INPLASY

Safety of gabapentinoid use in adults medicine populations with renal dysfunction: a systematic review of observational data

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202570115

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 July 2025 and was last updated on 16 May 2026.

INTRODUCTION

Review question / Objective What is the observational evidence regarding safety and clinical outcomes associated with real-world gabapentinoid use (versus non-use or active comparator medications) in adult medicine patients (i.e., non-surgical) with renal dysfunction?

Rationale Gabapentinoids (gabapentin and pregabalin) are together two of the most commonly-prescribed medications, often for off-label indications in the US. Gabapentinoids are primarily eliminated by the kidneys and require dose-adjustment with diminishing levels of renal function. We seek to synthesize real-world literature to assess the degree to which studies account for renal dysfunction within their study populations and whether there exists an association between harms, safety events, and adverse clinical outcomes among gabapentinoid users (versus non-users or patients using comparator medications) with renal dysfunction.

Condition being studied Gabapentinoid use or exposure to gabapentinoids, particularly when considered in the setting of renal dysfunction. Gabapentinoids include gabapentin and pregabalin. Renal dysfunction includes entities such as acute kidney injury (AKI) or acute renal failure (ARF), chronic kidney disease (CKD) or any stage, kidney transplant, and end-stage renal disease with or without dialysis. Other definitions of renal dysfunction, including definitions based on a study-defined threshold of estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) will be considered if all other inclusion criteria are met.

METHODS

Search strategy Databases searched include: Cochrane, EMBASE, Web of Science, and Pubmed

PubMed:
("Gabapentin"[Mesh] OR gabapentin[tiab] OR "Pregabalin"[Mesh] OR pregabalin[tiab] OR gabapentinoids[tiab]) AND "Renal Insufficiency,

Chronic"[Mesh] OR “chronic renal insufficiency” [tiab] OR “chronic renal insufficiencies”[tiab] OR “chronic renal disease”[tiab] OR CKD[tiab] OR “chronic kidney disease”[tiab] OR “chronic kidney insufficiency”[tiab] OR "Renal Dialysis"[Mesh] OR “renal dialysis”[tiab] OR “renal dialyses”[tiab] OR “kidney dialysis”[tiab] OR “peritoneal dialysis”[tiab] OR “hemodialysis”[tiab] OR dialysis[tiab] OR "Renal Insufficiency"[Mesh] OR “renal insufficiency”[tiab] OR “renal insufficiencies”[tiab] OR “renal dysfunction”[tiab] OR "Inpatients"[Mesh] OR inpatients[tiab] OR inpatient[tiab] OR "Hospitalization"[Mesh] OR hospitalization[tiab] OR hospitalized[tiab] OR "Patient Admission"[Mesh] OR “patient admission”[tiab] OR “patient admissions”[tiab] OR admitted[tiab]) AND (“cohort study” OR “cohort studies” OR "Cohort Studies"[Mesh] OR “case control study” OR “case control studies” OR "Cohort Studies"[Mesh] OR “follow-up study” OR “follow-up studies” OR "Follow-Up Studies"[Mesh])

Web of Science:
(gabapentin OR pregabalin OR gabapentinoids) AND (“chronic renal insufficiency” OR “chronic renal insufficiencies” OR “chronic renal disease” OR CKD OR “chronic kidney disease” OR “chronic kidney insufficiency” OR “renal dialysis” OR “renal dialyses” OR “kidney dialysis” OR dialysis OR peritoneal dialysis OR hemodialysis OR “renal insufficiency” OR “renal insufficiencies” OR “renal dysfunction” OR inpatients OR inpatient OR hospitalization OR hospitalized OR “patient admission” OR “patient admissions” OR admitted) AND (“cohort study” OR “cohort studies” OR “case control study” OR “case control studies” OR “follow-up study” OR “follow-up studies”)

Embase:
('gabapentin'/exp OR gabapentin:ab,ti OR 'pregabalin'/exp OR pregabalin:ab,ti OR gabapentinoids:ab,ti) AND ('chronic renal insufficiency'/exp OR 'chronic renal insufficiency':ab,ti OR 'chronic renal insufficiencies':ab,ti OR 'chronic renal disease'/exp OR 'chronic renal disease':ab,ti OR ckd:ab,ti OR 'chronic kidney disease'/exp OR 'chronic kidney disease':ab,ti OR 'chronic kidney insufficiency'/exp OR 'chronic kidney insufficiency':ab,ti OR 'renal dialysis'/exp OR 'renal dialysis':ab,ti OR 'renal dialyses':ab,ti OR 'kidney dialysis'/exp OR 'kidney dialysis':ab,ti OR 'hemodialysis'/exp OR 'hemodialysis':ab,ti OR 'peritoneal dialysis'/exp OR 'peritoneal dialysis':ab,ti OR 'dialysis'/exp OR dialysis:ab,ti OR 'renal insufficiency'/exp OR 'renal insufficiency':ab,ti OR 'renal insufficiencies':ab,ti OR 'renal dysfunction'/exp OR 'renal dysfunction':ab,ti OR 'inpatients'/exp OR inpatients:ab,ti OR 'inpatient'/exp OR inpatient:ab,ti OR 'hospitalization'/exp OR hospitalization:ab,ti OR hospitalized:ab,ti OR 'patient admission'/exp OR 'patient admission':ab,ti OR 'patient admissions':ab,ti OR admitted:ab,ti) AND ('cohort study'/exp OR 'cohort study' OR 'cohort studies'/exp OR 'cohort studies' OR 'case control study'/exp OR 'case control study' OR 'case control studies'/exp OR 'case control studies' OR 'follow-up study'/exp OR 'follow-up study' OR 'follow-up studies'/exp OR 'follow-up studies') AND ('article'/it OR 'article in press'/it)

Cochrane Central Register of Controlled Trials (CENTRAL):
(gabapentin OR pregabalin OR gabapentinoids) AND (“chronic renal insufficiency” OR “chronic renal insufficiencies” OR “chronic renal disease” OR CKD OR “chronic kidney disease” OR “chronic kidney insufficiency” OR “renal dialysis” OR “renal dialyses” OR “kidney dialysis” OR dialysis OR “hemodialysis” OR “peritoneal dialysis” OR “renal insufficiency” OR “renal insufficiencies” OR “renal dysfunction” OR inpatients OR inpatient OR hospitalization OR hospitalized OR “patient admission” OR “patient admissions” OR admitted) AND (“cohort study” OR “cohort studies” OR “case control study” OR “case control studies” OR “follow-up study” OR “follow-up studies”).

Participant or population Adult medicine (i.e., non-surgical) populations with a quantifiable prevalence of renal dysfunction.

Intervention Gabapentinoid use (gabapentin or pregabalin) is the key intervention being studied, specifically in the context of renal dysfunction. Studies must meet at least one of the following criteria: 1) gabapentinoid use is a key explanatory variable or an exposure of interest in a study that accounts for the presence of renal dysfunction within the study population, or 2) renal dysfunction is examined as a key explanatory variable or potential effect modifier of gabapentinoid-related outcomes.

Comparator Comparator groups specifically include non-users of gabapentinoids or populations that receive a non-gabapentinoid active comparator medication. Active comparators may include medications such as other anti-epileptic drugs, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), alternative pain medications, or other central nervous system-acting (CNS-acting) medications depending on the clinical context in which the gabapentinoid is being

prescribed. If a study assesses only gabapentinoid-exposed patients, then outcomes should be compared between those with renal dysfunction versus those with normal or better renal function, as defined within each study.

Study designs to be included Observational, non-randomized studies. Given studies must report an association with outcomes, this review will primarily include cohort studies and case-control studies. Other observational designs may be considered only if the analysis accounts for or adjusts for the presence of renal dysfunction within study design or analysis.

Eligibility criteria Inclusion criteria: 1. Adult medicine populations (i.e. non-surgical) with any level of renal dysfunction reported (either as a population-level prevalence or patient-level marker of renal dysfunction including creatinine clearance [CrCl] or estimated glomerular filtration rate [eGFR]); 2. English language only; 3. study from any year (no exclusion placed based on publication year) up to last date of updated search; 4. observational studies examining any adverse effects, safety events, harms, or clinical outcomes in populations that include patients with renal dysfunction.

The following studies will be excluded upfront during the abstract review phase: 1. Duplicate studies; 2. Review articles, letters to editor, or commentaries; 3. Other systematic reviews or meta-analyses; 4. Case reports or studies with small sample size (n<5); 5. Genetic or molecular cell biology studies; 6. Studies on non-human subjects; 7. Non-adult medicine populations including surgical or peri-operative, pediatric, pregnant, critical care, or acute trauma populations; 8. Studies that are not published in English Language and therefore unable to abstract data in full text; 9. Randomized controlled trials and studies (non-observational studies).

Subsequently, for full text review, the following hierarchy of exclusion will be applied. Studies will be preferentially excluded for the top-most reason in the hierarchy if multiple reasons for exclusion exist: 1. Wrong intervention or exposure: neither gabapentin nor pregabalin are key explanatory or exposure variables with regards to study outcomes, nor does the study examine any measure of renal dysfunction as a key explanatory variable or effect modifier of gabapentinoid-related outcomes; 2. Wrong population: surgical, pre-operative, pediatric, pregnant, critical care, acute trauma patients were included and cannot be separated from the data or analysis of the study population; 3. Wrong study design: including randomized trials or cross-sectional studies with no outcomes reported; 4. No renal dysfunction prevalence reported: proportion of patients with renal dysfunction is unknown or unreported, and study also does not account for any patient-level measure of renal function (CrCl, eGFR, etc.); 5. No outcomes for renal dysfunction patients: study may identify or report measures some measured of patient- or population-level renal dysfunction however there is no data regarding outcomes in patients with renal dysfunction, or there are no adjusted measures of association that account for renal dysfunction (via adjusting for AKI, CKD, ESRD, dialysis, CrCl, eGFR, etc.); 6 . Wrong comparator – exposure to gabapentinoid is not compared to non-users or active comparator medications, as study only looks at a cross-section of outcomes among exposed patients with no clinically significant reference group. If renal dysfunction is a key explanatory variable or potential effective modifier of outcomes among gabapentinoid-users, there is no comparison to patients with either normal or better renal function, as defined by the study.

Information sources Studies published in Cochrane, EMBASE, Web of Science, and Pubmed. Additional gray literature sources will be identified by searching references sections of studies.

Main outcome(s) Mortality, over-sedation, hospitalization.

Additional outcome(s) Any other potentially meaningful harms, adverse events, clinical outcomes, or safety outcomes studied in the literature with respect to receipt of gabapentinoids in the context of renal dysfunction.

Data management COVIDENCE management system. References were managed with EndNote 21.

Quality assessment / Risk of bias analysis Robins-I tool for non-randomized studies will be used to assess risks of bias.

Strategy of data synthesis Two authors shall independently review, screen, and extract data (AJU, HMR) with joint resolution of conflicts. A third reviewer will resolve any unresolved conflicts (ADA).

Subgroup analysis Only where meta-analytic data are possible. Random effects meta-analysis would be used to combine poolable data outcomes from

comparable populations. Such pooled analyses would only be undertaken if studies have similar exposure and outcome definitions, without risk of overlapping study cohorts.

Sensitivity analysis N/A.

Language restriction English.

Country(ies) involved USA; study primarily synthesized at University of California, San Francisco.

Keywords gabapentinoids; gabapentin; pregabalin; renal dysfunction; chronic kidney disease; dialysis; systematic review.

Dissemination plans Publication of systematic review.

Contributions of each author

Author 1 - Aditya Ullal - Author 1 was responsible for study design, protocol drafting, independent abstract and full text screening, joint reviewer conflict resolution, data extraction, independent quality assessment, manuscript drafting and editing.

Author 2 - Hadi Roudsari - Author 2 was responsible for protocol editing, independent abstract and full text screening, joint reviewer conflict resolution, data extraction, independent quality assessment, manuscript drafting and editing.

Author 3 - Andrew Auerbach - Author 2 was responsible for protocol editing, reviewer conflict resolution, manuscript drafting and editing.