Deprescribing interventions for gabapentinoids in adults: a scoping review

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Abstract

The emerging issue of rising gabapentinoid misuse is being recognised alongside the lack of current evidence supporting the safe and effective deprescribing of gabapentinoids. This scoping review aimed to assess the extent and nature of gabapentinoid deprescribing interventions in adults, either in reducing dosages, or prescribing of, gabapentinoids. Electronic databases were searched on 23rd February 2022 without restrictions. Eligible studies included randomised, non-randomised and observational studies that assessed an intervention aimed at reducing/ceasing the prescription/use of a gabapentinoid in adults for any indication in a clinical setting. The research outcomes investigated type of intervention, prescribing rates, cessations, patient outcomes, and adverse events. Extracted outcome data was categorised as either short ([?] 3 months), intermediate (>3 but <12 months) or long ([?] 12 months) term. A narrative synthesis was conducted. The four included studies were conducted in primary and acute care settings. Intervention were of dose reducing protocols, education and/or pharmacological-based approaches. In the randomised trials, gabapentinoid use could be ceased in at least one-third of participants. In the two observational trials, gabapentinoid prescribing rates decreased by 9%. Serious adverse events and adverse events specifically related to gabapentinoids were reported in one trial. No study included patient-focussed psychological interventions in the deprescribing process, nor provided any long-term follow-up. This review highlights the lack of existing evidence in this area. Due to limited available data, our review was unable to make any firm judgements on the most effective gabapentinoid deprescribing interventions in adults, highlighting the need for more research in this area.

1. INTRODUCTION

Gabapentinoids are top selling drugs globally. In 2018, gabapentin became the 6$^{\text{th}}$ most commonly prescribed medication in the US, increasing from 39 million scripts in 2012 to 67 million scripts in 2018.(1, 2) In Australia, pregabalin prescribing increased eight fold between 2012 and 2018. (3) However, the global increase in gabapentinoid prescribing has been associated with subsequent increases in the harms including misuse of these drugs. Recently, gabapentinoids have been increasingly prescribed by physicians for several "off-label" uses, such as low back pain and sciatica. (4, 5) Whilst this escalation in off-label prescribing may, in part, have been in response to the challenges of the opioid epidemic and the subsequent push towards using non-opioid alternatives for pain management, (2, 4, 6) recent studies have found limited evidence supporting these off-label uses and demonstrated gabapentinoids to be no more efficacious than placebo. (4, 5, 7, 8)

The emerging issue of gabapentinoid misuse is recognised across several countries, including North America and in Europe. (9-11) In Australia, one in seven Australians prescribed pregabalin are considered at being at

high risk of misuse. (12) Since its listing on the subsidised list of medicines in Australia (Pharmaceutical Benefits Scheme) in 2013, pregabalin-associated deaths have increased by 57.8% per year, highlighting the rapidly increasing harms associated with the increased prescribing trends. (12) Some people who purposively take higher than recommended doses do so to experience sedation, euphoric effects, disassociation, analgesia and to potentiate the effects of other substances (e.g. opioids). (2) Concomitant consumption of gabapentinoids with other central nervous system depressants (e.g. benzodiazepines) and opioid analgesics significantly increases adverse events, such as respiratory depression and mortality. (2, 13) Moreover, gabapentinoid use has also been associated with increased risks of suicidal ideation and behaviour, particularly within adolescents and young adults (15-24 years) and women. (14-16) Furthermore, physical dependence, tolerance and withdrawal from gabapentinoids have been well documented at both recommended dosages and supratherapeutic dosages. (2, 14, 17, 18)

In cases where a drug is no longer needed or is associated with more harms than benefits, the medicine should cease (or reduce in dose). Deprescribing is the complex process of tapering or ceasing unnecessary medication, aimed at improving patient outcomes. (19) Deprescribing is most often indicated when the potential harms of a drug begin to outweigh the existing or potential benefits of continued treatment and is often prompted by the emergence of new adverse events, increase in the number of medicines being taken, or changing treatment priorities. (19, 20) Whilst prescribing a new medication is a relatively simple and often a well-received process, how and when to consider deprescribing can be more complicated. More so, deprescribing a medication that has a high risk of dependence, misuse and withdrawal can be an even more difficult task. Currently, there is no consensus on the best method to deprescribe gabapentinoids.

It is essential that clinicians have access to current evidence supporting the safe cessation of gabapentinoids. In order to deprescribe successfully, prescribers can be guided by strategies that have proved to be effective in the past. There is a clear lack of robust evidence in the literature surrounding tapering or ceasing gabapentinoid therapy. Previous research in deprescribing has been in other populations. For example, in older people or people living with dementia, or those prescribed a specific drug class, such as anticholinergics or opioid analgesics. (21-24) Thus, there is fundamental need and clinical value to investigate what strategies are effective to deprescribe gabapentinoids. Therefore, this review aimed to investigate the types and nature of previous gabapentinoid deprescribing interventions in adults, either in reducing gabapentinoid use (i.e. dose reduction/cessation) or the prescribing of gabapentinoids.

2. METHODS

2.1 Design and reporting

This scoping review complies with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist. (25) The original protocol was devised in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (26) and was registered on PROSPERO (CRD42022298382; www.crd.york.ac.uk). Details of the protocol changes are included in Appendix 1.

2.2 Research questions

To understand the extent and nature of previous gabapentinoid deprescribing interventions we developed six research questions around the intervention, outcomes and barriers, including:

1. What interventions have previously been tested to deprescribe gabapentinoids?
2. Describe gabapentinoid deprescribing interventions including the type of study designs, interventional arms, target populations (e.g. clinician, patient), setting (i.e. primary, secondary, tertiary), categorise the types of interventions (e.g. pharmacological, physiological, psychological, policy), and implementation process.
3. Were previous gabapentinoid deprescribing interventions successful in:

1. Reducing a patient's gabapentinoid dose,
2. Increasing the number or proportion of participants who ceased their gabapentinoid, and/or

3. Changing the rates of gabapentinoid prescribing?

1. Did patient outcomes improve after deprescribing (e.g. pain levels, quality of life) and did patients need support throughout the deprescribing process (e.g. counselling)?
2. What proportion of participants experienced adverse events? What withdrawal symptoms were experienced and how were these managed?
3. Were there barriers reported to the deprescribing of gabapentinoids?
4. What was the most effective strategy for deprescribing gabapentinoids?

2.3 Search strategy

Potential studies were identified by searching electronic databases of MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), International Pharmaceutical Abstracts, ClinicalTrials.gov, and the Worth Health Organization International Clinical Trials Registry Platform (WHO ICTRP) from database inception to 23rd February 2022. Terms such as "pregabalin", "gabapentin", "gabapentinoid" and "cease", "taper", "reduce" and "deprescribe" were used to identify potentially eligible studies. There were no language or publication date restrictions. The full search strategy is outlined in Appendix 2. We then conducted manual screening, searched the reference lists of included studies, as well as backward and forward citation tracking of the included studies using PubMed and Scopus. We also communicated with content experts to identify any missing studies.

2.4 Eligibility criteria

We included randomised controlled trials (RCTs), non-randomised controlled trials and observational studies that assessed an intervention aimed at reducing or ceasing the prescription or use of a gabapentinoid in adults ([?]18 years) for any indication (including off-label use) in a clinical setting. The comparator could be usual care (i.e. no intervention), placebo or an active control. Studies targeting deprescribing in the context of polypharmacy interventions (most commonly defined as [?]5 regular prescribed medications) were included if they reported gabapentinoid-specific data. The deprescribing intervention could be aimed at either the clinician, patient or both across any setting. Non-randomised trials were defined as trials where the allocation was not at random (e.g. quasi-randomised controlled trials). We excluded animal studies, non-interventional studies (e.g. commentaries) and those involving paediatric populations (<18 years) or patients living with cancer.

2.5 Data extraction and management

Two independent review authors (PA & SM) screened the titles and abstracts of identified studies and full texts of potentially eligible studies. Disagreements were resolved by discussion or arbitration by a third author (AM). Duplicates were removed both automatically using Endnote and by manual screening.

The two review authors independently extracted data from eligible studies into a piloted, standardised data extraction form (Microsoft Excel). If consensus was not reached, disagreements were resolved by discussion first and then arbitration by a third author (AM). Data extraction included bibliometric data (e.g. authors, title, country), study characteristics (e.g. setting, sample size, target population, funding, conflicts of interest), participant characteristics (e.g. age, sex, diagnosis, baseline number of gabapentinoids prescribed), interventions and controls (gabapentinoid type, dose, duration, intervention design and aim), co-interventions (e.g. use of other therapies), outcome data (pre/post gabapentinoid prescribing rates, adverse events including withdrawal symptoms (with descriptors and related characteristics), withdrawals from the intervention, patient-reported outcomes (pre/post intervention pain intensity (e.g. Visual Analogue Scale) and quality of life (e.g. Hamilton Anxiety Rating Scale, EuroQol-5-Dimension scores), barriers to deprescribing (for patients and clinicians) and data completeness (i.e. percentage of missing data, how missing data were handled).

Serious adverse events were defined as events that were life threatening, such as those that resulted in death, hospitalisation, significant incapacity, congenital anomaly, or birth defects. Adverse events were defined as non-serious adverse events, such as side effects e.g. dizziness, drowsiness, confusion, dry mouth. Successful

cessation of gabapentinoid therapy was defined as ceasing the medication without switching to another high-risk medication from another inappropriate drug class (e.g. benzodiazepine or opioid).

Follow-up time points for outcomes were categorised as either short ([?] 3 months), intermediate ($>$ 3 but $<$ 12 months) or long ([?] 12 months) term. The short-term follow-up was considered the primary outcome time point. If multiple time points fell within the same period, the one-time point closest to 7 weeks, 6 months and 12 months for each follow up period was used.

If relevant data were missing, the authors were contacted to request clarification or additional data (e.g. in the case where only an abstract was available (27, 28). If data were not available within the text, means and standard deviations (SDs) were estimated from graphs and figures, if available. If SDs were not reported, we attempted to estimate them from the confidence intervals (CIs) or other measures of variance. If SDs were missing for follow-up outcomes, we used the SD for that outcome at baseline.

2.6 Risk of bias

Risk of bias assessment was conducted by the two review authors (PA & SM) independently using the Cochrane methodology. Disagreements were resolved by discussion or arbitration by a third author (AM). Randomised controlled trials were assessed with the Cochrane risk of bias tool (29) and observational studies were assessed using the Non-Randomised Studies of Interventions (30) (ROBINS-I). For ROBINS-I, the classification 'no information' was used when there was insufficient data reported within the text to permit an accurate judgement of bias (e.g. when only an abstract was available). Therefore, an overall judgment was not given when it occurred due to the lack of available information potentially allocating an inaccurate overall score.

2.7 Data synthesis and analysis

Study characteristics were reported descriptively. Dichotomous variables, such as sex and adverse events, are reported as proportions, n/N (%) and continuous outcomes reported as means, with standard deviation (SD) if to describe sample variability. Meta-analysis, sensitivity analyses and the use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) could not be conducted due to the small number of studies and clinical heterogeneity. Thus a narrative synthesis was conducted. The results are summarized qualitatively, and are presented in order of the research questions, separating data between randomised and non-randomised studies.

3. RESULTS

The search identified a total of 13,934 records, of which four studies were eligible for inclusion plus three ongoing clinical trials (NCT04855578; NCT00647322; ACTRN12618000729224). A summary of the registered, ongoing clinical trials is available in Appendix 3. The study flow diagram is presented in Figure 1.

3.1 Study characteristics

Two studies were randomised controlled trials with a total of 7,248 participants randomised, conducted in Canada, and across multiple countries. (31, 32) The two observational studies were both conducted in the United Kingdom. (27, 28) Three studies (27, 28, 31) were implemented in a primary care setting, and one implemented in 'centres' across multiple countries. (32) A total of 1,302 participants were prescribed a gabapentinoid at baseline. One study had industry sponsorship for editorial support for manuscript preparation. (32) A summary of the study characteristics are reported in Table 1 and the interventions in Table 2.

3.2 Risk of bias assessment

Both randomised trials were assessed to have an overall low risk of bias. Performance and attrition bias were the two domains that the two trials had a common rating on low risk of bias. (31, 32) One trial had a high risk of bias for concealment of treatment allocation, as study sites became aware they were crossing over to the intervention phase four weeks prior. (31) The other RCT had a high risk of bias for method

of randomisation, as the text did not state how participants were randomised. (32) Detection bias and reporting bias were judged as unclear due to a lack of information. The non-RCTs studies were not given an overall risk of bias as these observational studies were abstracts only and insufficient information was available to assess most domains. (27, 28) A summary of risk of bias for all studies is reported in Table 3.

3.3 Outcomes

3.3.1 Deprescribing interventions

All studies implemented deprescribing interventions that targeted either the patient or the clinician. Randomised trials aimed to reduce or cease gabapentinoids dose and evaluated safety. Both randomised trials implemented pharmacological based interventions to patients. (31, 32) One trial evaluated the effect of an electronic decision support tool in deprescribing potentially inappropriate medications within older patients, including gabapentinoids, classed as an "intermediate risk medication". (31) The electronic decision support tool provided individualised deprescribing reports to treating physicians within three days of patient admission, suggesting opportunities where potentially inappropriate medications could be deprescribed and tapering instructions were indicated. This large trial (n = 6,633 with 925 receiving gabapentinoids) compared the intervention tool, MedSafer, to usual care and whilst focused on prompting the medical team to act on identified opportunities to deprescribe, patients or caregivers were also given educational pamphlets on deprescribing of selected classes of medications (e.g. gabapentinoids, antipsychotics, proton pump inhibitors). The other randomised trial was an industry funded, three arm trial of lorazepam (3 – 4 mg/day) and high dose (450 – 600 mg/day) and low dose pregabalin (150 – 300 mg/day and) to evaluate the prevalence and severity of discontinuation symptoms during the placebo phase in 412 patients with generalised anxiety disorder. (32)

The two observational studies employed education-based, clinician-focussed interventions to reduce gabapentinoid prescribing rates within their respective settings. (27, 28) One study validated the efficacy of a previously developed program, "The 10 Footsteps programme", in which clinicians underwent bi-weekly health training to improve confidence and motivation when helping manage pain patients, and in particular 'high-risk' pain patients. (28) The definition of a 'high-risk' pain patient was not stated within the text's abstract. The other observational study focused on a small cohort of 30 patients and involved the presentation of data and leaflets to general practitioners and nurse prescribers to change clinician prescribing trends and reduce the rate of gabapentinoid prescribing within the practice. (27)

3.3.2 Dose reduction, cessation and prescribing rates

Both randomised trials were successful in reducing the number of participants using a gabapentinoid. (31, 32) The MedSafer tool enabled 35.3% of gabapentinoid users considered to be an inappropriate medicine be deprescribed (ceased) at short-term follow-up, compared to the control group of whom 21.2% who deprescribed at short-term follow-up. (31) While, cessation was successful in two-thirds of participants with generalised anxiety disorder. (32) Non-randomised studies successfully changed prescribing rates of gabapentinoids at intermediate timeframe follow-up. (28) A summary of prescribing rates is reported in Table 4.

3.3.3. Patient reported outcomes

Patient reported outcomes were reported by both randomised trials but only at short and intermediate follow-up. The longest data collection point was at 26 weeks. (32) There was no long-term follow-up. Only one study reported pain outcomes (the Visual Analogue Scale (VAS) out of 100 at short-term follow-up). (31) There was no difference in pain intensity levels pre and post intervention. (31) Quality of life outcomes were reported in both randomised trials. The trials measured quality of life using the EuroQol-5 Dimension (EQ-5D-5L) system at a short-term follow-up (31) and the Mean Hamilton Anxiety Rating Scale (HAM-A) at intermediate-term follow-up (32) and the scores improved following implementation of the deprescribing interventions. (31, 32) Neither non-randomised controlled trials reported any patient outcomes. A summary of patient reported outcomes is reported in Table 4.

No studies reported participants needing additional support (e.g. patient counselling, co-prescribed med-

ication) throughout the ceasing/dose reduction process. Rescue medicine was permitted in one study in generalised anxiety disorder. (32)

3.3.4. Adverse events

Serious adverse events were reported in both randomised trials. The trial by Kasper et al reported 48/308 (15.6%) SAEs in the pregabalin groups and 22/153 (14.4%) in the active control (lorazepam) (32). The Kasper et al study also reported one death within the intervention group, and it was not considered related to the study drug. (32) The trial by McDonald et al reported SAEs resulting across all medicine groups deprescribed and gabapentinoid specific SAEs are unclear. (31) Serious adverse events were not reported from the observational studies. (27, 28)

Adverse events were reported in both randomised trials. The Kasper et al trial reported 242/308 (78.6%) AEs in the pregabalin groups and 115/153 (75.2%) in the active control (lorazepam) (29). The most common adverse events being headache, dizziness and insomnia. (32) The other trial reported the most common adverse events for the entire study cohort, and did not specify gabapentinoid-specific adverse events. (31) Adverse events were not reported in the observational studies. (27, 28)

Only one study reported adverse events that resulted in participant withdrawal from the trial. (32) There were 50 adverse drug events that resulted in withdrawal from the study. (32) Information regarding the number and types of adverse events for the non-randomised controlled trials was not reported. Adverse Drug Withdrawal Events were reported in the study by McDonald, but gabapentinoid-related events are unclear.

Only one study reported details of rescue medicine use to manage symptoms. (32) Rescue medicine was permitted in one study of a gradual 'rescue taper' (i.e. extending the two-week tapering period of the participant's allocated drug to four weeks) if participants experienced severe discontinuation symptoms during tapering periods and up to seven days afterwards. (32) A total of 39 (out of 615 randomised) participants required the extended rescue taper (10 participants in the high-dose (450 – 600 mg/d) pregabalin arm, 17 participants in the low-dose (150 – 300 mg/d) pregabalin arm, and 12 participants in the lorazepam control arm). (32)

3.3.5. Barriers to deprescribing

Only one of the four studies, a conference abstract, included some qualitative components in reporting midtrial data. (28) Key barriers identified from limited clinical data included low levels of clinician motivation and confidence surrounding how to manage pain with non-pharmacological techniques, and fear of dealing with aggressive patients, in particular since the changing of the National Institute for Health and Care Excellence (NICE) guidelines. (33)

4. DISCUSSION

4.1 Summary of findings

This review consolidated the current evidence surrounding gabapentinoid deprescribing interventions, and found only two eligible randomised trials, two observational studies and three ongoing clinical trials. At present, from the small number of studies gabapentinoid deprescribing can be successfully achieved (e.g. gabapentinoid use ceased in at least one third of participants in randomised trials (31, 32) and gabapentinoid prescribing rates reduced by 9% in observational studies) (27, 28). However careful consideration and management of the adverse effects, including withdrawal, is required. Deprescribing interventions that targeted clinicians were education-based, directed at improving clinician knowledge, confidence, clinical behaviour and patterns of prescribing and included the provision of individualised deprescribing reports. (31) Patient-focused interventions were similarly education-based, with the study by McDonald et al targeting older patient populations with the intention of improving patient's awareness of deprescribing. (28) Only one study investigated an intervention that involved a tapering/ceasing protocol (32), however it is unclear the extent of influence the 'rescue taper' may have had on the study's results. There was a lack of long-term

data and no study looked at the potential need or benefit of psychological support during the deprescribing process, despite qualitative research suggesting psychological support to be an essential part of effective deprescribing. (34)

4.2 Comparison to the literature

Much of the existing literature surrounding gabapentinoids focuses on the efficacy (35-37), increased prescribing trends and misuse (1-4, 6, 12, 13, 17, 18, 38) rather than on interventions to support deprescribing or clinical guideline recommendations. Whilst these drugs do work well for the conditions they have been approved for, a common theme emerging from more recent studies is a concern for the dramatic increase in gabapentinoid misuse and associated harms, as well as limited understanding of the use and efficacy of gabapentinoids in treating off-label conditions. (1-4, 6-8, 12, 13, 17, 18, 38) As awareness of these issues increase, deprescribing plays an important role in the clinical management of patients, and clinicians should not avoid deprescribing when the harms of the drug outweigh the benefits, particularly in at risk population groups. Existing evidence has found the most common 'high-risk' gabapentinoid misusers are more likely to be young males, often unemployed, concomitantly taking opioids, benzodiazepines, alcohol or illicit drugs and were likely to have been prescribed a gabapentinoid despite having history of a substance use disorder. (12, 18) Previous or current opioid abuse is the factor most commonly associated with higher-than-maximum-dose pregabalin prescriptions, and is well documented in studies of various settings, such as substance use disorder clinics, prison systems, and psychiatric wards. (18, 39) Finally, other reviews that have been conducted in areas of similar high-risk drug classes evaluating the effectiveness of deprescribing interventions have also encountered clinical heterogeneity and thus limited any conclusions from being made. (22, 40, 41) Studies have also concluded patients partaking in polypharmacy, particularly older patients, can also be classed as high-risk users due to oversedation contributing to an increased risk of falls. (42) Recently released guidelines from National Institute for Health and Care Excellence (NICE) in the UK detail the safe prescribing and withdrawal management of medications associated with dependence, including gabapentinoids, however do not provide an intervention to directly facilitate the safe tapering or ceasing of medication. (43)

4.3 Strengths and weaknesses

This review is the first review to explore the landscape surrounding the effectiveness of previous gabapentinoid deprescribing interventions and our robust search strategy did not have any language or publication date restrictions. We also included all indications for gabapentinoid use (including off-label) and included studies that reported gabapentinoid specific deprescribing data as either primary or secondary outcomes. Both randomised trials included were of a large sample size, however, only one trial was specific to focussing on gabapentinoid deprescribing. (32) Whilst the other trial had gabapentinoid-specific outcome data, its primary objective was to deprescribe any potentially inappropriate medications that contributed to polypharmacy. (31) Due to being an emerging research area, our original screening for the systematic review found no eligible studies for inclusion, and hence resulted the review being converted into a scoping review. Whilst the two recently published observational studies were abstracts only, (27, 28) correspondence with authors suggests these studies will be published in the near future and will add to the growing body of evidence in this area alongside three registered, ongoing trials. Due to the wide variation in types of interventions and the small pool of studies, we were unable to draw direct comparisons between the studies, but presenting the results and risk of bias assessments per randomised-controlled trials and observational studies can guide readers to make their own conclusions on the current body of evidence. Finally, the data collected from included studies was not specific to particular conditions (e.g. data from the McDonald et al study represented gabapentinoids perceived to be potentially inappropriate medications) and therefore cannot be generalisable to individual pain groups.

4.4 Gap and directions for future research

This review highlights the lack of evidence within existing literature and demonstrates the need for more high-quality studies surrounding the deprescribing of gabapentinoids. Future robust research is required to identify which deprescribing interventions are effective in safely ceasing or tapering gabapentinoids. Specifically, more

dose reduction/tapering protocols, such as the study by Kasper et al, (32) should be investigated and include well-defined tapering schedules and longer follow up timepoints, to better inform physicians of regimens that have proved to be effective. Non-pharmacological interventions that are primarily patient-focused and aimed to aid gabapentinoid cessation and decrease the desire and misuse of medications, such as mindfulness, cognitive behavioural therapy and counselling, are effective in deprescribing benzodiazepines and opioids (44, 45) that have still yet to be investigated for potential benefits in gabapentinoid deprescribing. Other interventions, such as electroacupuncture have been shown to reduce opioid consumption safely and effectively in participants with chronic musculoskeletal pain, and could potentially have similar results in gabapentinoid users. (46) It is important that future studies focus on deprescribing gabapentinoids in populations with non-cancer pain, especially in cases where there is no clear diagnosis of neuropathic pain or radiculopathy, and in high-risk patient populations (e.g. those with substance use disorders, polypharmacy). Although we found clinician-focused interventions reduced the number of patients taking gabapentinoids, future studies may consider interventions that target initial prescribing decisions to directly affect the current baseline prescribing trends. Included studies were based in primary and acute care, and future studies should also consider interventions to reduce initial prescribing by pain specialists and other medical specialists who may provide the initial prescription or recommendation for prescription. As this emerging area of research grows, it will inform and shape the foundations of gabapentinoid deprescribing guidelines for clinicians, and will help prompt change in current clinical prescribing patterns of gabapentinoids.

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TABLE AND FIGURE LEGENDS

Figure 1: PRISMA flow diagram.

Table 1: Study characteristics.

Table 2: Summary of interventions to reduce/cease gabapentinoid use or prescribing.

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APPENDICES

Appendix 1: Protocol changes.

Appendix 2: Search strategy.

Appendix 3: Characteristics of ongoing clinical trial

TABLE 1: Study characteristics.

Author	Country	Study design	Setting	Intervention target	Aim	Population
McDonald 2022	Canada	Cluster RCT	Acute care	Clinician, patient	To evaluate the effect of an electronic deprescribing decision support tool on adverse drug events after hospital discharge among older adults with polypharmacy	6,633 participants [?]65 years, taking [?]5 regular medications for any conditions, including gabapentinoids prior to hospital admission
Kasper 2014	Multiple[a]	RCT	Not reported[b]	Patient	To evaluate the frequency and severity of discontinuation and rebound symptoms associated with pregabalin in patients with moderate-to-severe Generalised Anxiety Disorder	615 participants 18 to 65 years with a primary diagnosis of Generalised Anxiety Disorder

Author	Country	Study design	Setting	Intervention target	Aim	Population
Chazot 2021[c]	United Kingdom	Observational	Primary care	Clinician, patient	To validate the efficacy of the Gabapentinoids and Opioids Tapering Toolbox (GOTT)	Clinicians who prescribe gabapentinoids (and opioid analgesics)
Collinson 2019[c]	United Kingdom	Observational	Primary care	Clinician	To reduce gabapentinoid prescribing at the Haworth Medical Practice by 10% in one year	Any patient prescribed regular gabapentinoids for any condition

Abbreviations: RCT: Randomised Controlled Trial.

[a] Argentina, Austria, Costa Rica, Croatia, Czech Republic, Finland, Greece, Guatemala, Indonesia, Lithuania, Mexico, Russian Federation, Serbia, Slovenia, Spain and Turkey.

[b] 60 "centres" in 16 countries.

[c] Abstract only.

TABLE 2: Summary of interventions to reduce/cease gabapentinoid use or prescribing.

Author	Intervention	Participants prescribed a gabapentinoid	Comparator	Outcomes	Time-points
McDonald 2022	The provision of individualised deprescribing reports supplied within 3 business days of patient admission, based on evidence-based guidelines for safer prescribing in older adults, with tapering instructions when indicated, generated by MedSafer software. Gabapentinoids were listed as a "potentially inappropriate medication".	925 participants of which 729 were identified to have potentially been inappropriately prescribed	Usual care (best-possible medication history performed)	Dose cessation or reduction, ADEs and SAEs, QoL	Short-term

Author	Intervention	Participants prescribed a gabapentinoid	Comparator	Outcomes	Time-points
Kasper 2014	A 24-wk placebo- and lorazepam-controlled, randomized, double-blind, multicentre trial. Period 1 contained a 6-week fixed dose of either high dose pregabalin (450-600mg/day), low dose pregabalin (150-300 mg/day), or lorazepam. Responders continued for another 6 weeks. Then, in the double-blind period 2, 25% of patients from each medication group were randomised to discontinue the active medication by receiving a matching placebo.	206 participant per group underwent 12 weeks of high or low dose pregabalin (Period 1), then randomised to: Maintain low dose (n =112) versus placebo (n = 39) OR Maintain high dose (n = 121) versus placebo (n = 38)]	Placebo	Does cessation, ADEs, including ADWEs, SAEs, QoL	Intermediate-term

Author	Intervention	Participants prescribed a gabapentinoid	Comparator	Outcomes	Time-points
Chazot 2021[a]	Clinicians received GOTT (Gabapentinoids and Opioids Tapering Tool Box), to improve confidence of clinicians and patients to self-manage pain with safe prescribing. 10 Footsteps programme to achieve this goal was developed to increase the motivation: (a) for health care professionals to listen to patients, (b) patients to understand their pain and engage with strategies that help their long-term management, (c) create communities that are sufficiently socially resilient to allow that to happen (Ten Footsteps - Live Well With Pain).	Not reported	Nil	Reduction in prescribing rates	Intermediate-term

Author	Intervention	Participants prescribed a gabapentinoid	Comparator	Outcomes	Time-points
Collinson 2019[a]	Chart review of patients in May 2018 to determine baseline prescribing of gabapentinoids (n = 144 patients), plus a review of prescription charts of a randomised sample (n = 30) were accessed to ascertain whether indications were listed by the British National Formulary. Airedale Clinical Commissioning Group reported that 2% of patients registered at Haworth Medical Practice were taking gabapentinoids.	30 participants randomly chosen out of the 144 patients prescribed a gabapentinoid in May 2018	Nil	Reduction in prescribing rates	Intermediate-term

Abbreviations: ADE: Adverse Drug Event, ADWE: Adverse Drug Withdrawal Event, SAE: Serious Adverse Events, QoL: Quality of Life.

[a] Abstract only.

TABLE 3: Risk of bias summary.

RCTs[a]	Selection Bias	Selection Bias
Author	**Was the method of randomisation adequate?**	**Was the treatment allocation concealed?**
McDonald 2022	Low	High
Kasper 2014	High	Low

RCTs[a]	Selection Bias	Selection Bias
Non-RCTs[b]	**Non-RCTs[b]**	**Non-RCTs[b]**
Author	**Bias due to confounding**	**Bias in selection of participants into the st**
Collinson 2021[c]	No information	Low
Chazot 2019[c]	No information	Low

TABLE 4: Gabapentinoid-related outcomes.

Study	Participants prescribed a gabapentinoid at baseline	Change in gabapentinoid use or prescribing	Number of participants who reported ADEs	Number of participants who reported SAEs	Pain and Quality of life outcomes
McDonald 2022	Intervention: 367 (16.3%) Control (usual care): 558 (20.9%)	Gabapentinoid deprescribed (ceased)(by 3 business days) Intervention: 114 (35.3%) Control: 86 (21.2%)[a]	Not reported[b]	Not reported[b]	Not reported[c,d]
Kasper 2014	Period 1 intervention: High dose pregabalin n = 206 Low dose pregabalin n = 206 Placebo groups n = N/A Period 2 intervention: High dose pregabalin n = 121 Low dose pregabalin n = 112 Placebo groups n = 77	Gabapentinoid use Intervention: 117/233 discontinued the pregabalin intervention (50.2%) Control: 51/77 completed the placebo intervention (66.2%)	High dose n = 121 Low dose n = 121 Placebo n = NR	High dose n = 27/154 Low dose n = 21 (plus one unrelated death)/154 Placebo n = NR	Improved (HAM-A) High dose group: -18.7 (95%CI -20.0 to -17.3) Placebo high dose group: -17.5 (95%CI -19.8 to -15.2) Low dose group: -18.2 (95%CI -19.5 to -17.0) Placebo low dose group: -14.9 (95%CI -17.6 to -12.3)
Chazot 2021[e]	NR	Change in prescribing 12 months post intervention: Gabapentinoid from 12.9% (SD 3.46) to 2.54% (SD 2.9) (p = 0.032). Pregabalin from 3.24% (SD 1.89) to 15.0% (SD 2.28%) (p = 0.001)	NR	NR	NR

Study	Participants prescribed a gabapentinoid at baseline	Change in gabapentinoid use or prescribing	Number of participants who reported ADEs	Number of participants who reported SAEs	Pain and Quality of life outcomes
Collinson 2019[e]	144	Reduction in prescribing of 9.7% at 5 months	NR	NR	NR

Abbreviations: NR: Not Reported, ADEs = Adverse Drug Events, SAEs = Serious Adverse Events, HAM-A: Mean Hamilton Anxiety Rating Scale.

[a] Deprescribed of those considered to have potentially inappropriate medication which were 323 participants in the intervention group, and 406 participants in the control group.

[b] ADEs reported overall regardless of the drug class deprescribed: intervention: 111/2,247 (4.9%) and control: 138/2,742 (5.0%). SAEs: post-discharge deaths and hospitalisations in the intervention group – 371/2247 (16.5%) and control group 590/2742 (21.5%).

[c] Overall pain outcomes did not change pre/post intervention (Visual Analogue Scale out of 100mm; Intervention: 60mm (Range: 50-75mm); Control: 60mm (Range: 50-75mm)).

[d] Overall quality of life outcomes did not change pre/post intervention ((EQ-5D-5L; Intervention: 0.722 (95%CI 0.406 to 0.871); Control: 0.743 (95%CI 0.425 to 0.871)).

[e] Abstract only

APPENDICES

Appendix 1: Protocol changes

The changes to the protocol were a result of converting the original systematic review protocol to a scoping review due to the lack of eligible studies found on the original search. The changes included:

Changing the aim of the systematic review from evaluating the efficiency of gabapentinoid deprescribing interventions, to including research questions related to assessing the extent and nature of gabapentinoid deprescribing interventions.

Expanding the population to include adults prescribed gabapentinoids for any indication.

Appendix 2 : Search strategy

Medline, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL) and International Pharmaceutical Abstracts (via Ovid)

((randomised controlled trial or randomized controlled trial or controlled clinical trial or comparative study or clinical trial or pragmatic clinical trial or cross-over stud* or random* or usual care or active control) and (pain or adults) and (pregabalin or lyrica or gabapentin or neurontin or gabapentinoid) and (withdraw* or wean* or detox* or ceas* or cessation or reduc* or taper* or stop* or terminat* or remove* or substitu* or deprescribe or discontinue* or mitigat* or inappropriate or treatment or (therapy or therapies) or interdisciplinary program))

Clinicaltrials.gov

Advanced search: https://clinicaltrials.gov/ct2/search/advanced

- *Study type: interventional studies*
- *Group: (tick) adult, senior*

- *Condition: pain*
- *Interventions: pregabalin, gabapentin, gabapentinoid*

International Clinical Trials Registry Platform (ICTRP)

Advanced search: http://apps.who.int/trialsearch/

Search terms: pregabalin, gabapentin, gabapentinoid

Appendix 3: Characteristics of ongoing clinical trials

Registration number	Title	Registration	Status	Date last updated	Country	Study design	Participants	Intervention	Control	Relevant outcomes
NCT04855578	The prescription of Gabapentinoids in Medical Inpatients (GABA-WHY)	19th April 2021	Recruiting	12th April 2022	Canada	Non-RCT	Inpatients [?]60 years who have a gabapentinoid prescription prior to admission.	In-hospital patient educational brochure Physician education about gabapentinoid prescriptions	Usual care	Cessation or dose reduction, QoL, pain intensity, initiation of new pain medication
NCT00647322	The impact of reducing overtreatment on quality of life in children with refractory epilepsy	26th March 2008	Unknown	31st March 2008	United Kingdom	Non-RCT	Patients 6 to 21 years with intractable epilepsy receiving antiepileptic drug polytherapy	Reduction of antiepileptic medications	Usual care	Dose reduction, QoL

Registration number	Title	Registration	Status	Date last updated	Country	Study design	Participants	Intervention	Control	Relevant outcomes
ACTRN12618000729224	Deprescribing anticholinergic and sedative medications in older people - a randomised controlled trial	3rd May 2018	Recruitment completed. Last follow-up completed 03/06/2021	3rd December 2021	New Zealand	RCT	Patients [?]60 years, prescribed at least one anticholinergic or sedative medication in the last year and currently undergoing or have had an InterRAI assessment in the previous 12 months.	Pharmacist-led comprehensive medication review	Usual care	Dose reduction, medication use, mortality

Abbreviations: RCT: Randomised Controlled Trial.

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Figure 1 BJCP.docx available at https://authorea.com/users/566604/articles/613220-deprescribing-interventions-for-gabapentinoids-in-adults-a-scoping-review