorders.

Since this study focused exclusively on older lithium users, that monitoring rates were low and comparable to those in younger adult/mixed-aged samples in different countries is of particular concern. Older adults are most vulnerable to lithium-associated adverse effects due to a number of factors, including a more narrow therapeutic range (0.4–0.8 mmol/L), physical comorbidity, drug-drug interactions, and decreased renal clearance of lithium with aging.[10] Without adequate clinical monitoring, lithium level elevations are more common, putting older adults at higher risk for acute renal injury[24] and acute neurotoxicity[25,26] as well as chronic kidney disease, hypercalcemia, hypothyroidism, and other chronic physical adverse effects.[2–5,8] These effects can then lead to scenarios in which many older patients need to discontinue lithium, which has often been associated with rates of mood episode relapse of > 33%–50%.[27,28]

Strengths, Limitations, and Future Directions

This study was the first to examine lithium monitoring exclusively in older lithium users, who are most vulnerable to lithium-associated adverse effects.[29] This study was also the largest to date examining lithium monitoring practices, 3 times larger than previous studies; previous UK and New Zealand studies have had sample sizes < 1,500,[13,16] except for 1 previous study[15] with 3,373 patients. We included a valproate comparator group (without a neurologic diagnosis), which allowed us to observe whether monitoring was more frequent relative to a mental illness cohort exposed to a medication that does not require renal, thyroid, or calcium monitoring[5] after using propensity score matching to control for important potential confounders (and thereby reduce bias). This study also systematically examined both calcium and thyroid monitoring in addition to lithium level and renal monitoring, which had not previously been done in lithium monitoring studies.

There were some limitations to this study. Although we had data on monitoring frequency, we did not have laboratory values of the lithium levels and renal function tests. Also, the findings of this study can be generalized only to outpatient lithium monitoring; we had data on outpatient laboratory tests, but not all inpatient blood tests since, in Ontario, regular bloodwork performed in hospitalized inpatients can often be paid under a hospital's global budget. Additionally, poor drug monitoring not only is an issue with lithium treatment, but could also be an issue for health care system(s) more generally or may be specific to older bipolar disorder medications. For example, although monitoring requirements are similar with warfarin, the majority of warfarin-treated patients are not only monitored adequately but also in the therapeutic window.[30] Since we used data from Ontario, Canada, which has universal health coverage, it may be difficult to generalize to other jurisdictions and health care contexts with different barriers to or facilitators of regular monitoring. Another limitation is that even with the

propensity score, there is still the potential for confounding since control for unmeasured variables is not possible. Future studies could examine how clinical variables, such as medication dosing, affect adherence to laboratory monitoring. It would also be interesting to examine whether provider specialty affected laboratory monitoring rates. At a first glance of our own data, the 3-month, 6-month, and 12-month monitoring rates appear similar in primary care physicians (23.7%, 41.7%, and 66.0%), psychiatrists (24.3%, 42.8%, 67.2%), and other physicians (25.1%, 43.9%, 68.5%). In our sample, > 50% of lithium and valproate prescribing was from primary care physicians, suggesting that this may be an important physician population to target for future interventions. Future population-based studies are also needed to examine the relationship between poor monitoring and lithium-related adverse events; such examination has not been previously performed).

From both a research and a public health perspective, finding ways to improve lithium monitoring is necessary. A successful example of such an initiative was documented by Kirkham and colleagues[13] in Norfolk, UK. Their objective was to ensure that all patients on lithium treatment have access to adequate information, education, and specialist advice and receive regular blood tests following an agreed-upon protocol. To implement their objective, the Norfolk group ensured close communication between the laboratories and primary and secondary care providers. Patients were given automatic reminders for testing lithium levels and renal function every 12 weeks, with additional letters, telephone calls, and family physician alerts if patients did not adhere to schedule. All of this translated to improved monitoring: in 2005, 83% of the sample had 1 renal function test or fewer, while in 2012, approximately 90% of patients received 2 or more creatinine measurements per year.[13] Similar centralized jurisdiction-wide monitoring approaches with close communication and education approaches may be helpful across the world.

CONCLUSION

Lithium monitoring in older lithium users was infrequent and did not appear consistent with international standards to screen for lithium levels and renal functioning ideally every 3 months in this population. We recognize the logistical challenges of laboratory monitoring and understand that international recommendations to screen adults (of all ages) at least every 3–6 months is a reasonable clinical compromise that would still be a great improvement from what was observed in this study. It is possible that the observed monitoring may reflect routine laboratory monitoring for older adults rather than monitoring for lithium safety. Previous research has found that suboptimal monitoring may be a possible contributor to increased risk of lithium-related adverse events, although this finding needs further investigation; should it be confirmed, the effects of clinician education strategies and jurisdiction-wide treatment algorithms for improving monitoring could be examined in future studies.

Submitted: December 22, 2017; accepted May 8, 2018.

Published online: November 20, 2018.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

Financial disclosure: **Dr Herrmann** has received research funding from Lundbeck, Roche, and Axovant and honoraria from AbbVie, Merck, Mediti, Astellas, and Eli Lilly. **Dr Rej** receives research funding from Satellite Healthcare. **Drs Gruneir**, **Dixon**, and **Garg**; **Ms Jandoc**; and **Mr McArthur** have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: This work was supported by an Ontario Mental Health Foundation grant awarded to Dr Herrmann, as well as the Institute for Clinical Evaluative Sciences Kidney, Dialysis and Transplantation (ICES KDT) Program. Dr Herrmann was supported by the Richard Lewar Chair in Geriatric Psychiatry. Dr Rej received salary support from the Canadian Institutes of Health Research (CIHR) Fellowship Award and the Fonds de Recherche Québec-Santé Chercheur Boursier Clinicien Junior 1 Award. Dr Gruneir is supported by a New Investigator Award from CIHR. Dr Garg was supported by a Clinician Investigator Award from the Canadian Institutes of Health Research and the Dr Adam Linton Chair in Kidney Health Analytics. This study was supported by the ICES Western site. ICES is a nonprofit research corporation funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Core funding for ICES Western is provided by the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University, and the Lawson Health Research Institute (LHRI).

Role of the sponsor: The study design and conduct, opinions, results and conclusions reported in this article are those of the authors and are independent of the funding sources. No endorsement by ICES, AMOSO, SSMD, LHRI, CIHR or the MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI).

Previous presentation: Some of these data were presented as part of a broader oral presentation at the European Association of Psychosomatic Medicine in Barcelona, Spain, June 30, 2017.

Disclaimer: The analyses, conclusions, opinions and statements expressed in the material are those of the authors and not necessarily those of CIHI.

Acknowledgments: The analysis was conducted by members of the ICES KDT team at the ICES Western facility, who are supported by a grant from CIHR. Authors also thank IMS Brogan Inc for use of their Drug Information Database.

Additional information: The analysis was conducted by members of the ICES Kidney Dialysis & Transplantation team at the ICES Western facility (London, Ontario). Mr McArthur and Dr Garg are responsible for the data analysis. The protocol can be obtained by e-mailing Ms Jandoc at racquel.jandoc@ices.on.ca.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord*. 2013;15(1):1–44.
2. Shine B, McKnight RF, Leaver L, et al. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet*. 2015;386(9992):461–468.
3. Marras C, Herrmann N, Fischer HD, et al. Lithium use in older adults is associated with increased prescribing of Parkinson medications. *Am J Geriatr Psychiatry*. 2016;24(4):301–309.
4. Shulman KI, Sykora K, Gill SS, et al. New thyroxine treatment in older adults beginning lithium therapy: implications for clinical practice. *Am J Geriatr Psychiatry*. 2005;13(4):299–304.
5. Rej S, Herrmann N, Shulman K, et al. Lithium use, but not valproate use, is associated with a higher risk of chronic kidney disease in older adults with mental illness. *J Clin Psychiatry*. 2017;78(8):e980–e985.
6. Kessing LV, Gerds TA, Feldt-Rasmussen B, et al. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. *JAMA Psychiatry*. 2015;72(12):1182–1191.
7. Kirkham E, Skinner J, Anderson T, et al. One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective

analysis of a monitoring database. *BMJ Open*. 2014;4(11):e006020.
8. Lehmann SW, Lee J. Lithium-associated hypercalcemia and hyperparathyroidism in the elderly: what do we know? *J Affect Disord*. 2013;146(2):151–157.
9. Dols A, Sienaert P, van Gerven H, et al. The prevalence and management of side effects of lithium and anticonvulsants as mood stabilizers in bipolar disorder from a clinical perspective: a review. *Int Clin Psychopharmacol*. 2013;28(6):287–296.
10. Sylvestre JD, Yu C, Dawson B, et al. Older adults with severe mental illness frequently require acute medical hospitalizations: an increased need for consultation-liaison services in future years? *J Psychosom Res*. 2015;79(1):87–88.
11. Vestergaard P, Amdisen A. Lithium treatment and kidney function: a follow-up study of 237 patients in long-term treatment. *Acta Psychiatr Scand*. 1981;63(4):333–345.
12. Ng F, Mammen OK, Wilting I, et al; International Society for Bipolar Disorders. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar Disord*. 2009;11(6):559–595.
13. Kirkham E, Bazire S, Anderson T, et al. Impact of active monitoring on lithium management in Norfolk. *Ther Adv Psychopharmacol*. 2013;3(5):260–265.
14. Sajatovic M, Strejilevich SA, Gildengers AG, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disord*. 2015;17(7):689–704.
15. Collins N, Barnes TR, Shingleton-Smith A, et al. Standards of lithium monitoring in mental health Ttrusts in the UK. *BMC Psychiatry*. 2010;10(1):80.
16. McKean A, Vella-Brincat J. Is it NICE to monitor lithium routinely? *N Z Med J*. 2012;125(1355):50–54.
17. Hwang YJ, Dixon SN, Reiss JP, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. *Ann Intern Med*. 2014;161(4):242–248.
18. Juurlink DN, Mamdani MM, Kopp A, et al. Drug-induced lithium toxicity in the elderly: a population-based study. *J Am Geriatr Soc*. 2004;52(5):794–798.
19. Shulman KI, Rochon P, Sykora K, et al. Changing prescription patterns for lithium and valproic acid in old age: shifting practice without evidence. *BMJ*. 2003;326(7396):960–961.
20. Rej S, Yu C, Shulman K, et al. Medical comorbidity, acute medical care use in late-life bipolar disorder: a comparison of lithium, valproate, and other pharmacotherapies. *Gen Hosp Psychiatry*. 2015;37(6):528–532.
21. Sajatovic M, Valenstein M, Blow F, et al. Treatment adherence with lithium and anticonvulsant medications among patients with bipolar disorder. *Psychiatr Serv*. 2007;58(6):855–863.
22. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38(6):1228–1234.
23. Rothman KJ. *Epidemiology: An Introduction*. 2nd ed. New York, NY: Oxford University Press; 2012.
24. Chen KP, Shen WW, Lu ML. Implication of serum concentration monitoring in patients with lithium intoxication. *Psychiatry Clin Neurosci*. 2004;58(1):25–29.
25. Schou M, Amdisen A, Trap-Jensen J. Lithium poisoning. *Am J Psychiatry*. 1968;125(4):520–527.
26. Shulman KI, Sykora K, Gill S, et al. Incidence of delirium in older adults newly prescribed lithium or valproate: a population-based cohort study. *J Clin Psychiatry*. 2005;66(4):424–427.
27. Fahy S, Lawlor BA. Discontinuation of lithium augmentation in an elderly cohort. *Int J Geriatr Psychiatry*. 2001;16(10):1004–1009.
28. Ross J. Discontinuation of lithium augmentation in geriatric patients with unipolar depression: a systematic review. *Can J Psychiatry*. 2008;53(2):117–120.
29. Rej S, Elie D, Mucsi I, et al. Chronic kidney disease in lithium-treated older adults: a review of epidemiology, mechanisms, and implications for the treatment of late-life mood disorders. *Drugs Aging*. 2015;32(1):31–42.
30. Ingram SJ, Kirkdale CL, Williams S, et al. Moving anticoagulation initiation and monitoring services into the community: evaluation of the Brighton and hove community pharmacy service. *BMC Health Serv Res*. 2018;18(1):91.

See supplementary material for this article at PSYCHIATRIST.COM.

POSTTEST

To obtain credit, go to PSYCHIATRIST.COM (Keyword: December CME) to take this Posttest and complete the Evaluation. A nominal processing fee is required.

1. **Your patient, Mr Y, is 70 years old and uses lithium. To comply with international guidelines for older adults, how often should you monitor Mr Y's lithium levels and renal function?**
   a. Every year
   b. Every 6 months
   c. Every 3 months
   d. Never
2. **Which of the following factors is *not* a reason for clinicians to avoid using lithium in patients with serious mood disorders?**
   a. Potential toxicity, especially in older patients
   b. Patient preference
   c. Lack of efficacy for bipolar disorder and treatment-resistant depression
   d. Cognitive, physical, and mental health issues that will hinder blood monitoring
3. **This study found that less than one-third of older patients taking lithium were monitored for lithium levels and renal function at recommended frequencies. How do these results compare with findings from studies of younger patients?**
   a. Younger patients are monitored more frequently
   b. Younger patients are monitored less frequently
   c. Neither age group is monitored frequently enough

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Blood Lithium Monitoring Practices in a Population-Based Sample of Older Adults

Author(s): Soham Rej, MD, MSc; Nathan Herrmann, MD; Andrea Gruneir, PhD; Racquel Jandoc, MSc; Eric McArthur MSc; Stephanie Dixon, PhD; and Amit X. Garg MD, PhD

DOI Number: https://doi.org/10.4088/JCP.17m12095

List of Supplementary Material for the article

1. **Table 1** Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement
2. **Table 2** Study Drugs From The Ontario Drug Benefit (ODB) Database
3. **Table 3** Variables included in the propensity score model
4. **Table 4** Coding definitions for baseline characteristics
5. **Table 5** Coding definitions for laboratory testing outcomes
6. **Table 6** All baseline characteristics of chronic valproate and chronic lithium users post-matching

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplemental Table 1: Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement

	Item No	STROBE items	RECORD items	Reported
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 geographic region and time frame 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.	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported.		Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses.		Introduction
Methods				
Study design	4	Present key elements of study design early in the paper.		Methods: Design and setting
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.	(6.1) The methods of study population selection (such as codes or algorithms used to identify subjects) 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.	Methods: Patients; Supplemental Table 2, 4
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.	Methods; Supplemental Tables 2-5

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.		Methods: Data sources, Statistical analysis
Bias	9	Describe any efforts to address potential sources of bias.		Methods; Discussion
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.		Methods: Statistical analysis
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.		(a, b) Methods: Patients, Statistical analysis; (c) Data sources; (d, e) N/A
Data access and cleaning methods		N/A	(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.	Methods: Data sources, Patients
Linkage		N/A	(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.	Methods: Data sources
Results				
Participants	13	(a) Report numbers of individuals at each stage of study--e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (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 persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Results; Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (e.g. average and total amount).		Results; Table 1
Outcome data	15	Report numbers of outcome events or summary measures over time.		Results; Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95%		Results; Table 2

		confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
Other analyses	17	Report other analyses done (e.g. analyses of subgroups and interactions, and sensitivity analyses).		N/A
Key results	18	Summarize key results with reference to study objectives.		Discussion
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.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.		Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results.		Discussion
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.		Acknowledge-ments
Accessibility of protocol, raw data, and programming code		N/A	(22.1) Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Acknowledge-ments

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, Local Health Integration Network
Comorbidities	Angina, bipolar disorder, chronic lung disease, congestive heart failure, coronary artery disease, diabetes, hypertension, Charlson comorbidity score
Medications	ACE inhibitors, angiotensin II blockers, antibiotics, anticonvulsants, antidepressants, COX-2 inhibitors, inhalers (combined acetylcholine, beta-agonist, corticosteroid), loop diuretics ,narcotics, potassium-sparing diuretics, statins, thiazide diuretics
Health care use	Visits to general practitioner, visits to nephrologist, visits to neurologist, visits to psychiatrist, number of hospitalizations, number of emergency department visits
Other	Prescriber specialty, number of unique drug names, baseline eGFR category

Abbreviations: ACE, angiotensin converting enzyme; COX,cyclo-oxygenase; eGFR, estimated glomerular filtration rate

Supplemental Table 4: Coding definitions for baseline characteristics

Characteristic	Database	Codes / Details
DEMOGRAPHICS		
Age	RPDB	
Sex	RPDB	
Long-term care residence	ODB	
Socioeconomic status	Statistics Canada	
Local Health Integration Network	RPDB	
PRESCRIBER INFORMATION		
Prescribing physician	IPDB	General practitioner Psychiatrist Other/missing
COMORBIDITIES		
Angina	CIHI-DAD	**ICD9:** 413 **ICD10:** I20, I23
	OHIP	413
Bipolar disorder	CIHI-DAD	**ICD9:** 2960, 2961, 2964, 2965, 2966, 2967, 2968 **ICD10:** F300, F301, F302, F308, F309, F310, F311, F312, F313, F314, F315, F316, F317, F318, F319
	OHIP	296, Q020
	OMHRS	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
Chronic lung disease	CIHI-DAD	**ICD9:** 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 5064, 5069, 5081, 515, 516, 517, 5185, 5188, 5198, 5199, 4168, 4169 **ICD10:** 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	491, 492, 493, 494, 496, 501, 502, 515, 518, 519, J889, J689
Congestive heart failure	CIHI-DAD	**ICD9:** 425, 5184, 514, 428 **ICD10:** I500, I501, I509, I255, J81
	CCP	4961, 4962, 4963, 4964
	CCI	1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR
	OHIP	R701, R702, Z429, 428
Coronary artery disease (excluding angina)	CIHI-DAD	**ICD9:** 412, 410, 411 **ICD10:** I21, I22, Z955, T822
	CCP	4801, 4802, 4803, 4804, 4805, 481, 482, 483
	CCI	1IJ50, 1IJ76
	OHIP	R741, R742, R743, G298, E646, E651, E652, E654, E655, Z434, Z448, 410, 412
Diabetes	ODB	Insulin and combinations, Acarbose, Acetohexamide, Chlorpropamide, Glicazide, Glimepiride, Linagliptin, Linagliptin, Metformin HCl, Metformin, Metformin HCl, Nateglinide, Pioglitazone HCl, Repaglinide, RepaglinideHCl, Rosiglitazone Maleate, SaxagliptinHCl, Sitagliptin Phosphate, Tolbutamide
Hypertension	ODB	ACE inhibitors, angiotensin II blockers, beta blockers, calcium channel blockers, thiazide diuretics
Lithium toxicity	CIHI-DAD	**ICD9 :** 9698, 9859 **ICD10 :** T438, T439, T568, T569
Obesity	CIHI-DAD	**ICD9:** 2780 **ICD10:** E660, E661, E662, E668, E669
	OHIP	278
Parkinson's disease	CIHI-DAD	**ICD9:** 332 **ICD10:** G20, F023
	OHIP	332
Peripheral vascular disease	CIHI-DAD	**ICD9:** 4402, 4408, 4409, 5571, 4439, 444 **ICD10:** I700, I702, I708, I709, I731, I738, I739, K551
	CCP	5125, 5129, 5014, 5016, 5018, 5028, 5038, 5126, 5159

	CCI	1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76MI, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87, 1KA87LA, 1KE57
	OHIP	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	**ICD9:** 600 **ICD10:** N40
	OHIP	600
Prostatitis	CIHI-DAD	**ICD9:** 6010, 6011, 6012 **ICD10:** N410, N411, N412
	OHIP	601
Schizophrenia or other psychotic disorders	CIHI-DAD	**ICD9:** 2950, 2951, 2952, 2953, 2954, 2955, 2956, 2957, 2958, 2959, 2970, 2971, 2972, 2973, 2978, 2979, 2980, 2981, 2983, 2984, 2988, 2989 **ICD10:** 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	291, 292, 295, 297, 298, Q021
	OMHRS	29130, 29150, 29211, 29212, 29381, 29382, 29510, 29520, 29530, 29540, 29560, 29570, 29590, 29710, 29730, 29880, 29890
Stroke – hemorrhagic	CIHI-DAD	**ICD9:** 430, 431 **ICD10:** I600, I601, I602, I603, I604, I605, I606, I607, I609, I61
Stroke – ischemic	CIHI-DAD	**ICD9:** 436, 4340, 4341, 4349, 3623 **ICD10:** I630, I631, I632, I633, I634, I635, I638, I639, I64, H341
Stroke – transient ischemic	CIHI-DAD	**ICD9:** 435 **ICD10:** G450, G451, G452, G453, G458, G459, H340
Unipolar depression and/or anxiety disorder	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	311
	OMHRS	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
MEDICATION USE		
ACE inhibitors	ODB	Cilazapril& Hydrochlorothiazide, Hydrochlorothiazide & Lisinopril, Hydrochlorothiazide & Quinapril HCl, Hydrochlorothiazide & Ramipril, Indapamide& Perindopril Tert.Butylamine, Benazepril Chlorohydrate, Benazepril HCl, Captopril, Cilazapril, Enalapril Sodium, Fosinopril, Fosinopril Sodium, Lisinopril, Perindopril Tert.Butylamine, Quinapril, Ramipril, Trandolapril, Cilazapril& Hydrochlorothiazide, Hydrochlorothiazide & Lisinopril, Hydrochlorothiazide & Quinapril HCl, Hydrochlorothiazide & Ramipril, Indapamide& Perindopril Tert.Butylamine
Angiotensin II blockers	ODB	Amlodipine Besylate&Telmisartan, Candesartan Cilexetil, Candesartan Cilexetil& Hydrochlorothiazide, EprosartanMesylate, EprosartanMesylate& Hydrochlorothiazide, Hydrochlorothiazide &Irbesartan, Hydrochlorothiazide & Losartan Potassium, Hydrochlorothiazide &OlmesartanMedoxomil, Hydrochlorothiazide &Telmisartan, Hydrochlorothiazide & Valsartan, Irbesartan, Losartan Potassium, OlmesartanMedoxomil, Telmisartan, Valsartan
Antibiotics	ODB	Amikacin, Amikacin Sulfate, Amoxicillin, Amoxicillin &Clavulanic Acid Potassium, Amoxicillin Trihydrate, Amoxicillin Trihydrate& Clarithromycin & Lansoprazole, Amoxicillin Trihydrate& Clavulanic Acid Potassium, Ampicillin, Ampicillin Sodium, Ampicillin Trihydrate, Azithromycin, Azithromycin Dihydrate, Aztreonam, BacampicillinHCl, Bacitracin, Bacitracin Zinc & Cysteine & Glycine & Neomycin Sulfate & Threonine, Bacitracin Zinc & Neomycin Sulfate &Polymyxin B Sulfate, Bacitracin Zinc &Polymyxin B Sulfate, Carbenicillin, Carbenicillin Disodium, Cefaclor, Cefadroxil, Cefadroxil Monohydrate, Cefazolin Sodium, CefepimeHCl, Cefixime, Cefoperazone Sodium, Cefotaxime Sodium, Cefoxitin Sodium, Cefprozil, Ceftazidime, Ceftazidime Hydrate, Ceftriaxone Sodium, Cefuroxime, Cefuroxime Axetil, Cephalexin, Cephalexin Monohydrate, Cephalothin Sodium, Cephradine, Ciprofloxacin, Ciprofloxacin HCl, Ciprofloxacin HCl& Dexamethasone, Clarithromycin, Clindamycin, Clindamycin Phosphate, Clindamycin Phosphate Glycolic Acid, Cloxacillin, Cloxacillin Sodium, Colistin Sodium Methanesulfonate, Daptomycin, Dicloxacillin Sodium,

		Erythromycin, Erythromycin Estolate, Erythromycin Ethyl Succinate, Erythromycin Ethyl Succinate &Sulfisoxazole, Erythromycin Gluceptate, Erythromycin Lactobionate, Erythromycin Stearate, Fidaxomicin, Flucloxacillin Sodium, FluocinoloneAcetonide& Neomycin Sulfate &Polymyxin B Sulfate, Framycetin Sulfate, Fusidic Acid, Fusidic Acid Sodium, Gatifloxacin, Gentamicin, Gentamicin &Colistin, Gentamicin Sulfate, Gramicidin & Neomycin Sulfate &Polymyxin B Sulfate, Gramicidin &Polymyxin B Sulfate, GrepafloxacinHCl, Levofloxacin, Linezolid, Moxifloxacin HCl, Mupirocin, Neomycin Sulfate, Neomycin Sulfate &Polymyxin B Sulfate, Netilmicin Sulfate, Norfloxacin, Ofloxacin, Paromomycin, Penicillin G Benzathine, Penicillin G Potassium, Penicillin G Procain Salt, Penicillin G Sodium, Penicillin V, Penicillin V Benzathine, Piperacillin, Piperacillin Sodium &Tazobactam Sodium, Pivampicillin, Pivmecillinam, Polymyxin B Sulfate & Trimethoprim, SpectinomycinHCl, Spiramycin, Streptomycin, Streptomycin Sulfate, Sulfabenzamide&Sulfacetamide& Sulfathiazole, Sulfacetamide Sodium, Sulfadiazine, Sulfadiazine & Trimethoprim, Sulfamethoxazole, Sulfamethoxazole & Trimethoprim, Sulfapyridine, Sulfisoxazole, Telithromycin, Tobramycin, Tobramycin Sulfate, Trimethoprim
Anticonvulsants	ODB	Carbamazepine, Ethosuximide, Fosphenytoin Sodium, Gabapentin, Lacosamide, LacosamideHCl, Lamotrigine, Levetiracetam, Magnesium, Magnesium Sulfate, Mephenytoin, Methsuximide, Methylphenobarbital, Oxcarbazepine, Perampanel, Phenobarbital, Phensuximide, Phenytoin Sodium, Pregabalin, Primidone, Rufinamide, Secobarbital Sodium, Stiripentol, Topiramate, Vigabatrin
Antidepressants	ODB	Amitriptyline, Amitriptyline HCl, Amitriptyline HCl&Perphenazine, Amoxapine, Bupropion HCl, Citalopram HBr, Clomipramine, Clomipramine HCl, DesipramineHCl, Doxepin HCl, Duloxetine, Imipramine HCl, Isocarboxazid, MaprotilineHCl, Mirtazapine, Moclobemide, Nortriptyline, Nortriptyline HCl, Phenelzine Sulfate, ProtriptylineHCl, Tranylcypromine Sulfate, Trazodone HCl, Trimipramine, Trimipramine Maleate
COX-2 inhibitors	ODB	Celecoxin, Rofexoxib, Valdecoxib
Inhalers (acetylcholine or beta-agonist or	ODB	Albuterol, Albuterol & Albuterol Sulfate, Albuterol Sulfate, Beclomethasone Dipropionate, Budesonide, Budesonide &

corticosteroid)		Formoterol Fumarate, Ciclesonide, FenoterolHBr, Flunisolide, Fluticasone Propionate, Fluticasone Propionate & Salmeterol Xinafoate, Formoterol &Mometasone, Formoterol Fumarate, Glycopyrrolate Bromide, Indacaterol Maleate, Ipratropium Bromide, Metaproterenol Sulfate, Pirbuterol Acetate, ProcaterolHCl, Salmeterol Xinafoate, Terbutaline Sulfate, Tiotropium Bromide, Triamcinolone Acetonide
Loop diuretics	ODB	Bumetanide, Ethacrynic Acid, Furosemide
Narcotics	ODB	Acetaminophen & Caffeine & Codeine Phosphate, Acetaminophen & Caffeine Citrate & Codeine Phosphate, Acetaminophen & Codeine Phosphate, Acetaminophen & Oxycodone HCl, Acetylsalicylic Acid & Oxycodone HCl, AnileridineHCl, Belladona& Opium, Belladona Extract For Oral Use & Opium Powder, Butorphanol Tartrate, Codeine Phosphate, Codeine Sulfate, DextropropoxypheneHCl, DextropropoxypheneNapsylate, Fentanyl, Fentanyl Citrate, Hydromorphone, Hydromorphone HBr, Hydromorphone HCl, Levorphanol Tartrate, Meperidine HCl, Morphine, Morphine HCl, Morphine Sulfate, Naloxone HCl, Opium, Oxycodone HCl, OxymorphoneHCl, PentazocineHCl, Pentazocine Lactate, Propoxyphene HCl, Sufentanil Citrate
Potassium-sparing diuretics	ODB	AmilorideHCl, AmilorideHCl& Hydrochlorothiazide, Eplerenone, Hydrochlorothiazide &Spirnolactone, Hydrochlorothiazide & Triamterene, Spirnolactone, Triamterene
Statins	ODB	Atorvastatin Calcium, Cerivastatin Sodium, Fluvastatin, Fluvastatin Sodium, Lovastatin, Pravastatin, Pravastatin Sodium, Rosuvastatin Calcium, Simvastatin
Thiazide diuretics	ODB	Chlorthalidone, Hydrochlorothiazide, Hydrochlorothiazide &Timolol Maleate, Indapamide, Metolazone
HEALTHCARE USE		
Family physician visits	OHIP IPDB	
Nephrologist visits	OHIP IPDB	

Neurologist visits	OHIP IPDB
Psychiatrist visits	OHIP IPDB
Number of hospitalizations	CIHI-DAD
Number of emergency department visits	NACRS
eGFR	Gamma Dynacare

Abbreviations: ACE, angiotensin converting enzyme; CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI-DAD, Canadian Institutes for Health Information Discharge Abstract Database; COX, cyclo-oxygenase; eGFR, estimated glomerular filtration rate; ICD-9, International Statistical Classification of Diseases, Ninth Revision; ICD-10, International Statistical Classification of Diseases, Tenth Revision; IPDB: Institute for Clinical Evaluative Sciences Physicians Database; NACRS, National Ambulatory Care Reporting System; ODB: Ontario Drug Database; OHIP, Ontario Health Insurance Plan; OMHRS, Ontario Mental Health Reporting System; RPDB, Registered Persons Database

Supplemental Table 5: Coding definitions for laboratory testing outcomes

Test	Database	Codes
Lithium	OHIP fee codes	L157
Serum creatinine	OHIP fee codes	L065, L067, L068
Thyroid stimulating hormone	OHIP fee codes	G016, L341
Calcium	OHIP fee codes	L045, L046

Abbreviations: OHIP – Ontario Health Insurance Plan

Supplemental Table 6: All baseline characteristics of chronic valproate and chronic lithium users post-matching

Characteristic	Chronic valproate users (referent)		Chronic lithium users		Standard-ized difference
	N	%	N	%	
Total patients	5503	--	5503	--	--
DEMOGRAPHICS					
Age at cohort entry					
Mean (SD)	70.59	5.84	70.66	5.93	1%
Median (IQR)	68	(66-74)	68	(66-74)	--
66-69 years	3194	58.0%	3178	57.8%	0%
70-74 years	1069	19.4%	1030	18.7%	2%
75-79 years	710	12.9%	727	13.2%	1%
80-84 years	357	6.5%	379	6.9%	2%
85-89 years	123	2.2%	142	2.6%	3%
90+ years	50	0.9%	47	0.9%	0%
Sex					
Female	3266	59.3%	3231	58.7%	1%
Male	2237	40.7%	2272	41.3%	1%
Year of cohort entry					
2002-2003	1720	31.3%	1939	35.2%	8%
2004-2005	786	14.3%	640	11.6%	8%
2006-2007	821	14.9%	660	12.0%	9%
2008-2009	726	13.2%	747	13.6%	1%
2010-2011	651	11.8%	655	11.9%	0%
2012-2014	799	14.5%	862	15.7%	3%
Long-term care residence	267	4.9%	258	4.7%	1%
Neighbourhood income quintile					
1 (lowest)	1275	23.2%	1226	22.3%	2%
2	1101	20.0%	1087	19.8%	1%
3	1040	18.9%	1071	19.5%	2%
4	995	18.1%	999	18.2%	0%
5 (highest)	1092	19.8%	1120	20.4%	1%
Local Health Integration Network					
1	310	5.6%	326	5.9%	1%
2	484	8.8%	484	8.8%	0%
3	313	5.7%	299	5.4%	1%
4	759	13.8%	739	13.4%	1%
5	176	3.2%	176	3.2%	0%
6	283	5.1%	281	5.1%	0%
7	505	9.2%	513	9.3%	0%

8	506	9.2%	512	9.3%	0%
9	494	9.0%	508	9.2%	1%
10	335	6.1%	337	6.1%	0%
11	657	11.9%	648	11.8%	0%
12	241	4.4%	239	4.3%	0%
13	327	5.9%	332	6.0%	0%
14	113	2.1%	109	2.0%	1%
PRESCRIBER SPECIALTY					
General practitioner	2932	53.3%	2937	53.4%	0%
Psychiatrist	1611	29.3%	1596	29.0%	1%
Other	960	17.4%	970	17.6%	1%
COMORBIDITIES					
Angina	812	14.8%	810	14.7%	0%
Bipolar disorder	2986	54.3%	2967	53.9%	1%
Chronic lung disease	1453	26.4%	1455	26.4%	0%
Congestive heart failure	433	7.9%	437	7.9%	0%
Coronary artery disease (excluding angina)	1049	19.1%	1058	19.2%	0%
Diabetes mellitus	831	15.1%	804	14.6%	1%
Hypertension	2636	47.9%	2615	47.5%	1%
Charlson comorbidity index					
0	5090	92.5%	5081	92.3%	1%
1	211	3.8%	223	4.1%	2%
2	127	2.3%	116	2.1%	1%
3+	75	1.4%	83	1.5%	1%
MEDICATION USE (120 days prior to index date)					
ACE inhibitors	1287	23.4%	1288	23.4%	0%
Angiotensin II blockers	498	9.0%	475	8.6%	1%
Antibiotics	1228	22.3%	1241	22.6%	1%
Anticonvulsants	349	6.3%	390	7.1%	3%
Antidepressants	1397	25.4%	1421	25.8%	1%
COX-2 inhibitors	269	4.9%	263	4.8%	0%
Inhaler - acetylcholine	255	4.6%	250	4.5%	0%
Inhaler - beta-agonist	502	9.1%	488	8.9%	1%
Inhaler - corticosteroid	246	4.5%	257	4.7%	1%
Loop diuretics	372	6.8%	374	6.8%	0%
Narcotics	814	14.8%	797	14.5%	1%
Potassium-sparing diuretics	160	2.9%	173	3.1%	1%
Statins	1636	29.7%	1629	29.6%	0%
Thiazide diuretics	517	9.4%	511	9.3%	0%
Number of unique drug names					
Mean (SD)	7.15	4.01	7.11	4.15	1%

Median (IQR)	7	(4-9)	6	(4-9)	--
0-4	1544	28.1%	1587	28.8%	2%
5-8	2197	39.9%	2163	39.3%	1%
9-12	1217	22.1%	1185	21.5%	1%
13-16	408	7.4%	418	7.6%	1%
17+	137	2.5%	150	2.7%	1%
HEALTHCARE USE (365 days prior to index date)					
Visits to general practitioner					
Mean (SD)	11.77	11.8	11.72	11.49	0%
Median (IQR)	9	(5-15)	9	(5-15)	--
0	189	3.4%	204	3.7%	2%
1-2	495	9.0%	513	9.3%	1%
3-4	679	12.3%	652	11.8%	2%
5-6	745	13.5%	723	13.1%	1%
7-8	604	11.0%	646	11.7%	2%
9-10	534	9.7%	512	9.3%	1%
11+	2257	41.0%	2253	40.9%	0%
Visits to nephrologist					
Mean (SD)	0.12	0.69	0.11	1.02	1%
Median (IQR)	0	(0-0)	0	(0-0)	--
0	5188	94.3%	5255	95.5%	5%
1	165	3.0%	147	2.7%	2%
2	68	1.2%	55	1.0%	2%
3+	82	1.5%	46	0.8%	7%
Visits to neurologist					
Mean (SD)	0.26	1.05	0.23	1.2	3%
Median (IQR)	0	(0-0)	0	(0-0)	--
0	4762	86.5%	4957	90.1%	11%
1	415	7.5%	259	4.7%	12%
2	178	3.2%	158	2.9%	2%
3+	148	2.7%	129	2.3%	3%
Visits to psychiatrist					
Mean (SD)	6.14	13.68	5.96	14.85	1%
Median (IQR)	0	(0-6)	0	(0-5)	--
0	2901	52.7%	2847	51.7%	2%
1	298	5.4%	308	5.6%	1%
2	229	4.2%	278	5.1%	4%
3+	2075	37.7%	2070	37.6%	0%
Number of hospitalizations					
Mean (SD)	0.27	0.68	0.26	0.69	1%
Median (IQR)	0	(0-0)	0	(0-0)	--

0	4467	81.2%	4547	82.6%	4%
1	738	13.4%	648	11.8%	5%
2	202	3.7%	196	3.6%	1%
3+	96	1.7%	112	2.0%	2%
Number of emergency department visits					
Mean (SD)	0.64	1.19	0.63	1.55	1%
Median (IQR)	0	(0-1)	0	(0-1)	--
0	3300	60.0%	3476	63.2%	7%
1	1608	29.2%	1483	26.9%	5%
2	285	5.2%	240	4.4%	4%
3+	310	5.6%	304	5.5%	0%
LABORATORY DATA (most recent value in the 7-365 days prior to index date)					
Total patients with eGFRlaboratory data available	915	16.6%	932	16.9%	1%
Baseline eGFR					
Mean (SD)	74.56	17.74	72.15	16.15	14%
Median (IQR)	77	(62-90)	73	(62-85)	--
60+ ml/min/1.73m^2	718	13.0%	725	13.2%	1%
45 - <60 ml/min/1.73m^2	145	2.6%	153	2.8%	1%
30 - <45 ml/min/1.73m^2	41	0.7%	40	0.7%	0%
<30 ml/min/1.73m^2	11	0.2%	14	0.3%	1%
Missing	4588	83.4%	4571	83.1%	1%

Abbreviations: ACE, angiotensin-converting enzyme; COX, cyclo-oxygenase; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation