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

Kevin Yau, MD[1,2], Jorge G. Burneo, MD, MSPH[2,3], Racquel Jandoc, MSc[2], Eric McArthur, MSc[2], Flory Tsobo Muanda-, MD, PhD[2], Chirag R. Parikh, MD, PhD[5], Ron Wald, MDCM, MPH[2, 6], Matthew A. Weir, MD, MSc[1,2,4], and Amit X. Garg, MD, PhD[1,2,4]

[1] Division of Nephrology, Department of Medicine, Western University, London, Ontario, Canada;
[2] Institute for Clinical Evaluative Sciences, Ontario, Canada;
[3] Department of Clinical Neurological Sciences, Western University, London, Ontario, Canada;
[4] Department of Epidemiology & Biostatistics, Western University, London, Ontario, Canada;
[5] Department of Medicine, Yale University, New Haven, CT;

[6] Division of Nephrology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Corresponding Author: Amit X Garg, MD, PhD Institute for Clinical Evaluative Sciences Western facility (ICES Western) Victoria Hospital. 800 Commissioners Rd, Victoria Hospital, Room ELL-215. London, Ontario, Canada N6A 5W9 Tel: 519-685-8502. Email: amit.garg@lhsc.on.ca

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

Supplemental Table 7. Variables Included in the Propensity Score Model

Supplemental Table 8. Baseline Characteristics of Levetiracetam Users Not Matched vs. Matched in Study

Supplemental Table 9. Baseline Characteristics in Subpopulation with Laboratory Data After Propensity Score Matching

Supplemental Table 10. Case Report Checklist Ranking of Case Reports for Acute Kidney Injury

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

Supplemental Table 12. Levetiracetam Dosage Recommendations

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 observational 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 observational 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 observational 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.

References:

1. Tsai J, Yen D, Hsih M, Chen S, Hiersemenzel R, Edrich P, Lai C: Efficacy and Safety of Levetiracetam (up to 2000 mg/day) in Taiwanese Patients with Refractory Partial Seizures : A Multicenter, Randomized, Double-blind, Placebo-controlled Study. *Epilepsia* 47: 72–81, 2006

2. Beran RG, Berkovic SF, Black AB, Danta G, Hiersemenzel R, Schapel GJ, Vajda FJE: Efficacy and safety of levetiracetam 1000-3000 mg/day in patients with refractory partial-onset seizures: A multicenter, open-label single-arm study. *Epilepsy Res.* 63: 1–9, 2005

3. Abou-Khalil B, Hemdal P, Privitera MD: An open-label study of levetiracetam at individualised doses between 1000 and 3000 mg day−1 in adult patients with refractory epilepsy. *Seizure* 12: 141–149, 2004

4. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P: Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia* 41: 1179–1186, 2000

5. Piñea-Garza JE, Nordli DR, Rating D, Yang H, Schiemann-Delgado J, Duncan B: Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures. *Epilepsia* 50: 1141–1149, 2009

6. Cereghino J, Biton V, Abou-Khalil B: Levetiracetam for partial seizures Results of a double-blind, randomized clinical trial. *Neurology* 55: 236–242, 2000

7. Noachtar S, Andermann E, Meyvisch P, Andermann F, Gough WB, Schiemann-Delgado J: Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. *Neurology* 70: 607–616, 2008

8. Brodie MJ, Perucca E, Ryvlin P, Ben-Menachem E, Meencke HJ: Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology* 68: 402–408, 2007

9. Boon P, Chauvel P, Pohlmann-eden B, Otoul C, Wroe S: Dose – response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. *Epilepsy Res.* 48: 77–89, 2002

10. Ben-Menachem E, Falter U: Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 41: 1276–1283, 2000

11. Betts T, Waegemans T, Crawford P: A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure* 9: 80–87, 2000

12. Morrell MJ, Leppik I, French J, Ferrendelli J, Han J, Magnus L: The KEEPER^{TM} trial: Levetiracetam adjunctive treatment of partial-onset seizures in an open-label community-based study. *Epilepsy Res.* 54: 153–161, 2003

13. Kwan P, Lim SH, Chinvarun Y, Cabral-Lim L, Aziz ZA, Lo YK, Tonner F, Beh K, Edrich P: Efficacy and safety of levetiracetam as adjunctive therapy in adult patients with uncontrolled partial epilepsy: The Asia SKATE II Study. *Epilepsy Behav.*18: 100–105, 2010

14. Steinhoff BJ, Somerville ER, Van Paesschen W, Ryvlin P, Schelstraete I: The SKATE^{TM} study: An open-label community-based study of levetiracetam as add-on therapy for adults with uncontrolled partial epilepsy. *Epilepsy Res.* 76: 6–14, 2007

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

References:

1. U.S. Food and Drug Administration. Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS): January - March 2017 [Internet]. Available from: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm565425.htm. [cited 2018 Mar 1]

2. Government of Canada. Summary Safety Review - KEPPRA (levetiracetam) - Assessing the Potential Risk of Acute Kidney Injury. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-keppra- [Internet]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-keppra- [cited 2018 Mar 1]

3. European Medicines Agency. Levetiracetam [Internet]. Available from: http://www.ema.europa.eu/ema/ [cited 2018 Mar 7]

4. Revision of Precautions Levetiracetam [Internet]. Pharm. Med. Devices Agency. 2016 Available from: www.pmda.go.jp/english/ [cited 2018 Mar 7]

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

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

References:

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

2. Parentelli A, Phulphin-Weibel A, Mansuy L, Contet A, Trechot P, Chastagner P: Drug–Drug Interaction Between Methotrexate and Levetiracetam in a Child Treated for Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer* 60: 340–341, 2013

3. 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

4. Leblanc M, Plaisance M: Levetiracetam-Associated Acute Kidney Injury and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. *Open J. Nephrol.* 4: 152–155, 2014

5. Chau K, Yong J, Ismail K, Griffith N, Liu M, Makris A: Levetiracetam-induced severe acute granulomatous interstitial nephritis. *Clin Kidney J* 5: 234–236, 2012

6. Spengler DC, Montouris GD, Hohler AD: Levetiracetam as a possible contributor to acute kidney injury. *Clin. Ther.* 36: 1303–1306, 2014

7. Mahta A, Kim RY, Kesari S: Levetiracetam-induced interstitial nephritis in a patient with glioma. *J. Clin. Neurosci.* 19: 177–178, 2012

8. Hurwitz KA, Ingulli EG, Krous HF: Levetiracetam Induced Interstitial Nephritis and Renal Failure. *Pediatr. Neurol.* 41: 57–58, 2009

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:

1. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Peteresen I, Sørensen HT, von Elm E, Langan SM: The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med.* 12: 1–22, 2015

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]

Characteristic		Levetiracetam Users		
		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.

[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.

References:

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.

References:

1. Sohn S-Y, Kim JG, Kim D-H, Jang S-H, Lee, Yoon SJ, Lee SJ: Repeated Occurrence of HyperCKemia After Levetiracetam Administration. *EC Neurol.* 5: 150–154, 2017

2. Lorenzo R Di, Li Y: Rhabdomyolysis associated with levetiracetam administration. *Muscle and Nerve* 56: E1–E2, 2017

3. Kubota K, Yamamoto T: Levetiracetam-induced rhabdomyolysis: A case report and literature review. *Neurol. Asia* 22: 275–278, 2017

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

7. Akiyama H, Haga Y, Sasaki N, Yanagisawa T, Hasegawa Y: A case of rhabdomyolysis in which levetiracetam was suspected as the cause. *Epilepsy Behav. Case Reports* 2: 152–155, 2014

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