Patient Empowerment Brochures to Promote Gabapentinoid Deprescribing: Protocol for the Prospective Controlled Before-and-After GABA-WHY Study

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Dr. McDonald and Dr. Lee receive salary support from the Fonds de Recherche Quebec - Santé and jointly hold the copyright for MedSafer, a deprescribing software that links to the Canadian Deprescribing Network patient empowerment brochures used in this study.

Ethics:

Ethics was granted by the McGill University Health Centre (MUHC) Research Ethics Board.

Contributor Statement:

Emily McDonald, Todd Lee, and Marc-Alexandre Gringas are responsible for the study design, literature review, and ethics approval. Robert Dubé and Jérôme Williams are involved in participant recruitment and data collection. All authors contributed to the drafting of the manuscript and to critical revisions. Each author approves the publication of the manuscript and Dr. McDonald acts as guarantor of the work

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Abstract:

Background: Off-label gabapentinoid use is common among hospitalized medical patients, who are at risk of adverse drug events. Despite this, only a minority have targeted attempts at deprescribing during hospitalization. We aim to demonstrate that patient empowerment deprescribing brochures can augment gabapentinoid deprescribing in the hospital.

Methods: This prospective controlled before-and-after trial will evaluate the impact of educational brochures distributed to patients on medical wards of 2 hospitals in Montreal, Canada. The primary outcome is the proportion of patients with a gabapentinoid deprescribed at 8-weeks post discharge, compared to usual care. Eligibility includes a gabapentinoid prescription and age 60 years or older. Exclusion criteria are known seizure disorder, severe cognitive impairment, an expected prognosis of less than 3 months, or inability to read English or French.

We aim to recruit 160 participants, with a 1:1 distribution between the intervention and control groups. The control period event rate is expected to be 13% based on a prior observational study at our center. The sample size was calculated to detect an absolute increase of 20% in deprescribing with the intervention (two-sided type 1 error of 5% and 80% power) and accounts for up to 15% loss to follow up, including death in hospital and post-discharge.

Interpretation: If successful, this would be a scalable intervention to reduce gabapentinoid overuse by encouraging deprescribing conversations between patients and their healthcare provider. Results of the study will be disseminated through publication in a peer reviewed journal and through presentation at a conference.

Trial registration: NCT04855578

Introduction

The gabapentinoids are a class of antiepileptic drugs which includes gabapentin and pregabalin. Both bind voltage-gated calcium channels in the central nervous system, inhibiting neuronal calcium influx and consequently release of excitatory neurotransmitters. Since their initial release, the FDA and Health Canada have approved the use of gabapentin and pregabalin for treatment of postherpetic neuralgia, with additional indications for pregabalin including painful diabetic neuropathy, fibromyalgia and neuropathic pain associated with spinal cord injury [1-4].

Despite a short list of approved indications, gabapentinoid prescriptions have soared in the past decade in both the United States and Canada [5, 6]. In 2016, more than 4.4 billion US dollars were spent on pregabalin, making it the eighth highest invoice spending drug in the United States [7]. The rise in gabapentinoid prescriptions has been largely driven by its popularity for various off-label indications related to chronic pain, such as various types of neuropathic pain, osteoarthritis, chronic lower back pain, sciatica, and cancer-related pain, despite a lack of evidence [8]. Some of these uses have been the subject of negative clinical trials [9-13]. In areas where there is trial evidence, the benefit of treatment is limited by a high risk of adverse events at studied doses, leading to frequent drug discontinuation [13]. Common side effects of gabapentinoids include sedation, dry mouth, lower extremity edema and traumatic falls in older adults [14, 15].

These is a high prevalence of chronic gabapentinoid use in hospitalized patients with as many as 1 in 8 patients prescribed the drug prior to admission [16]. When evaluating these patients, fewer than 1 in 5 of them are using the drug for a clear FDA or Health Canada approved

indication, and the medication is rarely stopped at discharge [16]. Gabapentinoid users are also more likely to be co-prescribed opioids and benzodiazepines [16] which is concerning in light of the evidence of increased opioid-related death with co-prescription [17, 18]. The high prevalence of off-label use of gabapentinoids in older comorbid patients who are vulnerable to adverse drug events makes this class of drug an ideal target for deprescription.

Multiple strategies exist to improve deprescription of potentially inappropriate medications. One promising method includes the use of direct patient education through the distribution of brochures, which have been studied for deprescribing benzodiazepines both in hospital [19] and in the community [20]. These educational brochures contain knowledge self-assessments, provide information on harms and benefits, present non-pharmacological alternatives and propose tapering regimens. The goal of these brochures is to improve successful deprescription by promoting patient motivation and self-capacity, as well as soliciting opportunities for deprescription by encouraging patients to meet with their healthcare providers [21]. Specific brochures exist for different classes of drugs, such as benzodiazepines, opioids, gabapentinoids and proton pump inhibitors and are available on the Canadian Deprescribing Network website (https://www.deprescribingnetwork.ca/patient-handouts). Here we present a protocol for evaluating the efficacy of educational brochures for improving the deprescription of gabapentinoids among hospitalized medical patients.

Methods

This prospective before and after study will take place on medicine clinical teaching units of the McGill University Health Centre (comprised of 2 each at the Royal Victoria Hospital and the Montreal General Hospital) in Montreal, Canada. The primary goal is improving deprescription of

gabapentinoids using a patient educational brochure designed in collaboration with the Canadian Deprescribing Network. Recruitment began in May 2021 and is expected to end in December 2022.

Subject Selection, Inclusion and Exclusion Criteria

Any patient admitted to one of the participating clinical teaching units that has a prescription for gabapentin or pregabalin will be evaluated for the study. Patients will be identified as gabapentinoids users from their "best possible medication history" obtained by the unit pharmacist at the time of admission (this includes cross referencing community pharmacy records with a detailed history with the patient to determine which medications they actually take at home). Select patient demographics and co-morbidities will be collected from the detailed admission note that is available for all patients on our medical teaching units.

Participants must be 60 years or older and have an active pre-admission gabapentinoid prescription that they confirm they are taking as prescribed at home. The 60-year cut-off was selected as it was felt this group would benefit the most from a deprescribing intervention, given the higher prevalence of polypharmacy and risk for potential adverse drug events. The deprescribing brochures are also designed with the input of older adults and specifically address changes in physiology that accompany the aging process to underscore the risks of gabapentinoids. Exclusion criteria include having a known seizure disorder, not being enrolled in the provincial public health insurance plan, previous enrollment in the study, estimated life expectancy <3 months, inability to consent, major neurocognitive disorder, and inability to read in English or French.

Trial Interventions

All sites will begin in the control period of the trial. During this control period, participants will receive usual medical care. Participants will be informed that the goal of the trial is to evaluate their usual home pain medication and any trends in deprescribing at hospital discharge. They will be unaware that gabapentinoids are specifically studied, to reduce the risk of selection bias and of contamination of the control group. Furthermore, the medical staff will not receive specific information about the trial, or specific instructions with regards to deprescription. Once the target number of control participants are enrolled, all four sites will simultaneously transition to the intervention period. As medical staff and trainees rotate frequently between sites and units, and as this is an educational intervention, randomization at the level of the individual participant or at the level of the unit is not feasible (including stepped wedge design). Learned behaviour and access to the brochures would invariably lead to contamination of the control and thus a before-and-after study method was selected to minimize this source of bias in our data.

The intervention period will consist of two components. First, participants will receive during their hospitalization an educational brochure on gabapentinoids, available in either English or French [22, 23]. Second, on a monthly basis at the beginning of each rotation, a short 5-10 minute educational session about evidence for and against gabapentinoid use, the design and purpose of the study, and a brief overview of the purpose of the brochures will be delivered to physicians (staff and medical residents) at each site.

Data Collection

All participants will provide written informed consent. Demographics and co-morbidities will be collected by trained research assistants from the participants and their medical record. During the index admission, a first questionnaire will be administered in person and will collect

information about participant demographics, including age, gender and residence style (independent, assisted living, etc.). We will also obtain a medication history (for study drugs) and perform standardized questionnaires to assess global functioning, pain control and cognition [24-26]. A follow-up questionnaire 8 weeks post hospital discharge will collect any changes in co-morbidities or living situation, and will ask participants about planned or ongoing deprescribing of their gabapentinoid (dose decrease, ongoing taper or stop), as well as initiation or dose changes of other pain medications, such as opioids and non steroidal anti-inflammatory drugs (NSAIDs). Finally, we will repeat the global functioning, pain control and cognition questionnaires.

Outcomes

The primary outcome will be deprescription of gabapentinoids at 8 weeks post-hospital discharge, defined as complete cessation or dose reduction/taper with intention to stop.

Secondary outcomes assessed at 8 weeks post-hospital discharge will include:

a. Dose reduction without intention to stop
b. Participant-reported outcomes: changes in global functioning scores, pain control and cognitive function.
c. Initiation of new pain medications or increases in doses of pre-admission non-gabapentinoid pain medications.

Justification of Sample Size

The estimated sample size is 160 participants, with a 1:1 distribution between the intervention and control groups. The control period event rate (deprescription) is expected to be 13% [16]. The sample size was calculated to detect an absolute increase of 20% in deprescription rates with the intervention (number needed to treat 5), allowing for a two-sided type 1 error of

5% and a type 2 error of 20% (132 subjects) and accounting for an up to 15% loss to follow up, including death in hospital and post-discharge (156 subjects, rounded to 160).

Statistical Analysis and evaluation of results

We will provide a descriptive summary of the population enrolled in this study including participant age, gender, comorbidities, type of gabapentinoid prescription, other co-prescriptions, length of hospital stay and residence type.

We will use an "intention to treat" principle, thus participants will be analyzed according to their participation during the intervention or control period. Binary outcomes will be assessed using binomial regression comparing the intervention to no intervention and adjusting for age and sex. Continuous outcomes (T-scores) will be assessed using linear regression comparing the intervention to no intervention adjusting for baseline values (T-scores), age and sex.

We will perform several pre-planned subgroup analyses for the primary outcome, including an analysis of participants aged 80 or older; an analysis based on discharge destination (community vs long-term care facility) and an analysis looking at the effect of each clinical teaching unit. Subgroup analyses will be treated as hypothesis generating and presented graphically with 95% confidence intervals.

Ethics

Ethics was granted by the McGill University Health Centre (MUHC) Research Ethics Board.

Interpretation

Limitations

It will not be possible to blind participants or physicians in this study. However, this is typical in pragmatic study designs and we do not expect that this will have a substantial impact on our results. We have selected hard outcomes whenever possible, including validated standardized questionnaires, that do not involve individual judgement by the assessor. In addition, during the control period of this study all participants will be informed that the study will be evaluating medications and deprescription trends but will not be made aware that gabapentinoids will be studied specifically. We believe this will help to reduce selection bias. Accordingly, medical staff will not be aware of the specifics of the study during the control period.

Another issue we are aware of is that given the simultaneous crossover of all sites into the intervention period, our study will be limited in our ability to account for temporal trends in deprescription of gabapentinoids over the years, which could be influenced by factors such as training level of junior residents or time-constraints from seasonal variations of workload intensity on the clinical teaching unit. However, reassuringly, previous retrospective data has not shown any temporal trends for gabapentinoid deprescribing on our medical wards [16].

Ethical Concerns

While we feel this intervention to be low risk to the participants involved, there are several ethical concerns we are cognizant of. With regards to privacy concerns, some patients may only agree to participate in the study if they are exempt from the follow up phone calls. This wish will be respected and such patients will only be enrolled if they consent to our use of the Dossier Santé Quebec (DSQ) provincial electronic medical record to evaluate the primary endpoint but will be excluded from some of the secondary analyses.

Special care will also need to be given to patients who are cognitively impaired or otherwise unable to provide consent. Although this subpopulation of patients may still greatly benefit from deprescription of potentially inappropriate medications, the educational brochures used in this study rely on instigating motivation and providing self-capacity, and are therefore aimed at patients who are cognitively intact or have only a mild form of cognitive impairment [27]. Although distribution of the educational brochures to the patient's proxy could be considered, this strategy is less feasible in the context of the SARS-CoV-2 pandemic, as family and caregivers often have limited access to the bedside, hindering contact with medical staff, which is crucial for initiation of the deprescription process.

Dissemination Plan

Results of this study will be disseminated through publication in a peer reviewed journal, as well as through presentations in national conferences.

Conclusion

Improving deprescription rates for potentially inappropriate medications is challenging, especially given the numerous demands on physicians' and pharmacists' time in the inpatient setting. Interventions must be simple, safe, and have strong evidence of efficacy if they are to be adopted into the workflow of busy healthcare teams, and thus evidence-based solutions are needed to address the issue of polypharmacy. Educational brochures, while by no means a complete solution, represent a good starting point as they have many of the characteristics of an ideal intervention. They are low-tech, inexpensive, safe, easy to administer, and aimed at bringing patients into the decision. As previous trials have shown, they have been highly effective

in improving deprescription of benzodiazepines and sedative hypnotics [19, 20] as well as first-generation antihistamines, glyburide and nonsteroidal anti-inflammatory drugs [28]. This study seeks to provide evidence that the gabapentinoid brochure can demonstrate a similar efficacy if targeted to hospitalized patients and would represent a scalable intervention for combatting gabapentinoid overuse, as well as encouraging conversations that lead to deprescribing.

Data-Sharing Statement

All data collected in this study will be available upon request to the study authors at the email of correspondence indicated on the title page.

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