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Title: Patient empowerment brochures to promote gabapentinoid deprescribing: protocol for the prospective controlled before-and-after GABA-WHY study
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Reviewer 1
General comments (author response in bold)

1. Why do the authors state the high rate of gabapentin prescribing in the US in 2016? Many similarities exist between our countries; however analgesia prescribing might vary between the two, and drug abuse patterns are volatile. Canadian readers might not appreciate the relevance to Canadian society. Citing the American data might attract American readership, but it would be nice to cite more current Canadian data, if known.
In Ontario, there was a significant increase in pregabalin prescriptions following its unrestricted access in April 2013.
In 2020, N03AX class antiepileptics (which include pregabalin and gabapentin) were ranked 18th in Canada for highest total program spending with 196 million dollars and 15th for use per capita.
This information has been added to the manuscript. (p. 5)

2. "The use of gabapentinoids for their analgesic effects leads to frequent co-prescription with opioids, which increases dramatically the risk of opioid-related death." What does "dramatically" mean? I do believe the authors, but I would also like to see some numbers.
The odds ratio of opioid-related death with pregabalin co-prescription is 1.68 compared to opioid prescription alone. For gabapentin, the odds ratio is 1.99.
This information has been added to both the checklist and manuscript. (p. 6)

3. "There is growing concern about abuse and misuse of gabapentinoids". Again, I do believe the authors, but what's the data ? In particular, are there Canadian data on the extent of gabapentinoid abuse ? In particular, I would like to know about diversion from elderly patients to family members, the prototypical teenager who nicks Granny's pills and takes them to a party. Otherwise, readers might not realize that prescribing gabapentinoids end up in the wrong hands.
No data is available specifically for Canada, but systematic reviews with studies from different countries in Europe, the USA and Asia report approximately 1% rate of gabapentin abuse in the general population and 40-65% among individuals with prescriptions.
This information has been added to the manuscript. (p. 6)

4. "Distribution of educational brochures to hospitalized patients has been shown to be effective in improving successful deprescription of potentially inappropriate medications." (References 18, 19, and 28). I am dubious, even if these studies were published in reputable medical journals. My 35 years of experience lead me to wonder about later relapse which may have evaded detection. I often resume care of my family practice patients who ask me to resume medications which had been discontinued during recent hospitalisations (usually hypnotics), and sometimes I comply. A longer-term follow-up would be more informative. I wonder how many study subjects will request a resumption of gabapentin once they know that researchers have stopped

following them and their DSQ's. (Having said that, I don't see very many patients asking to resume gabapentinoids, which patients do not perceive as being very effective, probably because they are not, and because many patients actually dislike their side effects.)

We agree with your statement. Long-term cessation is the ultimate goal, which we hope to achieve by including the patients in the decision to discontinue their medication. The biggest strength of the educational brochures is that they function as a self-empowerment tool, which means that the decision to deprescribe the medication ultimately relies on the patient's will. We hope this yields better long-term results compared to more paternalistic one-sided deprescription strategies. However, for reasons of practicality in the study, we've set our post-discharge follow-up visits at 8 weeks.

5. The title seems to be misleading. It seems that patients will also receive targeted educational interventions from house staff during the study period, and many staff and residents will likely initiate a re-evaluation of gabapentin at or before discharge whether of not patients bring it up. So it looks like this study will be more than just handing out brochures.

We felt it was important to include an educational component for medical staff to provide them evidence-based information on gabapentinoid prescribing. Furthermore, implementation of deprescribing tools such as patient educational brochures in a real-world setting would require buy-in from the medical staff with informed decision-making on deprescribing potentially inappropriate medications. Although there are two components to our intervention, the brochures are the backbone of the deprescription strategy. Although physicians are aware of the burden of potentially inappropriate medications in medical inpatients (including others such as benzodiazepines and PPIs), baseline deprescription rates are low during hospital admissions (Gingras et al., 2019; Wilson et al., 2018), which warrants the addition of brochures as a potential deprescription tool. Clarifications have been added to the manuscript in this regard. (p. 9)

6. After publication of this study, I wonder what the effects will be on medical practice. The authors cite the 3 previous studies, which showed impressive reductions in harmful medication prescribing. Did these studies impact upon medical practice? (They may have, I just don't know.) Either way, why are more studies necessary? Why not just put these interventions into practice? There should really be a global and comprehensive deprescribing programme in every hospital (and every medical office), and not a medication-specific programme which could be forgotten in the chaos of clinical practice.

Thank you for bringing this up. Indeed, previous studies have supported the use of educational brochures as a safe and effective deprescription tool for benzodiazepines, even in medical inpatients (Wilson et al.). There are a few motives for conducting a separate study for gabapentinoids. The high prevalence of chronic use in medical inpatients (1 out of 8) with the high rate of off-label use (<20% approved indications) makes this class of drugs a great target for deprescription. Furthermore, our experience has shown us that many users have little to no symptomatic benefit with these drugs. We therefore expect that the brochures will have a significant impact of deprescribing, possibly even greater than with benzodiazepines. However, deprescription of gabapentinoids has its own set of risks, including the risk of withdrawal symptoms or worsening pain control, which we will monitor during the study.

We hope that this study will show that educational brochures are equally effective and safe for gabapentinoids as previously reported for benzodiazepines, which will support their widespread use for other classes of drugs in medical inpatients (including PPIs, NSAIDs and opioids). This would ultimately support the creation of standardized deprescribing programs on medical wards using educational brochures.
This has been specified in the conclusion. (p. 15)

7. I give an annual pain-management course to our family medicine residents, during which I display PowerPoint slides of various disturbing gabapentin-related morbidities: confessions by gabapentin addicts; scandals involving promotions made by pharmaceutical companies; deaths related to combination gabapentoid / opiate / benzodiazepine use; etc. Then I go back to my office and resume prescribing gabapentoids to patients who are desperate for relief (pan, menopausal symptoms, etc). Hopefully not too often, hopefully temporarily (if ineffective), hopefully not to the elderly, and hopefully at low doses and avoiding dangerous combinations. As the authors correctly point out, there are many poor choices facing patients with chronic subjective conditions, and we are torn between avoiding harm, versus trying an endless array of weakly effective but dangerous medications.
Your statement highlights an important issue. Management of chronic pain is complicated and often suboptimal from the patient's point of view, with therapeutic options carrying a high risk of adverse effects. The objective of our work on gabapentinoid deprescribing is ultimately for patients and healthcare providers to regularly reassess the risks and benefits of gabapentinoids. Although a therapeutic trial of gabapentinoids might be reasonable in certain circumstances, we aim to highlight that these medications aren't benign and warrant ongoing monitoring for efficacy and side-effects.

Reviewer 2
General comments (author response in bold)

1. This is an uncontrolled before-and-after study design as the control group is identified as being the same study site (before the intervention was implemented). This type of design is subject to many bias (ie, staggered implementation, secular trends, etc). Design or analytical alternative could be used to better account for these limitations (interrupted time series, the use of controlled before and after design).
The study is currently enrolling and is close to 40% complete at this time, which limits the possibility of changes in the design.
To limit the risk of introducing bias from temporal trends we will be starting the intervention period 12 months after the beginning of the study. This should account for any trends in level of trainees and seasonal variations in medical staff workload. If the target number of 80 control participants is reached before the 12-month mark, recruitment will be suspended until then. (p. 8)
This has been clarified in the manuscript.
We have incorporated suggestions from other reviewers and will add adjustments in the analysis for the reason for admission and comorbidities.
This has been clarified in the manuscript. (p. 12)

2. As this is not an RCT, the TREND guidelines and checklist should be used to report this protocol (Haynes et al. JAMA Surgery, 2021).
The checklist has been changed to comply with the TREND guidelines

3. The study population is gabapentinoids chronic users that are admitted to the hospital. The abstract should mention this concept of the study question. It is also not clear if surgical patients are included in the study.
The abstract has been updated. (p. 3)
As specified in the Methods section, patients are recruited from the internal medicine clinical teaching units, which excludes patients admitted to surgical wards. Further clarification has been added in the manuscript. (p. 7)

4. According to page 6, line 54, the primary goal is "improving deprescription of gabapentinoids using a patient educational brochure ". This is not a hypothesis testing type of question, and it is more aligned with a quality improvement type of project. Please rephrase either the question or the design for it to be consistent with your primary aim.
The primary goal has been rephrased as "improving deprescription of gabapentinoids by 20% compared to usual care using a patient educational brochure designed in collaboration with the Canadian Deprescribing Network."
The modification has been made to the manuscript in this regard. (p. 7)

5. Some information is reported in the CONSORT checklist but not in the protocol. The protocol should be comprehensive with all the necessary information. The checklist should be brief with only the key points.
The necessary modifications have been made to the checklist.

6. Page 5, line 10: There is still uncertainty regarding the action mechanism of gabapentinoids; this should appear in the description.
Both gabapentin and pregabalin bind with high affinity to the alpha-2-delta subunit of voltage-gated calcium channels, as shown in in vitro studies. This has been shown to lead to reduction in release of glutamate, Substance P and norepinephrine in in vivo models.
Clarifications have been added to the manuscript. (p. 5)

7. Page 9, line 50: Regarding the control period event rate, it is not clear what event it is referring to. (prescription? deprescription ? use ?)
The event rate refers to the gabapentinoid deprescription rate at 8 weeks post-hospital discharge.
Clarifications have been added to the manuscript in this regard. (p. 11)

8. Page 7, line 16: Based on your screening and recruitment method, will some patients be excluded because of the timing of the admission (night, weekend)
Patients admitted and discharged over a single weekend (ex: admitted after Friday 8AM and discharged before Monday 8AM) will not be enrolled in the study, as there are no research assistants on-site during the weekend. However, given the typical length of stay on our internal medicine wards, we expect this will only represent a minority of cases. Furthermore, this will be an issue during both the control and intervention periods of the trial and therefore should not lead to any kind of differential selection bias.

Patients admitted overnight will be assessed for study eligibility by the research assistants on the following weekday morning.

9. Page 8, line 25: Although blinding of the patient would not be possible for this intervention, I think randomization (participant or center level) would be possible. As for contamination, this is also a challenge with before and after study design during the implementation period.
When designing the study, we felt that randomization at the participant or unit level would expose the results to a higher risk of bias.
The first issue is that physician staff and residents regularly rotate among the different clinical teaching units. Therefore, having 2 units simultaneously in a control and intervention phase could lead to increased deprescription rates in the control units. Indeed, it is plausible that residents having rotated recently in a unit where brochures are being distributed to inpatients might be more inclined to deprescribing gabapentinoids while rotating in a unit that is still in the control phase.
The second issue is the difference in patient populations among units. The Royal Victoria Hospital has a large oncology department and often admits patients with advanced malignancies. The Montreal General Hospital is a trauma and orthopedic centre and regularly admits patients with related complications such as skin and soft tissue infections. This will inevitably create heterogeneity in terms of indications for gabapentinoid use, which will likely impact deprescription rates among inpatients. By having each unit serve as its own control, we can mitigate this bias.
Although before-and-after studies are subject to bias from temporal trends, we will attempt to counter this by starting the intervention period 12 months after the beginning of the study. This should account for any trends in level of trainees and seasonal variations in medical staff workload. If the target number of 80 control participants is reached before the 12-month mark, recruitment will be suspended until then.
This has been clarified in the manuscript. (p. 8)

10. Page 8, line 45 : Why not involve nurses and pharmacists in this monthly basis information ?
Nurses and pharmacists have been informed of the nature of the study via a newsletter sent by the head of each participating clinical teaching unit.
We've decided to only include staff physicians, residents and medical students for the monthly teaching sessions given their high turnover on the clinical teaching units. We want to ensure that they are familiar with the study and the brochures, as they will be the main members of the medical team involved in the deprescription process.

11. Other: please define the duration of the control and the intervention period. There could also be a period in-between to mitigate bias from staggered implementation.
The intervention period will start 12 months after the beginning of the study to limit any bias from temporal trends. If the target number of 80 control participants is reached before the 12-month mark, recruitment will be suspended until then. The intervention period will end once the target number of 80 intervention participants will be reached. (p. 8)

12. Page 9, line 10: How is the follow-up questionnaire administered (phone vs. in person?) Can a caregiver provide the information? Some information reported in ethical concerns should also be part of the data collection.
The follow-up questionnaire will be administered over the phone by the research assistants. Clarifications have been added to the manuscript in this regard.
As we will be excluding from the trial individuals unable to consent for themselves, we plan to administer the questionnaires to the patients directly and not via a proxy, such as a caregiver. Clarifications have been added to the "Ethical Concerns" section. (p. 10)

13. Which score will be used to evaluate global functioning? What is the minimum and maximum value, was it validated?
The questionnaires used to assess pain, cognition and global functioning are adapted from questionnaires of the Patient-Reported Outcomes Measurement Information System (PROMIS) bank which have been previously validated. This information has been added to the manuscript, along with the citations for each questionnaire.
The global functioning questionnaire in the study has 4 items, with a minimal total score of 4 and a maximal total score of 20, with higher scores indicating better functioning. (p. 10)

14. Page 10, line 13: perhaps sex also? What is meant by type of gabapentinoids prescription? (is it the class of drug, pregabalin vs. gabapentin?)
We've collected data related to gender defined as "male" or "female". However, "sex" might be the more appropriate term here, as we're referring to the biological aspects of the participants. The modifications have been made to the manuscript in this regard. (pp. 10, 12)
By "type" of gabapentinoid, we are referring to pregabalin vs. gabapentin. (p. 12)
This has been clarified in the manuscript.

15. Page 11, line 21: why not include comorbidities, co-prescriptions and baseline residence type as covariates for adjustment in your model? How were these potential confounding covariates chosen?
We have incorporated suggestions from other reviewers and will add adjustments in the analysis for the reason for admission and comorbidities.
This has been clarified in the manuscript. (p. 12)

16. How are death and loss to follow up analyzed?
For the primary outcome, we will perform a sensitivity analysis for patients lost to follow-up or having died using the most recent available data on their gabapentinoid use (inpatient pharmacy records, discharge prescriptions or the provincial electronic medical record *Dossier Santé Québec*). (p. 12)
Clarifications have been added to the manuscript in this regard.