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Risk Factors Associated With Adverse Outcomes In Adults Taking Gabapentinoids: A Systematic Review and Meta-Analysis

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Introduction

Gabapentinoids are recommended for the treatment of neuropathic pain. Prescribing and illicit use of gabapentinoids have been increasing and this has coincided with an increase in drug-related deaths linked to the drugs. Despite rising concerns about the safety of gabapentinoids, little is known about the patients most at risk of harm.

Objectives

- To conduct a systematic review to identify all published studies of risk factors associated with adverse outcomes in adults taking gabapentinoids.
- To summarise the risk factors for adverse outcomes in gabapentinoids through narrative synthesis and meta-analysis.

Methods

- The study was conducted using a pre-registered protocol (PROSPERO ID: CRD42021249664) in line with PRISMA guidelines.
- Cochrane, MEDLINE, EMBASE, Scopus, and PubMed were searched for eligible studies using a pre-defined strategy.
- All titles and abstracts were screened by one reviewer (J.M.E.) with ~1/3 screened by a second reviewer (H.L.H.) for quality control.
- Risk of bias was assessed using the National Institutes of Health quality assessment tool (J.M.E. and H.L.H.).
- A random effects meta-analysis was conducted where ≥2 studies reported the same drug, risk factor, and outcome and I^2 test of heterogeneity < 50%.
- Statistical analysis was conducted using R Studio.

Table 1 – Inclusion and exclusion criteria using the PICO framework

Parameter	Inclusions	Exclusions
Population	- Human adults taking gabapentin (GAB), pregabalin (PGB) or mirogabalin (prescribed or non-prescribed)	- Participants under 18 years (except studies in countries where age of consent is below 18 years) - Participants with acute pain (pain present for less than 3 months)
Exposure	- Any clinical, biomarker, demographic, psychosocial or genetic factor	n/a
Control	- Comparator groups of exposures	n/a
Outcomes	**- Primary**: Dependence, addiction, misuse/abuse, overdose and death **- Secondary**: all other adverse events (AE)	n/a
Timing	- January 1993 to June 2021	n/a
Study Type	- Cross-sectional, case-control, cohort, RCT and systematic reviews (where additional meta-analysis conducted)	- Studies without an abstract, without access to full-text or not in English

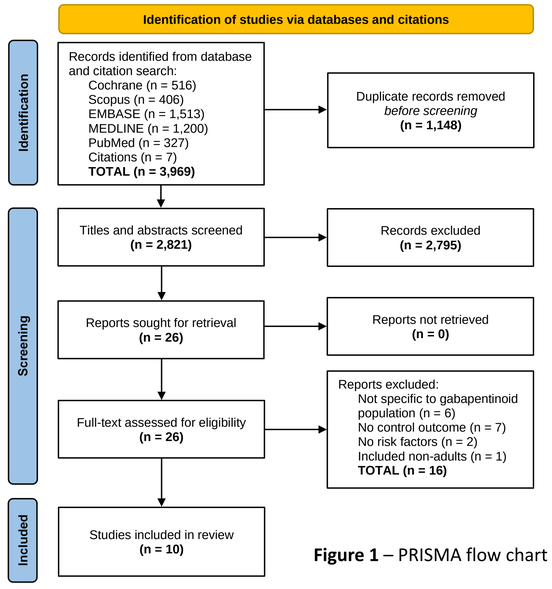

Figure 1 – PRISMA flow chart

Results

Table 2 – Study characteristics

Study	Country	Design	Drug	Reported Outcome	Quality Rating
Boden *et al.*, 2014	Sweden	Retrospective Cohort	PGB	Misuse	Good
Kanbayashi *et al.*, 2014	Japan	Retrospective Cohort	PGB	Various AEs	Good
Kato *et al.*, 2015	Japan	Retrospective Cohort	PGB	Somnolence, dizziness	Good
Shaparin *et al.*, 2015	USA	Nested case-Control	GAB	Various AEs	Fair
Schjerning *et al.*, 2016	Denmark	Retrospective Cohort	PGB	Abuse	Good
Kose, 2018	Japan	Nested case-control	PGB	Various AEs	Good
Peckham *et al.*, 2018	USA	Retrospective Cohort	GAB	Overuse	Good
Driot *et al.*, 2019	France	Retrospective Cohort	GAB, PGB	Misuse	Good
Mukai *et al.*, 2019	Japan	Nested case-control	PGB	Various AEs	Good
Ibiloye *et al.*, 2021	USA	Retrospective Cohort	GAB, PGB	Misuse	Fair

AE, adverse event; GAB, gabapentin; PGB, pregabalin

Table 3 – Risk factors associated with different gabapentinoid outcomes

Drug	Outcome	Risk factors
GAB	Misuse	Younger age, higher number of prescribers
	Overuse	Males, anxiety, depression
	Any AEs	Females, non-white
PGB	Abuse	Males, early retirement, younger age, antidepressants, antipsychotics, benzodiazepines, opioids, antiepileptics, no anticholinergics
	Misuse	Younger age, males, higher number of prescribers, cancer, multiple sclerosis, neuropathy, personality disorders, methadone, lower income, epilepsy, neuropathic pain, an addictive disorder, drug with an abuse potential
	Dizziness	Older age, opioid use
	Oedema	Higher neurotropin and serum creatinine levels
	Somnolence	Older age, higher duration of therapy, opioid use
	Unsteadiness	Older Age, no NSAIDs, lower PGB dose
	Weight gain	Higher serum creatinine level
GAB, PGB	Misuse	Younger age, males, neuropathic pain, gabapentinoid type (PGB), opioid use

- Only two studies met the inclusion criteria for a meta-analysis

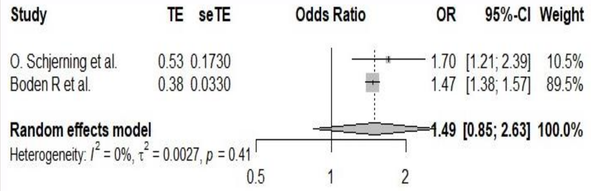

Figure 2 – Forest plot of male gender as a risk factor for misuse/abuse of pregabalin.

Conclusions

Understanding the risk factors for gabapentinoid-related adverse outcomes has the potential to inform treatment strategies. The development of screening tools to quantify risk of harm will assist treating physicians further. No studies examined gabapentinoid-related death or genetic factors, and these should be areas of future research.

References

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