Population-Based Study of Risk of AKI with Levetiracetam

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Abstract

Background and objectives Regulatory agencies warn about the risk of AKI with levetiracetam use on the basis of information from case reports. We conducted this study to determine whether new levetiracetam use versus nonuse is associated with a higher risk of AKI.

Design, setting, participants, & measurements This was a population-based retrospective cohort study of adults with epilepsy in Ontario, Canada. Patients who received a new outpatient prescription for levetiracetam between January 1, 2004 and March 1, 2017 were matched to two nonusers on stage of CKD, recorded seizure in the prior 90 days, and logit of a propensity score for levetiracetam use. The primary outcome was a hospital encounter (emergency department visit or hospitalization) with AKI within 30 days of cohort entry. Secondary outcomes were AKI within 180 days and change in the concentration of serum creatinine. We assessed the primary outcome using health care diagnosis codes. We evaluated the change in the concentration of serum creatinine in a subpopulation with laboratory measurements.

Results We matched 3980 levetiracetam users to 7960 nonusers (mean age 55 years, 51% women). Levetiracetam use was not significantly associated with a higher risk of AKI within 30 days (13 [0.33%] events in levetiracetam users and 21 [0.26%] events in nonusers [odds ratio, 1.24; 95% confidence interval, 0.62 to 2.47]). Similarly, there was no significant association with AKI within 180 days (odds ratio, 0.70; 95% confidence interval, 0.43 to 1.13). The change in the concentration of serum creatinine did not significantly differ between levetiracetam users and nonusers.

Conclusions In this population-based study levetiracetam use was not associated with a higher risk of AKI.

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Introduction

Levetiracetam (trade name Keppra) is a popular second generation antiepileptic drug, with annual worldwide sales approximating $1 billion United States dollar (1). It is often used adjunctively with other antiepileptic drugs, is highly bioavailable, undergoes little metabolism, and is excreted by the kidneys with dose adjustment recommended in CKD (2,3). Levetiracetam has no reported clinically significant interactions with other antiepileptic drugs, and is perceived to have a more favorable adverse effect profile than other antiepileptic drugs (2). The most common adverse events reported with levetiracetam are somnolence, asthenia, dizziness, headaches, and behavioral changes (4).

Although the risk of AKI was not identified in randomized, controlled trials of levetiracetam use (Supplemental Table 1), postmarketing surveillance has identified a possible association between levetiracetam and AKI. In 2016 the World Health Organization issued a warning linking levetiracetam use with 150 cases of AKI, including 49 cases of interstitial nephritis (5). A detailed review of 39 cases of AKI established a possible causal relationship in nine cases, with a median onset of AKI 27 days from drug initiation.

Regulatory agencies in the United States, Canada, Europe, and Japan have issued warnings about the risk of AKI with levetiracetam use, which have resulted in changes in product monograph warnings (Supplemental Table 2). In January of 2017, the US Food and Drug Administration noted a potential safety signal in the Federal Adverse Event Reporting System (Supplemental Table 2). At the same time, Health Canada conducted a safety review and recommended that the risk of AKI be listed in all levetiracetam product monographs (Supplemental Table 2) (6).

We performed a search of bibliographic databases and identified only eight studies, all case reports, that suggested a greater risk of AKI with levetiracetam (Supplemental Table 3). In these reports, four cases of AKI were attributed to interstitial nephritis, two to rhabdomyolysis, and one to a pharmacokinetic interaction with methotrexate (7–14). Therefore, to provide additional safety data we conducted this population-based cohort study to determine whether levetiracetam use is associated with a higher risk of AKI compared with nonuse.

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Materials and Methods

Design and Setting

We conducted a population-based, retrospective cohort study using linked health care databases in Ontario, Canada between January 1, 2004 and March 1, 2017. Ontario has approximately 13.5 million residents who have universal access to hospital care and physician services, with individuals 65 years of age or older also receiving universal drug coverage (14% of the population or 1.9 million persons). Individuals under the age of 65 are eligible for universal drug coverage if they receive disability support, receive social assistance, or have high drug costs relative to their income. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that they may rely upon coding templates or macros that are unique to the ICES environment where the study was conducted. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Supplemental Table 4) (15).

Data Sources

We ascertained patient characteristics, drug use, covariate information, and outcome data using records from eight linked databases. We obtained vital statistics from the Ontario Registered Persons Database, which contains demographic information on all Ontario residents ever issued a health card. We used the Ontario Drug Benefit program database to determine prescription drug use. This database contains accurate records of all dispensed outpatient prescriptions, with an error rate of 0.7% (16). We identified diagnostic and procedural information on all hospitalizations and emergency department visits from the Canadian Institute for Health Information Discharge Abstract Database and National Ambulatory Care Reporting System database, respectively. We obtained covariate information from the Ontario Health Insurance Plan database, which includes health claims for physician services. We used the ICES Physician Database to ascertain levetiracetam prescriber information. In a subpopulation, we obtained serum creatinine laboratory measurements using data from the Ontario Laboratory Information System. We have previously used these databases to research adverse drug events including AKI (17–22).

International Classification of Diseases, ninth revision (ICD-9; pre-2002) and 10th revision (ICD-10; post-2002) codes were used to assess baseline comorbidities in the 5 years before receipt of a prescription (Supplemental Table 5). Only ICD-10 codes were used to ascertain outcomes, because all outcomes would have occurred after implementation of this coding system in 2002 (Supplemental Table 6). Comorbidities were evaluated using the Adjusted Clinical Group scoring system with the Johns Hopkins Adjusted Clinical Group System Version 10 (23). Databases were complete for all variables used except for levetiracetam prescriber data (18% missing) and income data (0.4% missing). The only reason for lost follow-up was emigration from the province, which occurs in <0.2% of the population each year and was not assessed in this study (24).

Cohort Build and Exposure Categorization

We established a cohort of patients in Ontario, Canada with evidence of a new outpatient prescription dispensed for oral levetiracetam (levetiracetam users). The date of dispensing served as the start date for follow-up, also referred to as the index date. As a referent group we identified a group of adult patients from the Ontario population who had never received a prescription for levetiracetam before a randomly assigned index date (levetiracetam nonusers). We did not choose another antiepileptic medication as a comparator because levetiracetam is often used adjunctively, and instead aimed to have similar baseline antiepileptic drug use in both groups.

From both the user and nonuser groups we excluded the following patients: (*1*) age<18 years on index date, (*2*) evidence of a prescription for levetiracetam in the 180 days before the index date (to ensure that these were new prescriptions), (*3*) patients with no evidence of a drug prescription in the 120 days before index date (to ensure eligibility and active use of the provincial universal drug benefit program), (*4*) those who had a hospital discharge or emergency department visit in the 2 days before index date (to ensure these were new outpatient levetiracetam prescriptions), (*5*) those with a history of ESKD, and (*6*) those with no evidence of epilepsy defined by no evidence of any of the following: a hospital encounter for seizure, electroencephalography in the prior 5 years, or a prescription for an antiepileptic in the prior 120 days (to capture both outpatient and hospital encounters with epilepsy). Patients with multiple eligible study prescriptions were restricted to the first eligible study prescription.

Outcomes

Primary Outcome. We assessed the primary outcome of a hospital encounter (emergency department visit or hospital admission) with AKI within 30 days after the index date, because most case reports describe AKI events from levetiracetam within this period. The primary outcome was assessed with an ICD-10 diagnosis code (Supplemental Table 6). In Ontario, we previously demonstrated that this AKI code identified a median increase in serum creatinine of 1.50 mg/dl at the time of emergency department visit (25th to 75th percentile, 0.70–3.26) above the most recent value (25). Although the specificity is >95%, the sensitivity of the AKI code is limited for milder forms of the condition. The incidence of AKI, as defined by the diagnosis code, can be underestimated up to five-fold compared with definitions using serum creatinine measurements. Therefore, we also examined a subpopulation with linked laboratory values as described below.

Secondary Outcomes. We assessed a hospital encounter with AKI within 180 days after the index date. This was done to account for any delay in the development of AKI and to account for any susceptibility levetiracetam may confer to other AKI insults over time (*i.e.*, two-hit hypothesis). To gain insights into the possible causes and severity of AKI, we assessed for a diagnosis of acute interstitial nephritis, rhabdomyolysis, receipt of acute dialysis, kidney

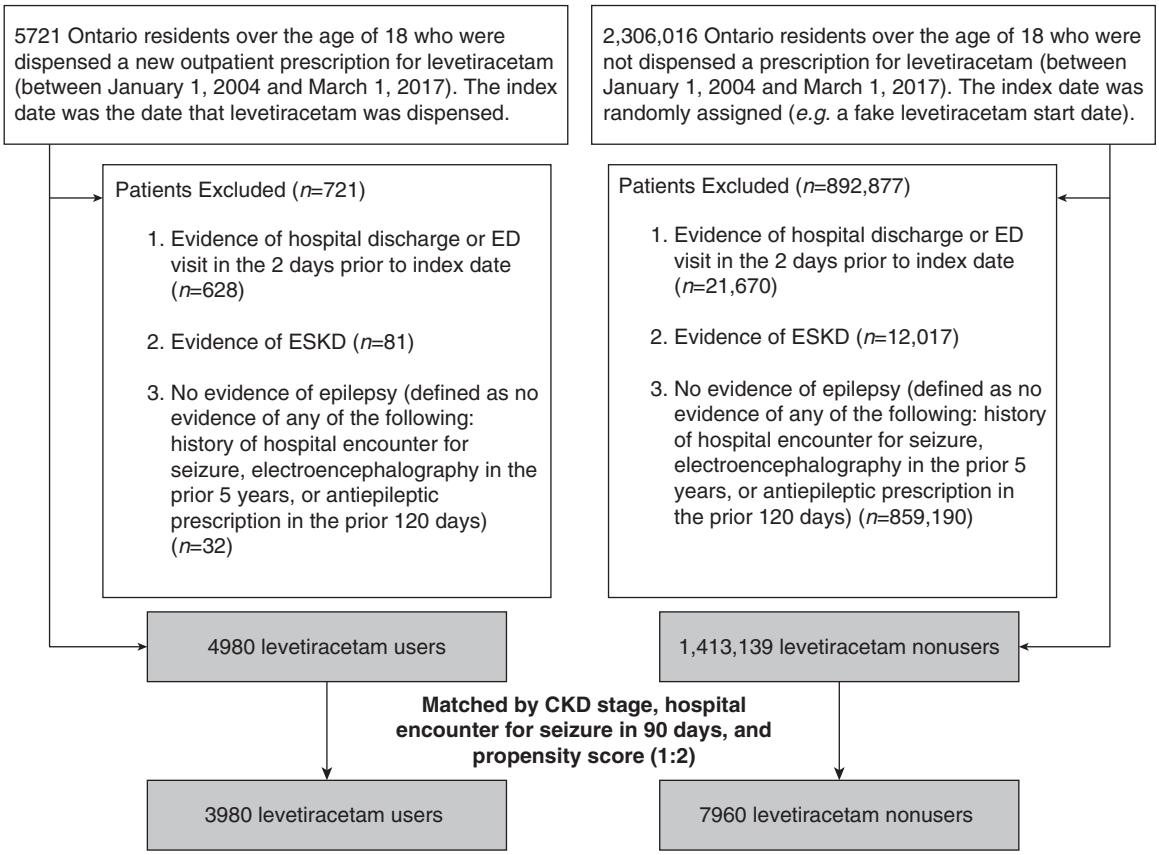


Figure 1. | Cohort selection with inclusion and exclusion criteria. We identified 3980 new levetiracetam users and matched them in a 1:2 ratio to 7960 levetiracetam non-users by CKD stage, hospital encounter with seizure in the prior 90 days, and a logit of the propensity score for levetiracetam use. ED, emergency department.

biopsy, or a nephrologist consultation within 180 days after the index date (codes are presented in Supplemental Table 6).

In a subpopulation of patients with serum creatinine measurements taken before and within 180 days after the index date, we defined AKI as evidence of an increase in concentration of serum creatinine value by ≥0.3 mg/dl or a ≥50% increase in the follow-up compared with preindex date baseline value, which are the laboratory thresholds used to define AKI in the Kidney Disease Improving Global Outcomes classification system (26). In addition, we compared the absolute and percentage change in serum creatinine between the two groups. We estimated baseline eGFR using the Chronic Kidney Disease Epidemiology Collaboration equation (27).

Statistical Analyses

Using a logistic regression model, we derived propensity scores for the predicted probability of receiving a new outpatient prescription for levetiracetam. Using a greedy matching algorithm without replacement, one levetiracetam user was matched to two nonusers on stage of CKD, whether they had a hospital encounter for epilepsy or seizure in the prior 90 days, and the logit of the propensity score for levetiracetam use (within a caliper width of 0.2 SD). Propensity score matching was used to ensure that user and nonuser groups were balanced on a wide range of measured baseline characteristics (variables included are provided in Supplemental Table 7). A 1:2 matching ratio was selected to maximize statistical power while minimizing the loss of levetiracetam users.

We used standardized differences to compare baseline characteristics between users and nonusers, with a value >10% indicating imbalance (28–30). We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs). In all outcome analyses we interpreted two-tailed P values <0.05 as statistically significant. To comply with ICES privacy regulations to minimize the chance of identifying a patient, numbers of patients were suppressed in the case of 1–5 patients (reported as ≤5). We performed all analyses using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Study Participants

The creation of our cohort is shown in Figure 1. From 2004 to 2017, there were 4980 levetiracetam users and 1,413,139 nonusers eligible for the study. Before matching, levetiracetam users compared with nonusers were more likely to be younger and have greater comorbidity, and had a greater number of hospitalizations and emergency department visits in the baseline period (Table 1).

Table 1. Baseline characteristics of levetiracetam users versus nonusers before and post propensity score matching

Characteristic[a]	Before Matching			Post Matching		
	Levetiracetam Users	Levetiracetam Nonusers	Standardized Difference[b] (%)	Levetiracetam Users	Levetiracetam Nonusers	Standardized Difference[b] (%)
Total patients, *N*	4980	1,413,139		3980	7960	
Demographics						
Mean age±SD, yr	54±21	69±16	76	55±21	55±21	0
≤65 yr	3092 (62)	395,028 (28)	73	2403 (60)	4878 (61)	2
Women	2549 (51)	837,046 (59)	16	2048 (52)	4013 (50)	2
Long-term care	352 (7)	52,086 (4)	15	273 (7)	522 (7)	1
Rural residence	496 (10)	167,640 (12)	6	409 (10)	829 (10)	0
Income quintile[c]						
1 (lowest)	1149 (23)	335,883 (24)	2	958 (24)	2009 (25)	3
3 (middle)	1002 (20)	267,725 (19)	3	808 (20)	1584 (20)	1
5 (highest)	897 (18)	246,083 (17)	2	696 (18)	1375 (17)	1
Comorbidities[d]						
Johns Hopkins ACG System Aggregated Diagnosis Groups, mean±SD[e]	10.0±4.3	8.2±3.8	45	9.7±4.3	9.8±4.2	4
AKI	16 (0.3)	2517 (0.2)	2	13 (0.3)	21 (0.3)	1
Anxiety disorder and depression	881 (18)	186,741 (13)	12	699 (18)	1495 (19)	4
Benign brain tumor	11 (0.2)	219 (0.0)	6	6 (0.2)	22 (0.3)	3
Bipolar disorder	344 (7)	76,931 (5)	6	280 (7)	624 (8)	4
Brain injury	220 (4)	7274 (0.5)	25	153 (4)	287 (4)	2
Brain cancer	329 (7)	726 (0.1)	37	142 (4)	167 (2)	11
Cancer[f]	1804 (36)	441,339 (31)	11	1333 (34)	2621 (33)	1
CKD	549 (11)	134,314 (10)	5	432 (11)	830 (10)	2
Chronic liver disease	361 (7)	68,436 (5)	10	273 (7)	598 (8)	3
Coronary artery disease, including angina[g]	1026 (21)	382,315 (27)	15	824 (21)	1668 (21)	1
Congestive heart failure	451 (9)	134,949 (10)	1	362 (9)	774 (10)	3
Diabetes	127 (3)	49,027 (4)	5	103 (3)	190 (2)	2
Epilepsy/seizure[h]	3481 (70)	25,154 (2)	202	2482 (62)	5019 (63)	1
Previous 90 d	1087 (22)	2772 (0.2)	74	460 (12)	920 (12)	0
Previous 90–365 d	1583 (32)	6731 (0.5)	94	1091 (27)	1984 (25)	6
Hypertension	1322 (27)	706,449 (50)	50	1095 (28)	2148 (27)	1
Migraine	618 (12)	85,403 (6)	22	485 (12)	987 (12)	1
Mood disorder	236 (5)	27,938 (2)	15	174 (4)	413 (5)	5
Multiple sclerosis	28 (0.6)	2612 (0.2)	6	15 (0.4)	92 (1)	11
Neuropathic pain	67 (1)	19,639 (1)	1	47 (1)	141 (2)	6
Parkinson disease	42 (0.8)	6712 (0.5)	4	36 (0.9)	136 (2)	9
Peripheral vascular disease	54 (1)	16,050 (1)	0	45 (1)	109 (1)	3
Stroke, including TIA	660 (13)	36,398 (3)	40	481 (12)	966 (12)	0
Trigeminal neuralgia	80 (2)	20,422 (1)	2	59 (2)	172 (2)	6
Concurrent medication use[i]						
ACE inhibitors or ARBs	851 (17)	460,963 (33)	36	706 (18)	1362 (17)	2
Antidepressants	239 (5)	80,146 (6)	4	199 (5)	405 (5)	0
Antiepileptics	942 (19)	74,430 (5)	43	703 (18)	1562 (20)	6
Antineoplastics	176 (4)	37,894 (3)	5	129 (3)	234 (3)	2
Antipsychotics	190 (4)	49,287 (4)	2	165 (4)	332 (4)	0
β blockers	642 (13)	304,371 (22)	23	518 (13)	1046 (13)	0
Benzodiazepines	413 (8)	149,512 (11)	8	309 (8)	653 (8)	2
Calcium channel blockers	556 (11)	285,732 (20)	25	456 (12)	899 (11)	1
Glucocorticoids	263 (5)	51,529 (4)	8	176 (4)	338 (4)	1
Diuretics—potassium sparing	58 (1)	40,865 (3)	12	51 (1)	98 (1)	1
Diuretics—thiazides	225 (5)	156,167 (11)	25	187 (5)	318 (4)	4
Diuretics—loop	228 (5)	102,693 (7)	11	185 (5)	388 (5)	1
Methotrexate	20 (0.4)	10,269 (0.7)	4	15 (0.4)	44 (0.6)	3
NSAIDs (excluding ASA)	141 (3)	128,727 (9)	27	117 (3)	219 (3)	1
Statins	1052 (21)	533,226 (38)	37	886 (22)	1757 (22)	1
Number of unique medications, mean±SD	3.4±5.0	4.9±4.6	31	3.4±4.9	3.4±5.1	0
Antiepileptic use (in prior 120 d)[i]						
Carbamazepine	162 (3)	7476 (0.5)	20	125 (3)	275 (4)	2
Clobazam	146 (3)	1079 (0.1)	24	85 (2)	159 (2)	1
Divalproex sodium	96 (2)	5104 (0.4)	15	67 (2)	162 (2)	3
Gabapentin	120 (2)	26,704 (2)	4	89 (2)	267 (3)	8
Lacosamide	56 (1)	178 (0.0)	15	37 (0.9)	52 (0.7)	4
Lamotrigine	115 (2)	2248 (0.2)	20	85 (2)	168 (2)	0
Phenytoin	426 (9)	11,026 (0.8)	37	291 (7)	677 (9)	5
Pregabalin	50 (1)	21,028 (2)	4	44 (1)	105 (1)	2
Primidone	27 (0.5)	2215 (0.2)	7	22 (0.6)	33 (0.4)	2
Topiramate	43 (0.9)	1887 (0.1)	10	31 (0.8)	62 (0.8)	0
Valproic acid	63 (1)	2104 (0.1)	13	46 (1)	90 (1)	0
Antiepileptic use (prescribed on index date)						
Carbamazepine	39 (0.8)	355 (0.0)	12	23 (0.6)	34 (0.4)	3

Table 1. (Continued)

Characteristic[a]	Before Matching			Post Matching		
	Levetiracetam Users	Levetiracetam Nonusers	Standardized Difference[b] (%)	Levetiracetam Users	Levetiracetam Nonusers	Standardized Difference[b] (%)
Clobazam	43 (0.9)	37 (0.0)	13	13 (0.3)	10 (0.1)	5
Divalproex sodium	31 (0.6)	316 (0.0)	11	14 (0.4)	21 (0.3)	2
Gabapentin	41 (0.8)	1139 (0.1)	11	24 (0.6)	49 (0.6)	0
Lamotrigine	32 (0.6)	113 (0.0)	11	18 (0.5)	18 (0.2)	5
Phenytoin	108 (2)	551 (0.0)	20	48 (1)	76 (1)	3
Healthcare contacts, mean±SD[j]						
Number of primary care physician visits	14.9±19.0	9.7±10.6	33	13.7±17.4	13.7±16.2	0
Number of internal medicine visits	3.1±8.5	0.8±3.0	35	2.4±6.9	2.3±6.8	1
Number of nephrology visits	0.2±1.3	0.1±0.8	10	0.2±1.1	0.2±1.3	0
Number of neurology visits	3.8±5.7	0.2±0.9	88	2.8±4.2	2.5±3.8	8
Number of psychiatry visits	0.9±5.6	0.6±4.1	7	1.0±6.1	1.0±4.9	1
Number of hospitalizations	1.1±1.6	0.4±1.0	49	0.9±1.4	0.9±1.4	1
Number of ED visits	2.2±3.1	0.8±1.9	54	1.9±2.8	1.9±3.2	2
Healthcare usage[k]						
Serum creatinine tests	3283 (66)	1,017,278 (72)	13	2617 (66)	5275 (66)	1
CT head	2362 (47)	143,204 (10)	90	1620 (41)	3315 (42)	2
MRI head	1781 (36)	50,669 (4)	89	1164 (29)	2185 (27)	5
Electroencephalography	1702 (34)	12,678 (0.9)	97	1113 (28)	2061 (26)	6
Chest x-ray	2413 (49)	445,900 (32)	35	1767 (44)	3579 (45)	1
Echocardiography	1044 (21)	240,986 (17)	10	770 (19)	1601 (20)	2
Epilepsy surgery	27 (0.5)	29 (0.0)	10	13 (0.3)	12 (0.2)	4
Video EEG monitoring	365 (7)	1578 (0.1)	39	209 (5)	336 (4)	6
Urinalysis	1554 (31)	555,062 (39)	17	1263 (32)	2493 (31)	1
Levetiracetam prescriber						
Primary care physician	1749 (35)	—	—	1435 (36)	—	—
Internal medicine	74 (2)	—	—	49 (1)	—	—
Neurology	2176 (44)	—	—	1754 (44)	—	—
Neurosurgery	19 (0.4)	—	—	11 (0.3)	—	—
Psychiatry	17 (0.3)	—	—	15 (0.4)	—	—
Other/missing	945 (19)	—	—	716 (18)	—	—
Laboratory data (in subpopulation)						
≥1 serum creatinine measurement	619	202,714		509 (13)	1018 (13)	
Mean serum creatinine level, mg/dl±SD	0.83±0.29	0.93±0.36	31	0.82±0.27	0.84±0.26	8
Median serum creatinine level mg/dl (IQR)	0.77 (0.66–0.94)	0.86 (0.72–1.04)		0.77 (0.66–0.93)	0.79 (0.67–0.96)	
Median eGFR, ml/min per 1.73 m^2 (IQR)	90 (73–105)	77 (61–89)		91 (74–108)	91 (75–105)	
eGFR Category, ml/min per 1.73 m^2						
≥60	528 of 619 (85)	153,348 of 202,714 (76)	1	442 of 509 (87)	884 of 1018 (87)	0
45–60	56 of 619 (9)	29,952 of 202,714 (15)	8	42 of 509 (8)	84 of 1018 (8)	0
15–45	35 of 619 (6)	18,907 of 202,714 (9)	6	25 of 509 (5)	50 of 1018 (5)	0
<15	0 of 619 (0)	507 of 202,714 (0.3)	0	0 of 509 (0)	0 of 1018 (0)	0
Random urine albumin creatinine ratio, mg/g						
<30	51 of 75 (68)	36,665 of 51,154 (72)	12	43 of 58 (74)	90 of 118 (76)	0
≥30	24 of 75 (32)	14,489 of 51,154 (28)	8	15 of 58 (26)	28 of 118 (24)	0

ACG, Adjusted Clinical Group; TIA, transient ischemic attack; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; ASA, acetylsalicylic acid; ER, emergency department; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; —, not applicable; IQR, interquartile range.

[a]Data are presented as the number (percentage) of patients, unless otherwise reported.

[b]Standardized differences are less sensitive to sample size than traditional hypothesis tests are. They provide a measure of the difference between groups with respect to the pooled SD; a standardized difference >10% was considered a meaningful difference between the groups.

[c]Income was categorized into fifths of average neighborhood income on the index date.

[d]Comorbid conditions in the 5 yr preceding the index date were considered.

[e]We used the ACG scoring system to score comorbidity. The ACG is a population/patient case-mix adjustment system that provides a relative measure of the individual's expected consumption of health services. ICD-9/ICD-9-CM codes are categorized into 32 groups, called Ambulatory Diagnostic Groups, on the basis of clinical similarity, chronicity, likelihood of requiring specialty care, and disability. These groups are further reduced to 12 "Collapsed Ambulatory Diagnostic Groups."

[f]Cancers include lung/bronchi, colon/rectum, breast, pancreas, prostate, leukemia, non-Hodgkin lymphoma, liver, ovarian, and esophageal.

[g]Coronary artery disease includes receipt of coronary artery bypass graft surgery, and percutaneous coronary intervention.

[h]Epilepsy/seizure codes are hospital diagnosis codes and do not capture those patients who do not present to hospital, which underestimates the prevalence of the condition.

[i]Dispensed medications in the 120 d preceding the index date were considered.

[j]Health care contacts in the year preceding the index date were considered.

[k]Health care use in the year preceding the index date was considered.

Table 2. Outcomes assessed using database codes

Outcome	No. Events (%)		Odds Ratio (95% CI)	*P* Value
	Levetiracetam Users (*n*=3980)	Nonusers (*n*=7960)		
30 d after prescription				
AKI[a]	13 (0.33)	21 (0.26)	1.24 (0.62 to 2.47)	0.55
180 d after prescription[a]				
AKI[a]	23 (1.15)	65 (1.63)	0.70 (0.43 to 1.13)	0.15
Rhabdomyolysis[a]	10 (0.50)	14 (0.35)	1.43 (0.64 to 3.22)	0.39
Nephrologist consultation	36 (1.80)	62 (1.55)	1.17 (0.77 to 1.77)	0.47
Acute dialysis[b]	0 (0.00)	≤5 (≤0.06)	—	—
Acute interstitial nephritis[b]	≤5 (≤0.12)	≤5 (≤0.06)	—	—
Kidney biopsy[b]	≤5 (≤0.12)	≤5 (≤0.06)	—	—

95% CI, 95% confidence interval; —, not applicable.
[a]The number of events (and the proportion of patients who experienced an event) for both outcomes were assessed using hospital diagnosis codes. This underestimates the true event rate because these codes have high specificity but low sensitivity.
[b]To comply with Institute for Clinical Evaluative Sciences privacy regulations to minimize the chance of identifying a study patient, numbers of patients were suppressed in the case of 1–5 patients (reported as ≤5).

We matched 3980 (79.9%) of our original cohort of levetiracetam users to 7960 levetiracetam nonusers. The two groups were well balanced on >100 different characteristics including patient demographics, comorbidities, concurrent medication use (including antiepileptics), health care contacts, and health care use. Standardized differences were <10% across all characteristics measured except for brain cancer and multiple sclerosis, which were 11% (Table 1). Among levetiracetam users, the median (25th to 75th percentile) age was 55 (36–73) years, and 60.4% of levetiracetam users were aged ≤65 years. Continuous use was defined as consecutive prescription claims within a period equivalent to 150% of the days supplied for the previous prescription. The median (25th to 75th percentile) duration of continuous prescriptions for levetiracetam users in follow-up was 287 (84–827) days. Levetiracetam users who were successfully matched to nonusers were less likely to have had a seizure in the prior 90 days compared with nonmatched levetiracetam users (Supplemental Table 8).

Primary Outcome

Levetiracetam use compared with nonuse was not significantly associated with a higher 30-day risk of hospital encounter with AKI, with 13 (0.33%) events in levetiracetam users versus 21 (0.26%) events in nonusers (OR, 1.24; 95% CI, 0.62 to 2.47; *P*=0.55) (Table 2).

Secondary Outcomes

Levetiracetam use compared with nonuse was also not significantly associated with a higher 180-day risk of hospital encounter with AKI (Table 2). At 180 days there were 23 (1.15%) events in levetiracetam users and 65 (1.63%) events in nonusers (OR, 0.70; 95% CI, 0.43 to 1.13; *P*=0.15).

Among the 23 patients with AKI in the levetiracetam group followed for 180 days from the index date, none were taking methotrexate or had a concurrent recorded diagnosis of rhabdomyolysis. When the 3980 levetiracetam users were followed for 180 days, no patients received acute dialysis, ≤5 (≤0.1%) had a hospital encounter with a diagnosis of acute interstitial nephritis, and ≤5 (≤0.1%) received a kidney biopsy. After extending follow-up to 365 days, the number of acute interstitial nephritis diagnoses remained ≤5 (≤0.1%) in the levetiracetam users. The risk of a hospital encounter with rhabdomyolysis (without the need for a concurrent recorded diagnosis of AKI) was not significantly different in levetiracetam users compared with nonusers over a period of 180 days after the index date (10 [0.50%] events in levetiracetam users and 14 [0.35%] events in nonusers [OR, 1.43; 95% CI, 0.64 to 3.22; *P*=0.39]). Over this same period there was also no significant difference between the two groups in the likelihood of having a nephrology consultation (36 [1.80%] events in levetiracetam users and 62 [1.55%] events in nonusers [OR, 1.17; 95% CI, 0.77 to 1.77; *P*=0.47]).

Levetiracetam use compared with nonuse was not significantly associated with a higher risk of AKI in the subpopulation with serum creatinine values (Table 3). A baseline creatinine value was available in 619 (15.5%) patients in the levetiracetam group, of which 509 (82.2%) were matched to levetiracetam nonusers who also had a baseline creatinine value. Within this subset, standardized differences were well balanced (Supplemental Table 9). Median baseline creatinine was 0.77 mg/dl in levetiracetam users and 0.79 mg/dl in nonusers. The baseline creatinine was measured a median (25th to 75th percentile) of 179 (65–297) days before the index date. In this cohort, 67 of 509 levetiracetam users (13.2%) had a baseline eGFR<60 ml/min per 1.73 m^2. At 30 days the OR for AKI on the basis of laboratory measurements was 1.25 (95% CI, 0.41 to 3.82; *P*=0.70). Similarly, at 180 days there were 19 (3.73%) AKI events in levetiracetam users by serum creatinine measurements and 27 (2.65%) events in nonusers (OR, 1.44; 95% CI, 0.78 to 2.66; *P*=0.24).

There were 151 levetiracetam users and 275 nonusers who had a baseline serum creatinine measurement and at least one measurement within 180 days of follow-up. The mean (±SD) rise in the concentration of serum creatinine in the 180 days after the index date was 0.09±0.21 mg/dl in levetiracetam users and 0.10±0.31 in

Table 3. AKI in subpopulation assessed using laboratory data

AKI[a]	No. Events (%)		Odds Ratio (95% CI)	*P* Value
	Levetiracetam Users (*n*=509)	Nonusers (*n*=1018)		
30 d	≤5 (≤0.1)[b]	8 (0.79)	1.25 (0.41 to 3.82)	0.70
180 d	19 (3.73)	27 (2.65)	1.44 (0.78 to 2.66)	0.24

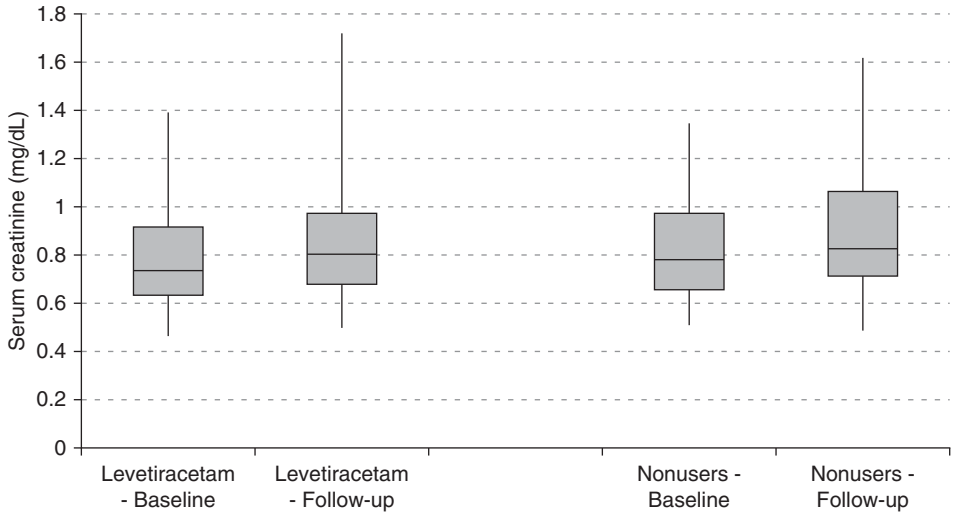
95% CI, 95% confidence interval.
[a]AKI was assessed by the change from a baseline serum creatinine concentration to peak serum creatinine concentration measured within the time period indicated after the index date. Peak serum creatinine concentration may have been measured in an outpatient laboratory, emergency department, or hospital setting. Index date was defined as the date of prescription dispensing in levetiracetam users and was randomly assigned in nonusers.
[b]To comply with Institute for Clinical Evaluative Sciences privacy regulations to minimize the chance of identifying a study patient, numbers of patients were suppressed in the case of 1–5 patients (reported as ≤5). Accordingly, an odds ratio assuming five events in the levetiracetam group is presented. This may overestimate the true rate.

nonusers with an absolute difference between the groups of 0.01 (95% CI, −0.06 to 0.05; *P*=0.86) (Figure 2).

Discussion

In this population-based cohort study we found no significant association with new levetiracetam use and the risk of AKI. This finding was consistent in our primary and secondary analyses. Our results suggest that those who developed AKI were not at serious risk, because no individuals in the levetiracetam group received acute dialysis.

Our results are consistent with the findings from prior randomized and open-label trials, which did not describe a significant risk of AKI with levetiracetam (Supplemental Table 1). Only a single case of kidney failure was noted in



	Levetiracetam (n=151)		Nonusers (n=275)		Difference (Levetiracetam - Nonusers)	
	Mean ±SD [a]	Percentage ±SD [b]	Mean ±SD [a]	Percentage ±SD [b]	Mean (95% CI)	Percentage (95% CI)
Change in Creatinine mg/dL	0.09 ± 0.21	13.5% ± 29.53%	0.10 ± 0.31	11.1% ± 37.77%	0.01 (-0.06, 0.05)	0.0% (-7.0%, 6.9%)

Figure 2. | Changes in serum creatinine level within 180 days of levetiracetam use. No significant differences were observed between baseline and follow-up serum creatinine levels in both levetiracetam users and non-users. [a]Change in serum creatinine was defined as the peak serum creatinine concentration in the 180 days after the index date minus the baseline serum creatinine concentration. Peak serum creatinine concentration may have been measured in an outpatient laboratory, emergency department, or hospital setting. [b]Percentage change defined as: ([peak serum creatinine concentration in the 180 days after the index date]−[baseline serum creatinine concentration])/baseline serum creatinine concentration×100. 95% CI, 95% confidence interval.

the largest postmarketing open-label trial, which included 1541 patients on levetiracetam (31).

On the basis of case reports, interstitial nephritis, rhabdomyolysis, and interaction with methotrexate have been proposed as potential mechanisms of levetiracetam-associated AKI. Given the findings of our population-based study, we evaluated the quality of the case reports associating levetiracetam use with AKI (Supplemental Table 10) (32). On the basis of the Naranjo algorithm, which we used to determine the likelihood that an adverse reaction was secondary to levetiracetam, all case reports fell in the category of "probable adverse drug reaction" (33).

Two of the four case reports attributing acute interstitial nephritis to levetiracetam use had biopsy confirmation (9,10), whereas another case attributed hypokalemia and hypomagnesemia to an acquired kidney tubular disorder secondary to levetiracetam use (34). The product monograph for levetiracetam lists nephritis as a possible manifestation associated with Drug Reaction with Eosinophilia and Systemic Symptoms. In our study levetiracetam use was not associated with a higher risk of acute interstitial nephritis when patients were followed for 365 days.

Rhabdomyolysis is a known cause of AKI (35). In our study, the incidence of rhabdomyolysis was not significantly different in levetiracetam users compared with nonusers. None of the levetiracetam users who developed AKI had evidence of rhabdomyolysis. Rhabdomyolysis with levetiracetam use has been documented in nine case reports in the literature (Supplemental Table 11), within 2 weeks of drug initiation, and with a higher prevalence reported in Japanese patients (7,13,36–42). Although prolonged seizures can independently cause rhabdomyolysis, two case reports of AKI have been attributed to rhabdomyolysis secondary to levetiracetam use (7,13).

High-dose methotrexate is known to cause AKI either through crystal deposition or direct kidney tubular injury. Health Canada issued a warning in October of 2016 regarding a possible drug interaction between methotrexate and levetiracetam that could result in acute kidney failure (43). Methotrexate is excreted through the kidneys, and a case of delayed methotrexate elimination with coadministration with levetiracetam resulting in kidney failure has been reported (44). A subsequent retrospective study in 81 patients by the same group did not support this interaction (45). None of the levetiracetam users who developed AKI in our study were using methotrexate.

Our study has several strengths. This is the first large observational study to investigate the association between levetiracetam use and AKI. It included 3980 levetiracetam users, which is 13-times larger than the number of patients taking levetiracetam in the largest randomized trial (46). Furthermore, we included patients excluded from prior studies such as those with CKD. We acknowledge that our study has limitations. A small number of events meant some estimates were imprecise, with inadequate statistical power to detect a small difference in risk. We did not have data on medications used in hospital and did not study levetiracetam use initiated in hospital. In our region levetiracetam is most often used adjunctively and we did not conduct a study of patients with new onset epilepsy who initiated levetiracetam as their first antiepileptic treatment. In addition, a dose-dependent effect was not evaluated. Only a limited number of patients had baseline and follow-up laboratory measurements available for analysis, reducing our precision to detect differences in risk for milder AKI. Follow-up laboratory measurements were assessed retrospectively in routine care rather than by a standardized protocol. Despite this, the lack of any appreciable AKI risk with levetiracetam was consistent in all of the analyses performed.

In conclusion, the findings from our population-based study do not support an association between levetiracetam use and risk of AKI. Currently, the risk of AKI is labeled in Canadian and American levetiracetam product monographs as a postmarketing adverse event. Popular prescribing references such as Lexicomp list kidney failure as an adverse event $<1\%$ of the time. Although this study found no association between new levetiracetam use and AKI, there was inadequate statistical power to detect a rare idiosyncratic event. At this time, for patients presenting with serious AKI while taking levetiracetam, all other causes should be excluded before carefully considering levetiracetam as a potential cause.

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Disclosures

None.

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Supplemental Material

Supplemental Table 1. Summary of Renal Adverse Events from Major Studies on Levetiracetam.

Supplemental Table 2. Current Warnings for Levetiracetam Relevant to Acute Kidney Injury.

Supplemental Table 3. Summary of Case Reports of Acute Kidney Injury Associated with Levetiracetam Use.

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Supplemental Table 11. Case Reports of Rhabdomyolysis Associated with Levetiracetam Use.

Supplemental Table 12. Levetiracetam Dosage Recommendations.

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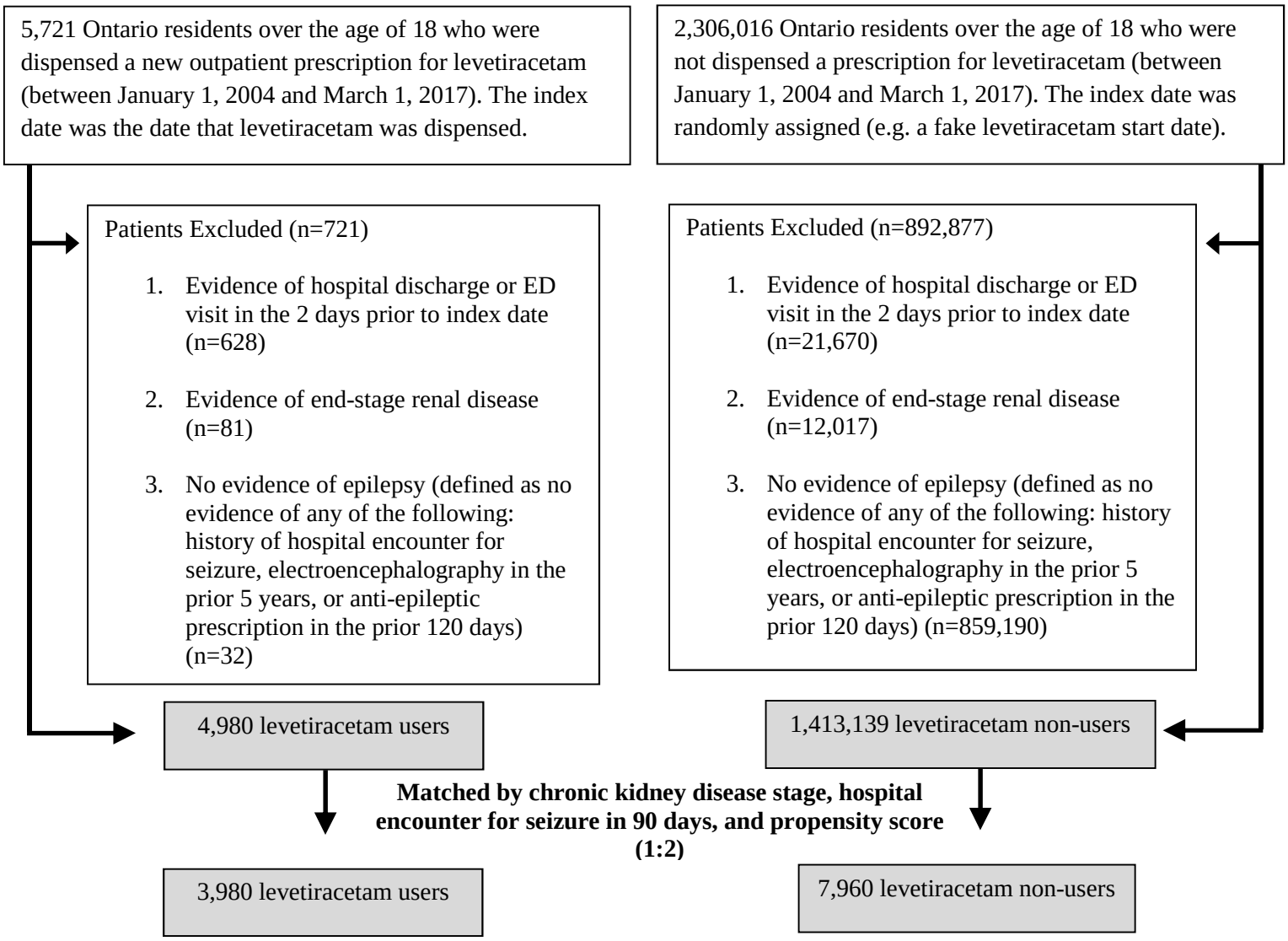
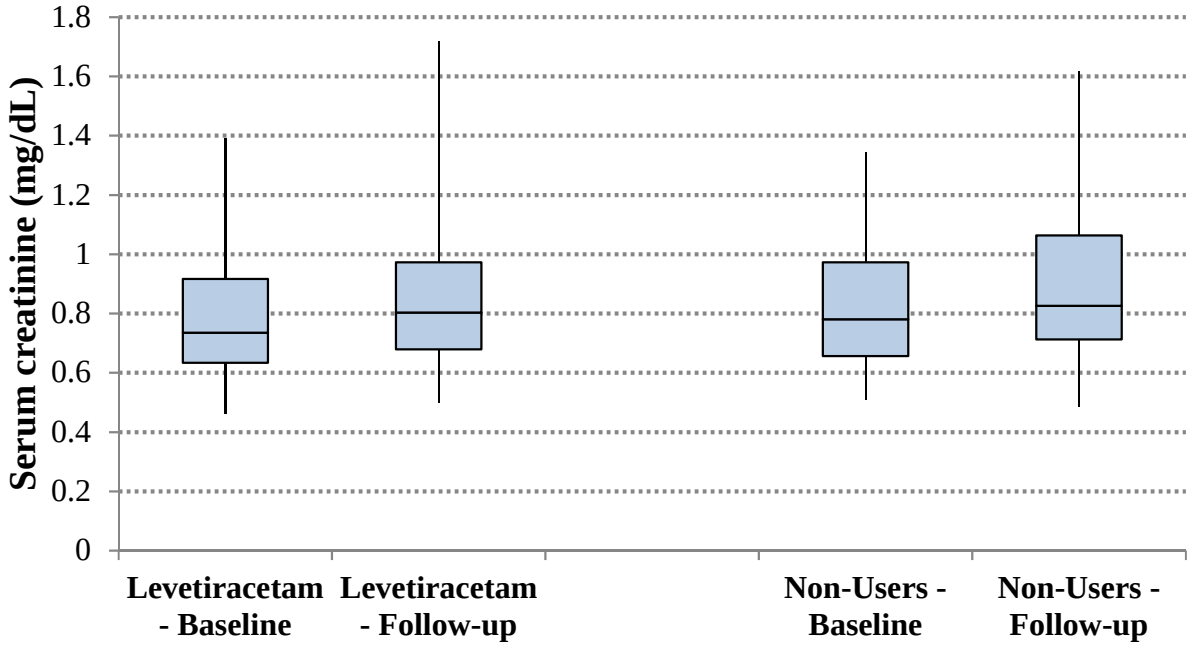

5,721 Ontario residents over the age of 18 who were dispensed a new outpatient prescription for levetiracetam (between January 1, 2004 and March 1, 2017). The index date was the date that levetiracetam was dispensed.
2,306,016 Ontario residents over the age of 18 who were not dispensed a prescription for levetiracetam (between January 1, 2004 and March 1, 2017). The index date was randomly assigned (e.g. a fake levetiracetam start date).
Patients Excluded (n=721)
1. Evidence of hospital discharge or ED visit in the 2 days prior to index date (n=628)
2. Evidence of end-stage renal disease (n=81)
3. No evidence of epilepsy (defined as no evidence of any of the following: history of hospital encounter for seizure, electroencephalography in the prior 5 years, or anti-epileptic prescription in the prior 120 days) (n=32)
Patients Excluded (n=892,877)
1. Evidence of hospital discharge or ED visit in the 2 days prior to index date (n=21,670)
2. Evidence of end-stage renal disease (n=12,017)
3. No evidence of epilepsy (defined as no evidence of any of the following: history of hospital encounter for seizure, electroencephalography in the prior 5 years, or anti-epileptic prescription in the prior 120 days) (n=859,190)
4,980 levetiracetam users
1,413,139 levetiracetam non-users
Matched by chronic kidney disease stage, hospital encounter for seizure in 90 days, and propensity score (1:2)
3,980 levetiracetam users
7,960 levetiracetam non-users



	Levetiracetam (n=151)		Non-Users (n=275)		Difference (Levetiracetam - Non-Users)	
	Mean ±SD [a]	**Percentage ±SD [b]**	**Mean ±SD [a]**	**Percentage ±SD [b]**	**Mean (95% CI)**	**Percentage (95% CI)**
Change in Creatinine mg/dL[c]	0.09 ± 0.21	13.5% ± 29.53%	0.10 ± 0.31	11.1% ± 37.77%	0.01 (-0.06, 0.05)	0.0% (-7.0%, 6.9%)

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

Population-based study of risk of acute kidney injury with levetiracetam

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SUPPLEMENTARY MATERIAL

Supplemental Table 1. Summary of Renal Adverse Events from Major Studies on Levetiracetam

Supplemental Table 2. Current Warnings for Levetiracetam Relevant to Acute Kidney Injury

Supplemental Table 3. Summary of Case Reports of Acute Kidney Injury Associated with Levetiracetam Use

Supplemental Table 4. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines

Supplemental Table 5. Coding Definitions for Demographic and Comorbid Conditions

Supplemental Table 6. Coding Definitions Used to Define Outcomes

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Supplementary Table 1. Summary of Renal Adverse Events from Major Studies on Levetiracetam

Randomized Controlled Trials					
Author	**Study Size (n=)**	**Study Type and Source Population**	**Patient Eligibility**	**Major Safety Findings**	**Renal Adverse Events**
Cereghino *et al.* (2000)	264	Multicenter double-blind, randomized, placebo-controlled, parallel-group trial.	Patients aged 16-70 with refractory partial seizures. Excluded patients with medical conditions other than epilepsy.	-Treatment-emergent adverse events (>10% with incidences higher than placebo were infection, headache, somnolence, dizziness, asthenia, rhinitis, and flu syndrome -No laboratory abnormalities	No renal adverse outcome reported.
Ben-Menachem *et al.* (2000)	286	Multicenter, double-blind, randomized placebo-controlled, parallel-group, responder-selected study.	Patients aged 16-70 with partial seizures. Excluded most comorbidities including impaired renal function.	-Most common adverse effects were asthenia, infection, and somnolence -One patient had a maculopapular rash -No changes in laboratory values except one patient had a WBC count below lower limit of normal that resolved without treatment	No renal adverse outcome reported.
Bett *et al.* (2000)	119	Multicenter, double-blind, randomized, parallel group study (followed by open label period).	Patients aged 16-70 with well-characterized refractory epilepsy and any seizure type. Excluded patients with serious medical comorbidities including renal impairment.	-Levetiracetam 2000 mg daily compared to 4000 mg -Higher incidence of somnolence in higher dosage group -No changes in laboratory values between groups -Higher dose not necessarily more effective	No renal adverse outcome reported.
Boon *et al.* (2000)	324	Multicenter, double-blind, randomized, placebo-controlled cross-over trial.	Patients between age 16-65 with predominantly partial seizures. Excluded patients with medical conditions other than epilepsy including those with renal impairment.	-Most common adverse effects were headache, asthenia, infection, somnolence, pharyngitis, dizziness, and pain -No changes in laboratory values between groups	No renal adverse outcome reported.

Brodie *et al.* 2007	576	Multicenter, double-blind, randomized non-inferiority, parallel-group trial with Levetiracetam vs. Carbamazepine.	Patients ≥16 years of age with newly diagnosed epilepsy.	-Depression and insomnia were reported more often with levetiracetam	No renal adverse outcome reported.
Noachtar *et al.* 2008	122	Multicenter, double-blind, randomized placebo-controlled trial.	Patients aged 12-65 with idiopathic epilepsy with myoclonic seizures.	-Headache, somnolence, neck pain, and pharyngitis were most common adverse effects -Laboratory tests showed CrCl < 70 mL/minute in 4/60 in placebo group and 3/60 in levetiracetam group	No renal adverse outcome reported.
Shorvon *et al.* 2000	324	Multicenter double-blind, randomized, placebo-controlled trial.	Patients aged 16-65 with refractory epilepsy and predominantly partial seizures. Those with renal impairment were excluded.	-No significant difference in adverse events between groups - No clinically significant abnormalities on laboratory values	No renal adverse outcome reported.
Tsai *et al.* 2006	94	Multicenter, double-blind, randomized, placebo-controlled study.	Patients aged 16-60 with partial seizures. Those with major comorbidities were excluded including renal impairment.	-Most common adverse events somnolence, dizziness and diplopia in levetiracetam - No clinically significant abnormalities on laboratory values	No renal adverse outcome reported.
Pina-Garza *et al.* 2009	116	Multicenter, double-blind, randomized, placebo-controlled study.	Children aged 1 month to <4 years with partial-onset seizures inadequately controlled with one or two antiepileptic drugs. Those with clinically significant medical condition or laboratory	-Somnolence and irritability were the most frequently reported drug-related events -Four subjects on levetiracetam had a potential clinically elevated lymphocyte count that resolved	No renal adverse outcome reported.

			abnormalities were excluded.		
Open-Label Trials					
Author	**Study Size (n=)**	**Study Type and Source Population**	**Patient Eligibility**	**Major Safety Findings**	**Renal Adverse Events**
KEEPER Trial Morrell *et al.* (2003)	1030	Phase IV prospective, open-label, multicenter, community-based observation al trial.	Patients aged ≥16 years with partial-onset seizures.	-Eight patients had previous renal impairment -Most common adverse events were somnolence, dizziness, asthenia, and headache	No renal adverse outcomes reported.
SKATE Study Steinhoff *et al.* (2007)	1541	Phase IV 16-week, open-label study.	Patients aged ≥16 years with treatment resistant partial seizures.	- 50.5% of patients reported at least one adverse event -Somnolence, fatigue, dizziness and headache were the most common adverse events	One case of renal failure possibly related to levetiracetam.
ASIA SKATE II Study Kwan *et al.* (2010)	251	Phase IV observation al study was a multi country, multicenter, open-label, single-arm study.	Patients aged ≥16 years as adjunctive therapy for partial seizures in every day clinical practice in Asian populations.	-Adverse events were reported by 73.3% of patients and were generally mild, leading to treatment withdrawal in only 7.2% -Most common adverse events were somnolence and dizziness	No renal adverse outcomes reported.
Beran *et al.* (2005)	91	Phase IIIB Open-label, single-arm prospective study. 8 week baseline followed by 16 week treatment.	Patients age 16-70 as add on therapy for refractory partial-onset seizures.	-Add on therapy up to 3000mg/day reduced frequency of seizures -Most frequent adverse events were fatigue, somnolence, headache and dizziness	Blood in urine in 10 urinalysis assumed to be peri-menstrual in 9/10 cases.
Abou-Khalil *et al.* (2003)	219	10-16 week open-label, multicentre observation al study.	Patients age 16-70 with epilepsy refractory to previous treatment with at least two anti-epileptics.	-Most common adverse events were asthenia, dizziness, and somnolence - Most adverse events occurred during up-titration -Did not alter concomitant anti-epileptic concentrations	No renal adverse outcomes reported.

Supplemental material is neither peer-reviewed nor thoroughly edited by CJASN. The authors alone are responsible for the accuracy and presentation of the material.

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Supplementary Table 2. Current Warnings for Levetiracetam Relevant to Acute Kidney Injury

		United States	Canada	Europe	Japan
Reaction Type					
Acute Kidney Injury	**Regulatory Agency Recommendation**	U.S. Food and Drug Administration Adverse Event Reporting System signal reported **Date:** January-March 2017	Health Canada Warning regarding risk of Acute Renal Failure (Acute Kidney Injury/Interstitial Nephritis) **Date:** January 2017	European Medicines Agency Revision of Product Monograph **Date:** September 2016	Pharmaceuticals and Medical Devices Agency Revision of Precaution
	Product Monograph	**Post Marketing Adverse Event:** "Acute Kidney Injury" **Date Listed:** October 26, 2016	**Post Marketing Adverse Event:** "Cases of acute kidney injury (including acute renal failure) have been reported in patients treated with levetiracetam." **Date Listed:** September 14, 2016	**Special warnings and precautions:** Rare Side Effect (may affect 1 to 10 users in 10,000 people): "The use of levetiracetam has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months." **Date Listed:** September 15, 2016	**Precautions:** "Acute renal failure may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted." **Date Listed:** May 31, 2016
Rhabdomyolysis	**Regulatory Agency Recommendation**	No specific recommendation	No specific recommendation	European Medicines Agency Revision of Product Monograph **Date:** September 2016	Pharmaceuticals and Medical Devices Agency Revision of Precaution

	Product Monograph	**Post Marketing Adverse Event:** "Muscle Weakness" **Date Listed:** March 7, 2014	**Post Marketing Adverse Event:** "Rhabdomyolysis and/or blood creatine phosphokinase increase has been reported in diverse patient populations, however, a higher prevalence of these reports in Japanese patients may signal an elevated risk." **Date Listed:** August 17, 2017	**Rare Side Effect (may affect 1 to 10 users in 10,000 people):** "Rhabdomyolysis (breakdown of muscle tissue) and associated blood creatine phosphokinase increase. Prevalence is significantly higher in Japanese patients when compared to non-Japanese patients." **Date Listed:** September 15, 2016	**Precautions:** "Rhabdomyolysis may occur. Patients should be carefully monitored. If signs or symptoms including myalgia, feeling of weakness, increased creatine kinase (creatine phosphokinase), increased blood myoglobin, and increased urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be taken." **Date Listed:** January 9, 2015
Methotrexate Interaction	**Regulatory Agency Recommendation**	No specific recommendation	Health Canada warning **Date:** October 2016	European Medicines Agency Revision of Product Monograph	No specific recommendation
	Product Monograph	No warning listed.	**Drug-Drug Interaction:** "Concomitant administration of levetiracetam and methotrexate has been very rarely reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs."	**Drug-Drug Interaction:** "Concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs."	

			Date Listed: September 14, 2016		
Skin Hypersensitivity Reactions	**Regulatory Agency Recommendation**	No specific recommendation	No specific recommendation	No specific recommendation	No specific recommendation
	Product Monograph	**Warnings and Precautions:** "Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both pediatric and adult patients treated with KEPPRA. The median time of onset is reported to be 14 to 17 days, but cases have been reported at least four months after initiation of treatment."	**Warning/Precaution:** "Serious hypersensitivity reactions with dermatological involvement have been reported in both children and adults in association with KEPPRA use, including Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)." "DRESS initially presents with fever and rash, and then with other organ system involvement that may or may not include eosinophilia, lymphadenopathy, hepatitis, nephritis, and/or myocarditis." **Date Listed:** July 2014 or earlier	**Rare Side Effects (may affect 1 to 10 users in 10,000 people):** "Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme"	**Precautions:** "Drug-induced hypersensitivity syndrome (DIHS): Rash or pyrexia may occur as the initial symptoms and signs followed by serious late-onset hypersensitivity symptoms with hepatic dysfunction, lymphadenopathy, increased white blood cells, increased eosinocyte, and atypical lymphocytes. Patients should be carefully monitored. If such symptoms are observed, administration of this drug should be discontinued and appropriate measures should be taken." **Date Listed:** April 2014

	Date Listed: December 16, 2011

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Supplementary Table 3. Summary of Case Reports of Acute Kidney Injury associated with Levetiracetam Use

Author	Age	Dose	Onset	Peak Creatinine[a]	Renal Biopsy	Required Dialysis	Cause of AKI	Outcome	Naranjo Adverse Drug Reaction Probability[b]
Hurwitz *et al.*	17	250 mg PO BID	10 days	7.70 mg/dL	Yes	No	Subacute Interstitial Nephritis	Resolved with prednisone but developed papillary necrosis likely secondary to interstitial nephritis	5
Spengler *et al.*	23	500 mg PO BID	1 day	4.22 mg/dL	No	No	Unknown	Resolved with levetiracetam discontinuation and fluids	4
Mahta *et al.*	45	3000 mg PO BID	2 month	3.59 mg/dL	No	No	Acute Interstitial Nephritis	Resolved with levetiracetam discontinuation	5
Leblanc and Plaisance	75	500 mg PO BID	10 weeks	5.79 mg/dL	No	No	DRESS and Acute Interstitial Nephritis	Resolved with pulse methylprednisolone and high dose prednisone	5
Chau *et al.*	69	500 mg PO BID	14 days	4.45 mg/dL	Yes	Yes	Granulomatous Interstitial Nephritis	Resolved with pulse methylprednisolone and 3 months prednisone	5
Singh *et al.*	16	750 mg PO BID	1 day	2.21 mg/dL	No	No	Rhabdomyolysis	Resolved with levetiracetam discontinuation and fluids	4
Parentelli *et al.*	15	15mg/kg/ PO daily	1 day	~2.71 mg/dL	No	No	Methotrexate Interaction with levetiracetam	Resolved with Alkaline Fluids, folinic acid, Carboxypeptidase G2, and discontinuation of levetiracetam	5
Isaacson *et al.*	19	2000 mg IV loading dose then 500 mg PO daily	4 days	2.17 mg/dL	No	No	Rhabdomyolysis	Resolved with levetiracetam discontinuation	4

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Abbreviations: BID, twice daily; DRESS, Drug reaction with eosinophilia and systemic symptoms; IV, intravenous; PO, per oral.

[a] Conversion factor for units: serum creatinine in mg/dL to μmol/L, x88.4.

[b] Naranjo Adverse Drug Reaction Probability Interpretation: ≥ 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR

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Supplementary Table 4. Checklist of recommendations for reporting of observational studies using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines

	Item No	STROBE Items	Reported	RECORD Items	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title, Abstract	RECORD 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.	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract	RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Abstract
				RECORD 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 - Setting and Study Design		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods - Setting and Study Design, Data Sources, Patients		

Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods - Cohort Build and Exposure Categorization; Figure 1	RECORD 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.	Methods - Cohort Build and Exposure Categorization
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Methods - Cohort Build and Exposure Categorization, Analysis; Results - Baseline Characteristics; Table 1; Figure 1; Table S7	RECORD 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.	Methods - Outcomes
				RECORD 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.	Not done
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods - Data Sources, Outcomes; Table S5; Table S6; Table S7	RECORD 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.	Table S5; Table S6; Table S7
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	Methods - Data Sources; Table S5; Table S6; Table S7		

		more than one group			
Bias	9	Describe any efforts to address potential sources of bias	Methods - Analysis; Discussion		
Study size	10	Explain how the study size was arrived at	Not applicable; use of existing health records		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods - Analysis		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods - Analysis		
		(b) Describe any methods used to examine subgroups and interactions	Methods - Analysis		
		(c) Explain how missing data were addressed	Table 1		
		(d) If applicable, explain how loss to follow-up was addressed	Methods – Data Sources; Results; Discussion		
		(e) Describe any sensitivity analyses	Methods - Outcomes, Analysis		
Data access and cleaning methods				RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Methods - Setting and Study Design, Data Sources
				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods - Setting and Study Design, Data Sources
Linkage				RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage	Methods - Setting and Study Design, Data Sources

				across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
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	Results - Baseline Characteristics; Figure 1; Table S8; Table S9	RECORD 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 - Baseline Characteristics; Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1		
		(c) Consider use of a flow diagram	Figure 1		
Descriptive data	14				
		(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Results - Baseline Characteristics; Table 1; Table S8; Table S9		
		(b) Indicate number of participants with missing data for each variable of interest	Methods - Data Sources; Table 1		
		(c) Summarize follow-up time (e.g. average and total amount)	Results - Primary Outcomes, Secondary Outcomes		
Outcome data	15	Report numbers of outcome events or summary measures over time	Results - Primary Outcomes; Table 2; Table 3; Figure 2		
Main results	16	(a) Give unadjusted estimates and, if applicable,	Results - Primary Outcomes,		

		confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Secondary Outcomes; Table 2; Table 3; Figure 2		
		(b) Report category boundaries when continuous variables were categorized	Not applicable		
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable		
Other analyses	17	Report other analyses done e.g. analyses of subgroups and interactions, and sensitivity analyses	Results - Secondary Outcomes; Table 2; Table 3; Figure 2		
Discussion					
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	Discussion	RECORD 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,	Discussion		

		multiplicity of analyses, results from similar studies, and other relevant evidence			
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	Article Information		
Accessibility of protocol, raw data, and programming code				RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Methods - Setting and Study Design

Abbreviations: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

References:

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Supplementary Table 5. Coding Definitions for Demographic and Comorbid Conditions

Characteristic	Database	Codes
Demographics		
Age	RPDB	
Sex	RPDB	
Location of residence – Rural status	Statistics Canada	
Long-term care	ODB	LTC
Socioeconomic Status (Neighbourhood Income Quintile)	Statistics Canada	
LHIN[a]	RPDB	LHIN
Prescriber	ODB	
Comorbidities (5 years)		
Acute kidney injury	CIHI-DAD	ICD-9: 584 ICD-10: N17
Anxiety disorder and depression	CIHI-DAD	ICD-9: 2962, 2963, 2965, 3000, 3002, 3003, 3004, 309, 311 ICD-10: F063, F064, F204, F313, F314, F315, F32, F33, F341, F400, F401, F402, F408, F409, F410, F411, F412, F413, F418, F419, F420, F421, F422, F428, F429, F430, F431, F432
	OHIP	OHIP DIAGNOSTIC: 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
Benign brain tumor	CIHI-DAD	ICD-9: 2250 ICD-10: D330, D331, D332, D339
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	OHIP DIAGNOSTIC: 296 OHIP FEE: 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
Brain injury	CIHI-DAD	ICD-9: 850, 851, 852, 853, 854 ICD-10: S06
Brain cancer	CIHI-DAD	ICD-9: 191 ICD-10: C71

Cancer	CIHI-DAD	ICD-9: V10, 140-165, 170-176, 179-208, 230-234 ICD-10: 80003, 80006, 80013, 80023, 80033, 80043, 80102, 80103, 80106, 80113, 80123, 802, 803, 80413, 80423, 80433, 80443, 80453, 80502, 80503, 80513, 80523, 807, 808, 80903, 80913, 80923, 80933, 80943, 80953, 81103, 81202, 81203, 81213, 81223, 81233, 81243, 81303, 81402, 81403, 81406, 81413, 81423, 81433, 81443, 81453, 81473, 81503, 81513, 81523, 81533, 81543, 81553, 81603, 81613, 81623, 81703, 81713, 81803, 81903, 82003, 82013, 82102, 82103, 82113, 82203, 82213, 823, 82403, 82413, 82433, 82443, 82453, 82463, 82473, 82503, 82513, 82603, 82612, 82613, 82623, 82632, 82633, 82703, 82803, 82813, 82903, 83003, 83103, 83123, 83143, 83153, 83203, 83223, 83233, 83303, 83313, 83323, 83403, 83503, 83703, 83803, 83813, 83903, 84003, 84013, 84103, 84203, 84303, 84403, 84413, 84423, 84503, 84513, 84603, 84613, 84623, 84703, 84713, 84723, 84733, 84803, 84806, 84813, 849, 85002, 85003, 85012, 85013, 85023, 85032, 85033, 85042, 85043, 851, 852, 85303, 854, 85503, 85603, 85623, 857, 85803, 86003, 86203, 86303, 86403, 86503, 86803, 86933, 87003, 87103, 87202, 87203, 87213, 87223, 87233, 87303, 87403, 87412, 87413, 87422, 87423, 87433, 87443, 87453, 87613, 87703, 87713, 87723, 87733, 87743, 87803, 88003, 88006, 88013, 88023, 88033, 88043, 88103, 88113, 88123, 88133, 88143, 88303, 88323, 88333, 88403, 88503, 88513, 88523, 88533, 88543, 88553, 88583, 88903, 88913, 88943, 88953, 88963, 89003, 89013, 89023, 89103, 89203, 89303, 89333, 89403, 89413, 895, 89603, 89633, 89643, 897, 89803, 89813, 89903, 89913, 90003, 90203, 90403, 90413, 90423, 90433, 90443, 90503, 90513, 90523, 90533, 906, 90703, 90713, 90723, 90803, 90813, 90823, 90833, 90843, 90853, 90903, 91003, 91013, 91023, 91103, 91203, 91243, 91303, 91333, 91403, 91503, 91703, 91803, 91813, 91823, 91833, 91843, 91853, 91903, 92203, 92213, 92303, 92313, 92403, 92503, 92513, 92603, 92613, 92703, 92903, 93103, 93303, 93623, 93643, 93703, 93803, 93813, 93823, 93903, 93913, 93923, 940, 941, 942, 94303, 944, 945, 94603, 947, 948, 94903, 95003, 95013, 95023, 95033, 95043, 951, 952, 95303, 95393, 95403, 95603, 95613, 95803, 95813, 959, 965, 966, 967, 968, 969, 970, 971, 972, 973, 97403, 97413, 97603, 97613, 97623, 97633, 97643, 980, 982, 98303, 984, 98503, 986, 98703, 98803, 989, 99003, 99103, 993, 994, C00-C26, C30-C34, C37, C38- C86, C88, C90, C91-C97, D00-D09, Z85
	OHIP	140-165, 170-175, 179- 208, 230-234

Stroke, including TIA	CIHI-DAD	ICD-9: 430, 431, 432, 434, 435, 436, 3623 ICD-10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340
Chronic kidney disease	CIHI-DAD	ICD-9: 4030, 4031, 4039, 4040, 4041, 4049, 583, 584, 585, 586, 5888, 5889, 592, 5939, 2504 ICD-10: E102, E112, E132, E142, I12, I13, N00, N01, N02, N03, N04, N05, N06, N07, N08, N10, N11, N12, N13, N14, N15, N16, N17, N18, N19, N20, N21, N22, N23
	OHIP	DIAGNOSTIC: 403, 585
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	OHIP DIAGNOSTIC: 571, 573, 070 OHIP FEE: Z551, Z554
Coronary artery disease, with angina	CIHI-DAD	ICD-9: 412, 410, 413, 414, 4292, 4296, 4297, 411 ICD-10: I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822 CCI: 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76 CCP: 4801, 4802, 4803, 4804, 4805, 481, 482, 483
	OHIP	OHIP DIAGNOSTIC: 410, 412, 413 OHIP FEE: R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448
Congestive heart failure	CIHI-DAD	ICD-9: 425, 5184, 514, 428 ICD-10: I099, I420, I425, I426, I427, I428, I429, I43, I500, I501, I509, I255, J81 CCP: 4961, 4962, 4963, 4964 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR
	OHIP	OHIP DIAGNOSTIC: 428 OHIP FEE: R701, R702, Z429
Epilepsy/seizure	CIHI-DAD	ICD-9: 34500, 34501, 34510, 34511, 3452, 3453, 34540, 34541, 34550, 34551, 34560, 34561, 34570, 34571, 34580, 34581, 34590, 34591, 7803 ICD-10: G40, G41, R5680, R5688
	OHIP	OHIP DIAGNOSTIC: 345, 780
Migraine	CIHI-DAD	ICD-9: 3460, 3461, 3462, 3468, 3469 ICD-10: G43
	OHIP	OHIP DIAGNOSTIC: 346
Mood disorder	CIHI-DAD	ICD-9:2960, 2968, 2964, 2965, 2966, 2967 2962, 2963 ICD-10: F30, F31, F32, F33, F34, F38, F39

Multiple sclerosis	CIHI-DAD	ICD-9: 340 ICD-10: G35
Neuropathic pain	CIHI-DAD	ICD-9: 354, 355, 356, 357, 358 ICD-10: G56, G57, G58, G59, G60, G61, G62, G63
Parkinson's disease	CIHI-DAD	ICD-9: 332 ICD-10: G20, F023
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, 1KG50, 1KG57, 1KG76MI, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87, 1KA87LA, 1KE57
	OHIP	OHIP FEE: 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
Trigeminal neuralgia	CIHI-DAD	ICD-9: 3501, 3502, 3508, 3509 ICD-10: G50
	OHIP	OHIP DIAGNOSTIC: 350
Healthcare Use (1 year)		
Primary care physician visits	OHIP IPDB	Mainspeciality = "GP/FP" or "FP/Emergency Medicine"
Internal medicine visits	OHIP IPDB	Mainspeciality = "INTERNAL MEDICINE"
Nephrologist visits	OHIP IPDB	Mainspecialty = "NEPHROLOGY"
Neurologist visits	OHIP IPDB	Mainspecialty = "NEUROLOGY"
Psychiatrist visits	OHIP IPDB	Mainspecialty = "PSYCHIATRY"
Number of any hospitalizations	CIHI-DAD	"ddate"
Number of any ER visits	NACRS	"regdate"
Serum creatinine test	OHIP	OHIP FEE: L065, L067, L068
CT head	OHIP	OHIP FEE: X188, X400, X401, X402, X405, X408
MRI head	OHIP	OHIP FEE: X421
Electroencephalography (EEG)	OHIP	OHIP FEE: G414, G415, G416, G417, G418, G540, G542, G544, G545, G546, G554, G555
Chest x-ray	OHIP	OHIP FEE: X090, X091, X092, X195
Echocardiography	CIHI-DAD	CCP: 0282 CCI: 3IP30

	OHIP	OHIP FEE: G560, G561, G562, G566, G567, G568, G570, G571, G572, G574, G575, G576, G577, G578, G581
Carotid ultrasound	CIHI-DAD	CCP: 0281 CCI: 3JE30, 3JG30
	OHIP	OHIP FEE: J201, J501, J190, J191, J490, J491, J492
Cardiac catheterization	CIHI-DAD	CCP: 4995, 4996, 4997, 4892, , 4893, 4894, 4895, 4896, 4897, 4898 CCI: 3IJ30GP, 3HZ30GP, 2HZ24GPKJ, 2HZ24GPKL, 2HZ24GPKM, 2HZ24GPXJ, 2HZ28GPPL, 2HZ71GP, 3IP10, 3IS10
	OHIP	OHIP FEE: G296, G297, G299, G300, G301, G304, G305, G306, G297, G509
Coronary angiogram	CIHI-DAD	CCP: 4892, 4893, 4894, 4895, 4896, 4897, 4898 CCI: 3IP10, 3IS10
	OHIP	OHIP FEE: G297, G509
Holter monitoring	CIHI-DAD	CCP: 0354 CCI: 2HZ24JAKH
	OHIP	OHIP FEE: G311, G320, G647, G648, G649, G650, G651, G652, G653, G654, G655, G656, G657, G658, G659, G660, G661, G682, G683, G684, G685, G686, G687, G688, G689, G690, G692, G693
Cardiac stress test	CIHI-DAD	CCP: 0341, 0342, 0343, 0344, 0605 CCI: 2HZ08, 3IP70
	OHIP	OHIP FEE: G315, G174, G111, G112, G319, G582, G583, G584, J607, J608, J807, J808, J809, J866, J609, J666
Coronary revascularization	CIHI-DAD	CCP: 481, 482, 483, 480 CCI: 1IJ50, 1IJ26, IIJ27, 1IJ57, 1IJ76, 1IJ57GQ, 1IJ54GQAZ
	OHIP	OHIP FEE: R741, R742, R743, E651, E652, E654, E646, G298, Z434, G262
Electrocardiography	CIHI-DAD	CCI: 2HZ24JAKE
	OHIP	OHIP FEE: G310, G313
Colorectal cancer screening	OHIP	OHIP FEE: G004, L179, L181, Q043, Q152, X112, X113, Z535, Z536, Z555, Z580
Cervical cancer screening	OHIP	OHIP FEE: E430, G365, G394, L713, L812
Prostate-specific antigen test	OHIP	OHIP FEE: Q005, Q118, Q119, Q120, Q121, Q122, Q123, Q133
Mammography	OHIP	OHIP FEE: X172, X178, X184, X185, X201
Influenza vaccination	OHIP	OHIP FEE: G590, G591
Bone mineral density test	OHIP	OHIP FEE: J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888
Hearing test	OHIP	OHIP FEE: G153, G154, G440, G441, G442, G443, G448, G450, G451, G452, G525, G526, G529, G530, G533, G815, G816

Cystoscopy	OHIP	OHIP FEE: Z606, Z607, Z628, Z632, Z633, Z634
Transurethral resection of the prostate	CIHI-DAD	CCI: 1QT59BAAD, 1QT59BAAG, 1QT59BAAW, 1QT59BAAZ, 1QT59BACG, 1QT59BAGX, 1QT87BA, 1QT87BAAG, 1QT87BAAK CCP: 721
	OHIP	OHIP FEE: S655
Computed tomography of other areas	OHIP	OHIP Fee: X126, X409, X410, X127, X412, X413, X124, X403, X404, X231, X232, X233, X128, X415, X416, X125, X406, X407
Pulmonary function test	OHIP	OHIP FEE: L354, L358
At-home physician service	OHIP	OHIP FEE: A901, B960, B961, B962, B963, B964, B966, B990, B992, B993, B994, B996, B997, B998
Urinalysis	OHIP	OHIP FEE: L253, L254, L255, L633
Sputum	OHIP	OHIP FEE: L629, L716, L815
Epilepsy surgery	OHIP	OIHP FEE: N110
Video EEG monitoring	OHIP	OHIP FEE: G540, G545, G542, G546

Abbreviations: CCI, Canadian Classification of Health Interventions (available after 2002); CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (before 2002); CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IPDB, Institute for Clinical Evaluative Sciences (ICES) Physician Database; LHIN, Local Health Integration Network; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Plan; OMHRS, Ontario Mental Health Reporting System; RPDB, Registered Persons Database of Ontario.

[a] LHIN refers to health authorities responsible for regional administration of public healthcare services in Ontario.

Supplementary Table 6. Coding Definitions Used to Define Outcomes

Outcome	Database	Codes
Acute Kidney Injury (Hospital Admission or ER Encounter)[a]	NACRS CIHI-DAD	ICD-10: N17
Renal biopsy	CCI	2PC71BA, 2PC71DA, 2PC71HA, 2PC71LA, 2PE71BA, 2PE71DA, 2PE71HA, 2PE71LA
	OHIP FEE	Z601, E820
	CCP	6781, 6782
Nephrologist Consultation	OHIP FEE	A160, A161, A163, A164, A165, A166, A168, A865, C160, C161, C162, C163, C164, C165, C166, C167, C169, C865, W165, W160, W865, W166, W862, W864, W867, W869, W164, W162, W161, W163, W168
Acute Dialysis	OHIP FEE	R849, G323, G866, G330, G331, G093, G095, G294, G295
Acute Interstitial Nephritis	NACRS CIHI-DAD	ICD-10: N10
Rhabdomyolysis	NACRS CIHI-DAD	ICD-10: M628, T796

Abbreviations: CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CIHI-DAD, Canadian Institute for Health Information Hospital Discharge Abstract Database; ICD-10, International Classification of Diseases, Tenth Revision; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan; IPDB, Institute for Clinical Evaluative Sciences (ICES) Physician Database.

[a] Validations of acute kidney injury were performed on approximately 39,000 hospitalizations with linked laboratory values. See Hwang YJ, Shariff SZ, Gandhi S, et al. Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. *BMJ Open*. 2012;2(6):1–11.

Supplementary Table 7. Variables Included in the Propensity Score Model

Category	Variables
Demographics	Age, sex, neighbourhood income quintile, index date, long-term residence, Local Health Integration Network
Comorbidities	Anxiety, bipolar disorder, brain cancer, brain injury, cancer, coronary artery disease, chronic kidney disease, diabetes, congestive heart failure, epilepsy, hypertension, Johns Hopkins ACG, liver disease, migraine, mood disorder, multiple sclerosis, neuropathic pain, Parkinson's disease, stroke, trigeminal neuralgia
Medications	Number of unique drug products, ACE inhibitor, anticonvulsants, antineoplastics, ARB, antipsychotics, beta blockers, benzodiazepines, calcium channel blockers, carbamazepine, carbamazepine on index date, clobazam, clobazam on index date, diuretics (loop), diuretics (thiazides), divalproex sodium, divalproex sodium on index date, gabapentin, gabapentin on index date, glucocorticoids, lacosamide, lamotrigine, lamotrigine on index date, methotrexate, NSAIDS, phenytoin, phenytoin on index date, potassium sparing diuretics, pregabalin, primidone, statins, thiazides, topiramate, valproic acid
Health Care Use	Emergency department visit, primary care physician visit, hospitalization, internist visit, nephrologist visit, neurologist visit, psychiatrist visit
Investigations	Bone mineral density test, carotid ultrasound, cardiac catheterization, cervical cancer screening, chest x-ray, colorectal cancer screening, computed tomography head, computed tomography of the abdomen, computed tomography of the abdomen, computed tomography of the extremities, computed tomography of the neck, computed tomography of the pelvis, computed tomography of the spine, computed tomography of the thorax, coronary angiogram, coronary revascularization, cystoscopy, echocardiogram, electrocardiogram, electroencephalography, epilepsy surgery, flu shot, hearing test, holter monitor, home physician visit, influenza vaccination, mammogram, MRI head, prostate-specific antigen test, pulmonary function testing, urinalysis, serum creatinine test, sputum, stress test, video electroencephalography,

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ACG, adjusted clinical groups; ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drug.

Supplementary Table 8. Baseline Characteristics of Levetiracetam Users Not Matched vs. Matched in Study[a]

		Levetiracetam Users		
Characteristic		**Not Matched**	**Matched**	**Standardized Difference[b]**
		N	**N**	
Total patients		1,000	3,980	
Demographics				
Mean age ± SD, y		50.6 ± 20.88	55.2 ± 21.4	22%
	≤ 65 years	689 (69%)	2403 (60%)	18%
Women		501 (50%)	2048 (52%)	3%
Long Term Care		79 (8%)	273 (7%)	4%
Rural Residence		87 (9%)	409 (10%)	5%
Income Quintile[c]	1 (lowest)	191 (19%)	958 (24%)	12%
	3 (middle)	205 (21%)	797 (20%)	1%
	5 (highest)	201 (20%)	696 (18%)	7%
Comorbidities[d]				
Johns Hopkins ACG System Aggregated Diagnosis groups, mean ± SD[e]		11.4 (4.1)	9.7 (4.3)	40%
Anxiety disorder and depression		182 (18%)	699 (18%)	2%
Bipolar disorder		65 (7%)	280 (7%)	7%
Brain injury		67 (7%)	153 (4%)	13%
Brain cancer		188 (19%)	142 (4%)	50%
Cancer[f]		471 (47%)	1333 (34%)	28%
Chronic kidney disease		117 (12%)	432 (11%)	3%
Chronic liver disease		88 (9%)	273 (7%)	7%
Coronary artery disease, including angina[g]		202 (20%)	824 (21%)	10%
Congestive heart failure		89 (9%)	362 (9%)	10%
Diabetes		24 (2%)	103 (3%)	1%
Epilepsy/seizure[h]		820 (82%)	1760 (44%)	85%
	Previous 90 days	627 (63%)	460 (12%)	125%
	Previous 90-365 days	492 (49%)	1091 (27%)	46%
Hypertension		227 (23%)	1095 (28%)	11%
Migraine		133 (13%)	485 (12%)	3%
Mood disorder		63 (6%)	174 (4%)	8%
Multiple sclerosis		13 (13%)	15 (0.4%)	10%
Neuropathic pain		20 (2%)	47 (1%)	6%
Parkinson's disease		6 (0.6%)	36 (0.9%)	3%
Peripheral vascular disease		9 (0.9%)	45 (1%)	2%
Stroke, including TIA		183 (18%)	481 (12%)	17%
Trigeminal neuralgia		21 (2%)	59 (2%)	5%
Concurrent medication use[i]				

ACE inhibitors or ARBs	145 (15%)	706 (18%)	9%
Antidepressants	40 (4%)	151 (4%)	24%
Anti-epileptics	239 (24%)	703 (18%)	15%
Antineoplastics	47 (5%)	129 (3%)	8%
Antipsychotics	25 (3%)	165 (4%)	9%
Beta blockers	124 (12%)	518 (13%)	2%
Benzodiazepines	104 (10%)	309 (8%)	9%
Calcium channel blockers	100 (10%)	456 (12%)	5%
Glucocorticoids	87 (9%)	176 (4%)	17%
Diuretics - potassium sparing	7 (0.7%)	51 (1%)	6%
Diuretics - thiazides	38 (4%)	187 (5%)	4%
Diuretics - loop	43 (4%)	185 (5%)	1%
NSAIDs (excluding ASA)	24 (2%)	117 (3%)	3%
Statins	166 (17%)	886 (22%)	14%
Number of unique medications, mean ± SD	3.2 ± 5.4	3.4 ± 5.0	3%
Anti-epileptic use (in prior 120 days)[i]			
Carbamazepine	37 (4%)	125 (3%)	3%
Clobazam	61 (6%)	85 (2%)	20%
Divalproex Sodium	29 (3%)	67 (2%)	8%
Gabapentin	31 (3%)	89 (2%)	6%
Lacosamide	19 (2%)	37 (0.9%)	9%
Lamotrigine	30 (3%)	85 (2%)	6%
Phenytoin	135 (14%)	291 (7%)	20%
Pregabalin	6 (0.6%)	44 (1%)	5%
Topiramate	12 (1%)	31 (0.8%)	4%
Valproic Acid	17 (2%)	46 (1%)	4%
Anti-epileptic use (prescribed on index date)			
Carbamazepine	16 (2%)	23 (0.6%)	10%
Clobazam	30 (3%)	13 (0.3%)	21%
Divalproex Sodium	17 (2%)	14 (0.4%)	13%
Gabapentin	17 (2%)	24 (0.6%)	10%
Lamotrigine	14 (1%)	18 (0.5%)	9%
Phenytoin	60 (6%)	48 (1%)	26%
Healthcare contacts, mean ± SD[j]			
Number of primary care physician visits	19.7 ± 23.6	13.7 ± 17.4	29%
Number of internal medicine visits	5.6 ± 12.7	2.4 ± 6.9	31%
Number of nephrology visits	0.3 ± 1.9	0.2 ± 1.1	8%
Number of neurology visits	7.7 ± 8.6	2.8 ± 4.2	73%
Number of psychiatry visits	0.7 ± 2.9	1.0 ± 6.1	7%
Number of hospitalizations	1.8 ± 1.9	0.9 ± 1.4	58%
Number of ER visits	3.3 ± 3.7	1.9 ± 2.8	44%
Healthcare usage[k]			

Serum creatinine tests	666 (67%)	2617 (66%)	2%
CT head	742 (74%)	1620 (41%)	72%
MRI head	617 (62%)	1164 (29%)	69%
Electroencephalography (EEG)	589 (59%)	1113 (28%)	66%
Chest x-ray	646 (65%)	1767 (44%)	41%
Echocardiography	274 (27%)	770 (19%)	19%
Epilepsy surgery	14 (1%)	13 (0.3%)	12%
Video EEG monitoring	156 (16%)	209 (5%)	34%
Urinalysis	291 (29%)	1263 (32%)	6%
Levetiracetam prescriber			
Primary care physician	314 (31%)	1435 (36%)	10%
Internal medicine	25 (3%)	49 (1.2%)	10%
Neurology	422 (42%)	1754 (44%)	4%
Neurosurgery	8 (0.8%)	11 (0.3%)	7%
Other/missing	229 (23%)	716 (18%)	12%
Laboratory data (in subpopulation)			
Mean serum creatinine level, mg/dL ± SD[l]	0.89 ± 0.37	0.82 ± 0.27	21%
Median serum creatinine level mg/dL, (IQR)[l]	0.80 (0.64-1.06)	0.77 (0.66-0.93)	
Median eGFR, mL/min per 1.73 m^2, (IQR)	71 (57-94)	68 (58-82)	
eGFR Category, mL/min per 1.73 m^2, n (%)			
≥60	86	442	-
45-60	14	42	-
30-45	8	22	-

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ACG, adjusted clinical group; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TIA, transient ischemic attack.

[a] Data are presented as the number (percentage) of patients, unless otherwise reported.

[b] Standardized differences are less sensitive to sample size than traditional hypothesis tests are. They provide a measure of the difference between groups with respect to the pooled standard deviation; a standardized difference >10% was considered as a meaningful difference between the groups.

[c] Income was categorized into fifths of average neighborhood income on the index date.

[d] Comorbid conditions in the 5 years preceding the index date were considered.

[e] We used the Adjusted Clinical Group (ACG) scoring system to score comorbidity. The ACG is a population/patient case-mix adjustment system that provides a relative measure of the individual's expected consumption of health services. ICD-9/ICD-9-CM codes are categorized into 32 groups, called Ambulatory Diagnostic Groups (ADGs), on the basis of clinical similarity, chronicity, likelihood of requiring specialty care, and disability. These groups are further reduced to 12 'Collapsed ADGs' or CADGs.

[f] Cancers include lung/bronchi, colon/rectum, breast, pancreas, prostate, leukemia, non-Hodgkin lymphoma, liver, ovarian, esophageal.

[g] Coronary artery disease includes receipt of coronary artery bypass graft surgery, and percutaneous coronary intervention.

[h] Epilepsy/seizure codes are hospital diagnosis codes and do not capture those patients who do not present to hospital, which underestimates the prevalence of the condition.

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[i] Dispensed medications in the 120 days preceding the index date were considered.

[j] Health care contacts in the year preceding the index date were considered.

[k] Health care use in the year preceding the index date was considered.

[l] Conversion factor for units: serum creatinine in mg/dL to μmol/L, x88.4.

Supplementary Table 9. Baseline Characteristics in Subpopulation with Laboratory Values after Propensity Score Matching[a]

Characteristic		Levetiracetam Users	Levetiracetam Non-users	Standardized Difference[b]
		N	N	
Total patients		509	1,018	
Demographics				
Mean age ± SD, y		60 ± 20	58 ± 21	10%
	≤ 65 years	261 (51%)	559 (55%)	7%
Women		244 (48%)	529 (52.0%)	8%
Long Term Care		45 (11%)	84 (8%)	9%
Rural Residence		20 (4%)	43 (4%)	2%
Income Quintile[c]	1 (lowest)	112 (22%)	235 (23%)	3%
	3 (middle)	110 (22%)	219 (22%)	0%
	5 (highest)	82 (16%)	186 (18%)	6%
Comorbidities[d]				
Johns Hopkins ACG System Aggregated Diagnosis groups, mean ± SD[e]		11.3 ± 4.2	11.0 ± 4.1	6%
Anxiety disorder and depression		110 (22%)	203 (20%)	4%
Bipolar disorder		44 (9%)	79 (8%)	3%
Brain injury		24 (5%)	54 (5%)	3%
Brain cancer		26 (5%)	41 (4%)	5%
Cancer[f]		225 (44%)	421 (41%)	6%
Chronic kidney disease		84 (17%)	133 (13%)	10%
Chronic liver disease		49 (10%)	107 (11%)	3%
Coronary artery disease, including angina[g]		147 (29%)	262 (26%)	7%
Congestive heart failure		62 (12%)	126 (12%)	1%
Diabetes		24 (5%)	58 (4%)	7%
Epilepsy/seizure[h]		361 (71%)	719 (71%)	1%
	Previous 90 days	80 (16%)	160 (16%)	0%
	Previous 90-365 days	201 (40%)	342 (34%)	12%
Hypertension		176 (35%)	338 (33 %)	3%
Migraine		69 (14%)	130 (13%)	2%
Mood disorder		34 (7%)	56 (6 %)	5%
Neuropathic pain		9 (2%)	15 (2%)	2%
Parkinson's disease		6 (1%)	17 (2%)	4%
Peripheral vascular disease		11 (2%)	13 (1%)	7%
Stroke, including TIA		94 (19%)	175 (17%)	3%
Trigeminal neuralgia		6 (1%)	29 (3%)	11%
Concurrent medication use[i]				
ACE inhibitors or ARBs		116 (23%)	219 (22%)	3%

Antidepressants	28 (6%)	65 (6%)	4%
Anti-epileptics	119 (23%)	245 (24%)	2%
Antineoplastics	24 (5%)	40 (4%)	4%
Antipsychotics	28 (6%)	42 (4%)	7%
Beta blockers	82 (16%)	172 (17%)	2%
Benzodiazepines	51 (10%)	92 (9%)	3%
Calcium channel blockers	82 (16%)	173 (17%)	2%
Glucocorticoids	30 (6%)	57 (6%)	1%
Diuretics - potassium sparing	11 (2%)	14 (1%)	6%
Diuretics - thiazides	27 (5%)	41 (4%)	6%
Diuretics - loop	34 (7%)	59 (6%)	4%
NSAIDs (excluding ASA)	15 (3%)	22 (2%)	4%
Statins	152 (30%)	298 (29%)	1%
Number of unique medications, mean ± SD	4.7 ± 5.7	4.2 ± 5.6	8%
Anti-epileptic use (in prior 120 days)[i]			
Carbamazepine	24 (5%)	40 (4%)	4%
Clobazam	19 (4%)	33 (3%)	3%
Divalproex Sodium	14 (3%)	23 (2%)	3%
Gabapentin	10 (2%)	38 (38%)	10%
Lacosamide	12 (2%)	8 (0.8%)	13%
Lamotrigine	8 (2%)	29 (3%)	8%
Phenytoin	52 (10%)	108 (11%)	1%
Pregabalin	8 (2%)	20 (2%)	3%
Topiramate	7 (1%)	7 (0.7%)	7%
Valproic Acid	10 (2%)	10 (1%)	8%
Anti-epileptic use (prescribed on index date)			
Carbamazepine	9 (2%)	6 (0.6%)	11%
Phenytoin Sodium	7 (1%)	11 (1%)	3%
Healthcare contacts, mean ± SD[j]			
Number of primary care physician visits	20.1 ± 23.7	16.5 ± 17.2	17%
Number of internal medicine visits	4.8 ± 11.5	3.7 ± 9.0	10%
Number of nephrology visits	0.4 ± 1.5	0.3 ± 1.4	4%
Number of neurology visits	3.6 ± 4.1	3.2 ± 4.2	8%
Number of psychology visits	1.0 ± 4.6	1.3 ± 6.8	7%
Number of hospitalizations	1.3 ± 1.7	1.1 ± 1.4	14%
Number of ER visits	2.4 ± 2.7	2.5 ± 3.5	3%
Healthcare usage[k]			
CT head	295 (58%)	552 (54%)	8%
MRI head	202 (40%)	383 (38%)	4%
Electroencephalography (EEG)	208 (41%)	332 (33%)	17%
Chest x-ray	311 (61%)	573 (56%)	10%
Echocardiography	144 (28%)	295 (29%)	2%

Urinalysis	208 (41%)	386 (38%)	6%
Video EEG monitoring	44 (9%)	82 (8%)	2%
Levetiracetam prescriber			
Primary care physician	215 (42%)	-	-
Internal medicine	9 (2%)	-	-
Neurology	199 (39%)	-	-
Other/missing	86 (17%)	-	-

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ACG, adjusted clinical group; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; TIA, transient ischemic attack.

[a] Data are presented as the number (percentage) of patients, unless otherwise reported.

[b] Standardized differences are less sensitive to sample size than traditional hypothesis tests are. They provide a measure of the difference between groups with respect to the pooled standard deviation; a standardized difference >10% was considered as a meaningful difference between the groups.

[c] Income was categorized into fifths of average neighborhood income on the index date.

[d] Comorbid conditions in the 5 years preceding the index date were considered.

[e] We used the Adjusted Clinical Group (ACG) scoring system to score comorbidity. The ACG is a population/patient case-mix adjustment system that provides a relative measure of the individual's expected consumption of health services. ICD-9/ICD-9-CM codes are categorized into 32 groups, called Ambulatory Diagnostic Groups (ADGs), on the basis of clinical similarity, chronicity, likelihood of requiring specialty care, and disability. These groups are further reduced to 12 'Collapsed ADGs' or CADGs.

[f] Cancers include lung/bronchi, colon/rectum, breast, pancreas, prostate, leukemia, non-Hodgkin lymphoma, liver, ovarian, esophageal.

[g] Coronary artery disease includes receipt of coronary artery bypass graft surgery, and percutaneous coronary intervention.

[h] Epilepsy/seizure codes are hospital diagnosis codes and do not capture those patients who do not present to hospital, which underestimates the prevalence of the condition.

[i] Dispensed medications in the 120 days preceding the index date were considered.

[j] Health care contacts in the year preceding the index date were considered.

[k] Health care use in the year preceding the index date was considered.

Supplementary Table 10. CARE Checklist Ranking of Case Reports for Acute Kidney Injury[a]

	Acute Kidney Injury Case Reports							
CARE Checklist Item No.	Hurwitz *et al.* 2009	Spengler *et al.* 2014	Leblanc *et al.* 2014	Mahta *et al.* 2012	Chau *et al.* 2012	Singh *et al.* 2016	Parentelli *et al.* 2013	Isaacson *et al.* 2014
1	0	1	1	0	0	1	0	1
2	0	1	1	1	1	0	0	1
3a	1	1	1	0	1	1	0	0
3b	1	1	1	1	1	1	0	1
3c	1	1	1	1	1	0	0	1
3d	1	1	1	1	1	1	0	1
4	1	1	1	1	1	1	0	1
5a	1	1	1	1	1	1	1	1
5b	1	1	1	1	1	1	1	1
5c	1	1	1	1	1	1	1	1
5d	1	1	1	1	1	1	1	1
6	1	0	1	0	1	1	1	0
7	1	1	1	1	1	1	1	1
8a	1	1	1	1	1	1	1	1
8b	0	0	0	0	0	0	0	0
8c	1	1	1	0	1	0	1	1
8d	0	0	0	0	0	0	0	0
9a	1	1	1	1	1	1	0	1
9b	1	1	1	1	1	1	1	1
9c	0	1	1	1	1	1	1	1
10a	1	1	1	1	1	1	1	1
10b	1	1	1	0	1	1	1	1
10c	1	1	1	1	1	1	1	1
10d	1	1	1	1	1	1	1	1
11a	1	1	1	0	1	0	1	1
11b	1	1	1	1	1	1	1	1
11c	1	1	1	0	1	0	1	1
11d	1	1	1	1	1	1	1	1
12	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0
Total	23	25	26	19	25	21	18	24
Percentage Criteria Met (%)	82.14	89.29	92.86	67.86	89.29	75.00	64.29	85.71

[a] Articles were rated based on the number of CARE Checklist Criteria met and the percentage of criteria met was calculated. Items 12 and 13 were not included in scoring.

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1. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, Allaire A, Aronson J, Carpenter J, Gagnier J, Hanaway P, Hayes C, Jones D, Kaszkin-Bettag M, Kidd M, Kiene H, Kienle G, Kligler B, Knutson L, Koch C, Milgate K, Mittelman M, Oltean H, Plotnikoff G, Rison RA, Sethi A, Shamseer L, Smith R, Tugwell P: The CARE guidelines: Consensus-based clinical case reporting guideline development. *Glob Adv Heal. Med* 2: 38–43, 2013

Supplementary Table 11. Summary of Case Reports of Rhabdomyolysis Associated with Levetiracetam Use

Author	Age	Dose	Concurrent Medications	Time to Onset	Peak Creatine Kinase (IU/L)	Acute Kidney Injury	Outcome	Naranjo Adverse Drug Reaction Probability[a]
Akiyama *et al.*	29	1000 mg PO daily	Clobazam, Phenytoin, Valproic Acid	1 day	2,410	No	Resolved with discontinuation	4
Incecik *et al.*	13	250 mg PO then up-titrated to 500 mg PO daily	None	7 days	986	No	Resolved with discontinuation	4
Isaacson *et al.*	19	2000 mg IV loading dose then 500 mg PO daily	Lorazepam, Oxcarbazepine	4 days	29,136	Yes	Resolved with discontinuation	4
Ramon *et al.*	25	500 mg PO BID	Clobazam, Clonazepam, Esomeprazole, Fosphenytoin, Suxamethonium, Sufentanil, Thiopental	1 day	14,000	No	Resolved with discontinuation	4
Kubota *et al.*	26	500 mg PO daily	Carbamazepine, Phenobarbital	15 days	2,723	No	Resolved with discontinuation	4
Lorenzo and Li	27	1000 mg IV BID	Docusate, Heparin, Lorazepam	1 day	49,538	Unknown	Resolved with discontinuation	4
Singh *et al.*	16	750 mg IV BID	Lorazepam	1 day	15,111	Yes	Resolved with discontinuation	4
Shabaz *et al.*	43	1000 mg IV daily	Diazepam,Valproic Acid	1 day	29,750	No	Resolved with discontinuation	4
Sohn *et al.*	40	750 mg PO daily then up-titrated to 1500 mg PO daily. Re-challenge: Loading dose 2000 mg IV 2000 mg IV then 1000 mg daily	Diazepam, Lorazepam, Phenytoin	4 days	7,800	No	Resolved with discontinuation. Re-occurred with re-challenge	7

Abbreviations: BID, twice daily; IV, intravenous; PO, per oral.

[a]Naranjo Adverse Drug Reaction Probability Interpretation: ≥ 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR.

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4. Ramon M, Tourteau E, Lemaire N, Gautier S, Béné J: HyperCKemia induced by levetiracetam. *Press. Medicale* 45: 943–944, 2016

5. Shahbaz N, Khan SA, Younus SM, Qurrat-ul A, Khan MA, Memon MH: Levetiracetam induced increase in creatine phosphokinase levels. *J. Coll. Physicians Surg. Pakistan* 27: S63–S64, 2017

6. Isaacson JE, Choe DJ, Doherty MJ: Creatine phosphokinase elevation exacerbated by levetiracetam therapy. *Epilepsy Behav. Case Reports* 2: 189–191, 2014

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8. Incecik F, Herguner OM, Besen S, Altunbasak S: Acute rhabdomyolysis associated with levetiracetam therapy in a child. *Acta Neurol. Belg.* 116: 369–370, 2016

9. Singh R, Patel DR, Pejka S: Rhabdomyolysis in a Hospitalized 16-Year-Old Boy: A Rarely Reported Underlying Cause. *Case Rep. Pediatr.* 1–2, 2016

Supplementary Table 12. Levetiracetam Dosage Recommendations[a]

Scenario	Dosage Recommendation
Initial Up-Titration	• Initiate at 500mg every 12 hours • Depending on clinical response and tolerability, the daily dose may be increased every two weeks by increments of 500mg every 12 hours • Maximum Dose: 1500mg every 12 hours
Renal Dosage Adjustment	
≥80 ml/min per 1.73 m^2	500 to 1,500 mg every 12 hours
50–79 ml/min per 1.73 m^2	500 to 1,000 mg every 12 hours
30–49 ml/min per 1.73 m^2	250 to 750 mg every 12 hours
<30 ml/min per 1.73 m^2	250 to 500 mg every 12 hours
Hemodialysis	500 to 1,000 mg every 24 hours Supplemental dose of 250-500 mg recommended post-dialysis (50% Dialyzable)
Peritoneal Dialysis	500 to 1,000 mg every 24 hours (Aronoff *et al.,* 2007)
Continuous Renal Replacement Therapy (CRRT)	250 to 750 mg every12 hours (Aronoff *et al.,* 2007)
Elderly	Dose adjustment recommended

[a] Recommendations from CPS and Lexicomp are equivalent and taken from the UCB pharmaceutical product monograph.

References:

1. Aronoff GR, Bennett WM, Berns JS, Brier ME, Kasebar N, Mueller BA, Pasko DA, Smoyer WE: *Drug Prescribing in Renal Failure*: *Dosing Guidelines for Adults and Children*, 5th ed.,Philadelphia, American College of Physicians, 2007