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Title	Benzodiazepine receptor agonist and Z-drug dispensations in Alberta: a population-based descriptive study
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Reviewer 1	Kate Smolina
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General comments (author response in bold)	1. Literature review is not extensive and missing some key and relevant studies (example: there are two recent studies from BC on this topic that should have been cited instead of the 2006 one: http://cmajopen.ca/content/5/1/E52.full and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916346/) **Please see response to editors comment, #1.** 2. Study population - why start at 10? The authors cite clinical practice guidelines in the intro that only apply to those 20 and older. **We agree that clinical practice guidelines only apply to adults. However, we still wanted to present information for individuals younger than 20 years of age for descriptive purposes, even though we may not be able to make statements related to appropriateness. Moreover, age 10 was recommend by the College of Physicians and Surgeons in the province for 2 reasons: First, the rationale for this cut point was not necessarily utilization of BZRA's in children per se but more related to the fact that the College has had concerns of abuse of BZRA's by parents (i.e., using children to obtain BZRA's prescriptions for abuse by adults). Second, there is an increasing body of literature indicating that teenagers are abusing BZRA's and other prescription medications. As result, we felt that the use of these drugs in the younger age group was warranted.** **We have included a sentence in the limitations section of the discussion (lines 267-270) which states,** **"Additionally, clinical practice guidelines for the appropriate use of BZRA's typically apply to the adult population alone. We have included individuals younger than 18 years of age in our analysis as an increasing body of literature suggests the BZRA's are a class of medications increasing being abused by this age group. However, we acknowledge we are limited in our ability to draw conclusions around appropriate use in this age group."** 3. Why not use Diazepam Equivalents instead of DDDs? **We agree that diazepam equivalents is a suitable alternative to defined daily dose, however, most of the descriptive papers published in this area use DDD's, therefore, for comparison purposes, we opted to present DDD's. If the editors have a strong preference for the presentation of diazepam equivalents we would be happy to provide in a subsequent revision.** 4. Unclear how DDDs were calculated for overlapping prescriptions - were they added? **DDD's were never calculated for overlapping prescriptions; the only place that DDD's are presented in the manuscript are Table 1, which specifies that the level of analysis is at the dispensation level rather than at the individual level.** 5. 3-day gap supply seems too short. **We conducted additional analyses to better understand the impact that extending this gap to 7-days would have on the main results of our analysis and found that it did not significantly impact our main measures such as days of consecutive use.** **We have included this additional analysis in our methods section (lines 127-128) which reads:** **"We also conducted a sensitivity analysis in to determine the impact that extending this gap to 7-days would have on our findings related to days of consecutive use."** **And have added the following sentence (lines 177-179-) to our results section,** **"We did not observe substantial differences in our days of consecutive use measures when we altered our definition to include a gap of 7 days rather than 3 days."** 6. Results presentation is lengthy and yet too simplistic. Reporting specific measures is not as meaningful for interpretation as summarizing the extent of inappropriate use (i.e. meeting at least one criteria - or multiple - in a population) in a way that is clinically meaningful and easy to understand. **We have made efforts to reduce the length of the results and make the reporting more straight forward and easy to understand. We have cut down table 2, removed most of the figures, and have re-written the results section.** 7. Given that these medications are more often prescribed to men than women, a greater analysis and discussion of sex and gender aspect to this would have been helpful. **Thank you for your comment. We believe that the reviewer meant to say that these medications are most often prescribed to women, not that they are more often prescribed to men. Moving forward with this assumption, we agree that important differences in the prevalence of use between men and women do indeed exists, however, we did not observe any differences in any of our indicators (other than prevalence of use) between men and women. This is acknowledged in the results section of the paper.** **We have included the following sentence in the discussion section of the manuscript (lines 231-235) in order to explore this important issue related to prevalence of use further.** **"Our study was similar to others in that prevalence of use was higher amongst females compared to males.[13,15] Although additional studies are required to explore differences in prevalence of use according to sex, it may be explained in part by biological differences in the prevalence of conditions which are indications for BZRA treatment or differences in health services use such as the frequency of visits to healthcare providers."** 8. Graphs are fairly simple and do not offer much new insight **We have removed all figures except Figure 1 from the analysis.** 9. Table 2 is too long and difficult to navigate. It doesn't identify problematic thresholds that would be indicative of inappropriate prescribing. **We have significantly cut the results presented in Table 2 and have also attempted to make thresholds for potentially inappropriate use more clear.** 10. Discussion - "our study is the first to characterize consecutive/concurrently daily use of BZRAs..." I am not convinced that this statement is entirely accurate. There have been many studies on this topic. **We have removed this sentence from the discussion of our analysis.**

	11. Discussion - a more comprehensive literature review is necessary to support the statement that results of this study are generalizable across Canada. **On further reflection, as well as in light of our expanded literature search, we have removed the section on generalizability across Canada as is seems as though prevalence of BZRA use does indeed appear to differ from province to province. In order to address this, we have included an additional sentence to the discussion (lines 235-245) which states,** **"However, our results differed from a study of older Quebec residents in that fewer residents filled concurrent prescriptions in Quebec than in Alberta. Moreover, a recent study of BC residents over the age of 65 found that women were more likely to receive inappropriate benzodiazepines prescription than men, however, we did not find differences in measures of potentially inappropriate use according to sex. Black et al observed substantial differences in prevalence of use of BZRA's between provinces for older adults. The authors suggest that although access to drug classes through public drug programs is generally similar across most provinces, based on a search of relevant formularies, utilization differences are likely driven by factors unrelated to formulary listing, such as stricter policies around prescribing of these medications and mandated monthly clinical reviews of continued used.[19]"**
Reviewer 2	Dick Bijl
Institution	Utrecht, Netherlands
General comments (author response in bold)	1. Page 7/24.Line 26. It is a pity that the data-base doesn't contain the diagnoses related to the prescriptions. **We agree with the reviewer, indication for BZRA use would have been very informative for our analysis. Unfortunately we were limited to the information available in the PIN database.** 2. Page 9/24.Line 23 It is not really interesting whether it is a primary, secondary or tertiary analysis. It is not a trial so you can analyse anything you want. **We have removed this section of the sentence.** 3. Page 12/24. In the discussion the authors should make a broader review of who is participating already in this enormous health problem. So, mention the actions of Health Canada on the dosage of z-drugs. Also, Therapeutics Initiative has written about this. **Thank you for your comment. We have included an additional section to the discussion (lines 207-210) which states;** **"At the federal level, Health Canada issued guidance on the dosing of z-drugs recommending that the starting dose of zopiclone be reduced to 3.75 mg daily, the maximum daily dose of zopiclone be reduced to 7.5 mg in healthy individuals, and to 5 mg in the elderly or those with renal or liver failure."** 4. It may be that effective tools exist, yet the problem gets bigger every year in a lot of Western countries. Mention also that for many people it is very difficult to stop these drugs, e.g. The sedated society by James Davies. At the start of prescribing benzo's or z-drugs doctors must inform patients that it can be extremely difficult to stop these drugs. **We agree with the reviewers comments. We have included an additional sentence to the discussion (lines 199-202) which states:** **"It should still be acknowledged, however, that for many people it is very difficult to stop taking BZRA's once they've started.[25,26] Communicating to patients the potential for addiction and difficulty stopping these medications is likely warranted upon initiation of BZRA's."** 5. Page 14/24. Line 36. This underlines the necessity to write the indication on the receipt. **Yes, we agree with the reviewers comment.** 6. Line 41. The authors should convince the readers and show the numbers of patients with epilepsy. **We have included the prevalence of epilepsy at the population level in Canada in line 266-267 of the discussion which now reads,** **"However, at the population level, we would expect this to account for a small proportion of individuals (0.4% of the Canadian population in 2012).[30]"** 7. Page 17-18/24. **Many references contain more than 6 names.** **This was reference style dependent and we are happy to change this at the request of the editors.** 8. There are 3 references (2, 4, 19) published in supplements which in most cases are not peer reviewed and should not be used. **We acknowledge that these references are not peer reviewed, however, they come from reputable sources and we believe they still provide important information for the current study in terms of local prescribing practice and guidelines.**