Author's response to reviews

Title: Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review

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Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review

Dear BMC Pharmacology and Toxicology Editors;

Thank you kindly for considering our manuscript for publication in BMC Pharmacology and Toxicology. The paper appears to have been well received by reviewers and we are grateful for their time and constructive comments. We have gone through the comments and responded to each item individually and indicated any changes. Within the manuscript, we have highlighted in yellow any amendments made in reference to reviewer feedback, while changes in syntax are indicated in blue font. On the next pages you will find a point-by-point description of the changes made.

I trust that we have responded in full to the reviewers’ comments and we look forward to hearing from you further.

Sincerely,

[Signature]
André Pollmann, on behalf of all authors
Response to Reviewer’s Comments
We would like to thank all reviewers for their time and their comments and suggestions for improvement of this manuscript. We have addressed each point below and highlighted (in yellow) the changes in the revised manuscript.

Reviewer 1
Major Compulsory Revisions

1) Why did authors limit this review to community-dwelling people only? Why not consider other settings – e.g. residential aged care?

Response: Our choice to include only community-dwelling people was based on several factors. Although people who are considered “community-dwelling” can still receive significant supports from the formalized health care system, our tacit and research-based knowledge informs us that there are distinct differences in the contexts for those with short- or long-term stays in the institutional (e.g., hospital) or residential-care settings versus those living in the community. There can also be significant differences in treatment goals for medicines, such as benzodiazepines, in which frailty, quality of life, and complexity of multiple comorbidities can impact the initiation, maintenance, and discontinuation of prescription medicines. The goal of our work in this review is to 1) provide knowledge on what exists through mapping and characterizing the literature and 2) to make recommendations and suggest directions for where future research is needed for those living in the community. From a very pragmatic perspective that is informed on current incidence and prevalence trends with the use of these medicines, benzodiazepine and Z-drug discontinuation in community-dwelling individuals warrants attention. Building knowledge for this population may in fact serve to contribute to preventative solutions for long-term benzodiazepine use, including in individuals that will transition among contexts including institutions (e.g., hospitals) and long-term care or aged care facilities. We have now clarified our choice of target population for the review by expanding on our rationale in the ‘Methods’ section (starting at line 105):

“We limited our target population to patients taking benzodiazepines and Z-drugs in the community or outpatient settings as individuals receiving care in inpatient, long-term care, or residential aged care facilities can differ systematically with respect to numerous factors. These factors include, but are not limited to, the context of the environment, frailty, nature and number of illnesses, and treatment goals.”

2) It is unclear from the methods which patient subgroup was targeted. Is it older people only (>65 yrs) or adults aged over 18 years of age?

Response: The intent of the review was to examine adults 18 years of age and older. We have included clarification of this by editing the ‘Study Selection’ section under ‘Methods’ (line 141):

“We included those studies that were published in English and investigated or discussed methods for discontinuing benzodiazepines and sedative hypnotics in community-dwelling individuals aged 18 years and older.”

3) Should you list ‘key words’ used to search for articles?

Response: We agree that key words could be helpful and have now included a list of those used for the literature search. The sentence in the ‘Definitions and Search Strategies’ section, starting at line 125 has been amended:

“Systematic combinations of the medical subject headings “benzodiazepine”, “hypnotics and sedatives”, “substance withdrawal syndrome”, “dependency”, “sleep disorders”, and “anxiety disorders” were used in together with the
keywords “hypnotic”, “sedative”, “zopiclone”, “eszopiclone”, “zolpidem”, “zaleplon”, “withdraw*”, “deprescrib*”, “taper”, “stop”, and “discontinu*”. Search terms were translated as appropriate for each database.

4) Why were narrative reviews included in this scoping review? I would not anticipate for original research to be reported in a narrative review.

Response: Narrative reviews are eligible for inclusion based on one of the most widely cited frameworks for undertaking a scoping review by Arskey and O’Malley (2005). The goal is to attempt to be as comprehensive as possible in the searching for available information, which includes many sources of evidence such as other reviews and grey literature. We intended to map and characterize the existing literature regarding benzodiazepine and Z-drug deprescribing strategies, which would include non-experimental literature. This is important for our topic area given that clinicians and people taking benzodiazepines can find information of lower levels of evidence and use these to contribute to decision-making about medicines. For this reason, we wanted to describe the broad difference in recommendations that originated in review articles versus original research. Inclusion of review articles with lengthy reference lists also facilitated the discovery of other citations that added to our search results. In order to clarify this, we have added the following sentence, starting at line 149:

“Original investigations, research syntheses, guidelines, and narrative review articles were all eligible for inclusion in order to capture potential differences amongst these publications with respect to benzodiazepine and Z-drug deprescribing recommendations.”

5) Results section on deprescribing strategies – I think it’s more appropriate to say that RCTs is a study design used to assess the impact of interventions on reducing exposures not a ‘deprescribing strategy’.

Response: The first sentence of the section ‘Deprescribing strategies’ (starting line 222) has been amended to state:

“Among original research studies, pharmacologic interventions were the most common types of interventions assessed for their impact on reducing benzodiazepine and Z-drug exposure…”

6) In relation to my previous comment, I suggest authors expand on what various interventions entailed in terms of their approaches to reduce sedative drug use. Have any of the interventions assessed impact on clinical outcomes? Any evidence to suggest that either intervention type is safe and effective?

Response: We have added two columns to Table S2 to show the outcomes that were studied in the literature and the corresponding direction of the effect size. Also, Table 2 has been amended to include information on the interventions (also addresses a question that follows). For many studies, the information reported on the intervention lacked a substantial amount of details and few to no articles used standardized reporting criteria or other mechanisms regarding the description of their intervention (e.g., WIDER, TIDieR, etc.). Further, a main goal/purpose of the scoping review was to map and characterize literature and to identify potential gaps and areas of further study. We have commented generally on the direction of effect of the interventions but the intention was not to do a quality assessment of studies for the purpose of meta-analyzing data. We are therefore not able to say with any degree of certainty that one strategy is more effective or safer than another.

7) Table 1 could go into appendix. Also, the table could be improved by summarising the actual intervention approach used to deprescribe sedatives.
Response: Table 1 is in keeping with other tables published within the main text of scoping reviews and we think it provides a concise overview of the characteristics of the literature in this topic. However, we do agree that the table’s utility for readers is improved by summarizing the actual deprescribing interventions utilized in original research and discussed in non-original articles. Based on this feedback and feedback from another reviewer, we have added this data in a separate table located near the end of the manuscript (Table 2).

8) Figure 1 is somewhat consuming. What do you mean by ‘mixed’ and ‘other’ interventions?

Response: Figure 1 quantifies and illustrates the search process and outlines how articles were selected for inclusion in this review. The terms ‘mixed’ and ‘other’ interventions appear in Figure 2, which is intended to show the distribution of RCT evidence for different methods of reducing benzodiazepine and Z-drug exposure. While the majority of RCTs are in the area of pharmacologic interventions, the majority of study participants have actually been enrolled in trials investigating “other” methods of deprescribing sedatives. Figure 2 has been removed and replaced with Table 2, based on the suggestion of another reviewer. We acknowledge that it is difficult to interpret what we mean with ‘other’ and ‘mixed’ interventions and we have expanded on our definitions for these terms in the ‘Definitions and Search Strategies’ section beginning at line 114:

“We classified pharmacologic interventions as those adding additional drug therapy (non-benzodiazepine or Z-drug) to facilitate discontinuation of the sedative or mitigate withdrawal symptoms. Psychological interventions were those utilizing behavioural techniques, such as cognitive behavioural therapy (CBT), to reduce benzodiazepine or Z-drug use. We categorized studies as mixed interventions if they compared various pharmacologic, psychological, or other interventions with each other. GDR included employing a taper regimen or switching between sedatives to facilitate benzodiazepine or Z-drug withdrawal. The remaining intervention types not falling within these categories were classified as ‘other’ (i.e., letter or brief consultation).”

9) Discussion section – suggest to delete first sentence or move to results section.

Response: We believe it is best suited at the start of the discussion as it introduces the contrast between the quantity of studies in our scoping review compared to other previously published research syntheses.

10) What do you mean by this sentence ‘The meta-analytical approach, which aims to answer a specific clinical question, is a narrower approach and therefore ignores a substantial amount of knowledge on this topic, albeit from lower levels of evidence’?

Response: This sentence is intended to communicate the difference in objectives between scoping reviews and meta-analysis. Meta-analyses generally aim to answer a specific question and have strict inclusion criteria often limited to RCTs. While they offer an accurate answer to a specific question and aggregate data from higher quality studies, meta-analysis lack the ability to answer other related questions. Scoping reviews have less stringent inclusion criteria and no formal quality assessment occurs. The scoping review is able to describe the nature and extent of the literature but, because of the broader approach, findings cannot be used to recommend policy/practice. We have re-constructed the sentence to better communicate the intended message (starting at line 279):

“While meta-analyses of data can offer valuable answers to specific research and clinical questions, the strict inclusion criteria based on study methodology and quality can limit the amount of information they provide on the research area as a whole. Research and publications that would be characterized as lower levels of evidence in hierarchies (Atkins 2004, Guyatt 2000, Guyatt 1995) (e.g., non-randomized trials, guidelines, narrative reviews) can be captured in scoping reviews,
which is important in many clinical questions given the kinds of evidence that inform clinicians and patients in decision-making.”

11) I would like to see some recommendation for future studies in the conclusion section.

Response: We agree with this suggestion and have added our two key suggestions for future studies into the conclusion, starting at line 355:

“Future studies in this area should describe interventions in sufficient detail, including information on various behaviour change techniques, to allow for their replication in research and clinical practice. This process could be facilitated by the use of standardized reporting guidelines and various checklists that currently exist (Albrecht 2013, Hoffmann 2014). More research regarding the impact of deprescribing strategies on patient-centered in real-world settings is required.”

Reviewer 2
Minor Essential Revisions

1) In the Abstract, the Background section should be expanded, in particular as regards the first sentence “Long-term sedative use is prevalent and associated with significant morbidity”.

Response: The background section of the abstract has been modified and expanded. Starting line 30:

“Long-term sedative use is prevalent and associated with significant morbidity, including adverse events such as falls, cognitive impairment, and sedation. The development of dependence can pose significant challenges when discontinuation is attempted as withdrawal symptoms often develop. We conducted a scoping review to map and characterize the literature and determine opportunities for future research regarding deprescribing strategies for long-term benzodiazepine and Z-drug (zopiclone, zolpidem, and zaleplon) use in community-dwelling adults.”

2) In the Background, epidemiological data from more than one single country should be provided and clearly indicated in the text (i.e., what does it mean that “benzodiazepines are extensively prescribed medications”?). Moreover, prevalence rates of long-term use of benzodiazepines in clinical practice should be provided.

Response: We have noted these suggestions and revised the background section by describing epidemiological data from several countries. The sentence beginning at line 59 has been amended and now reads:

“The annual incidence of long-term benzodiazepine use across North America and Europe is estimated to be between 0.4% to 6%, with higher rates of chronic use in patients older than 65 years (Tannenbaum 2014, Cunningham 2010, Lagnaoui 2004, Alessi-Severini 2014).”

3) As regards the reasons for chronic use of benzodiazepines, only two studies are cited. This is a very important issue, strongly related to the relevance of the present paper, that should be expanded and commented on.

Response: We have added three key references and expanded the discussion of factors that may influence long-term benzodiazepine and Z-drug use. Research by Martinsson and colleagues (2012) suggests that specialized knowledge about benzodiazepine prescribing may be lacking in physicians who prescribe this drug class most frequently. Everitt et al. (2014) surveyed physicians and found that sedatives are often prescribed in favor of alternate treatments such as CBT and sleep-
hygiene. Cook et al. (2007) provide further support that patients may be reluctant to stop these medications. The paragraph (starting line 68) now reads:

“Several prescriber related factors are believed to influence this process. These factors may include the prescriber’s attitudes toward these medications and toward the ‘deserving’ patient, deficits in specialized knowledge about sedative prescribing, the clinical work environment, conflicting patient health priorities, and the prescribing practices of others involved in the patient’s care (Sirdifield 2013, Martinsson 2012). The perceived or real inaccessibility to alternative treatment modalities may further encourage the renewal of benzodiazepine and Z-drug prescriptions in favor of initiating other interventions that are perceived as less effective (Everitt 2014). Patient factors including disagreement with appropriateness of cessation, fears of symptom return, withdrawal experiences, and the impression of unsuitability of alternatives also act to promote continued use (Reeve 2013, Cook 2007). Considering the highly varied contributing factors that lead to long-term benzodiazepine and Z-drug use, discontinuation or deprescribing strategies will need to be flexible and acceptable to both patients and clinicians.”

4) In the Methods, in the paragraph “Definition and search strategies”, the authors should define the range of search. Moreover, keywords entered in the search must be reported.

Response: As per the previous reviewers comments, we agree that key words could be helpful and have now included a list of those used for the literature search, starting at line 127. We are interpreting the “range of search” to include the keywords, dates, and databases. In addition to the key words described above, the dates can be found at line 125 and the databases are found starting at line 133. Please clarify further if more information is warranted.

5) In the Methods, in the paragraph “definition and search strategies”, as well as in the paragraph “Collating, summarizing and reporting results”, Table S1 should be cited.

Response: Additional file 1 (Table S1) is now cited at lines 105 and 162.

6) In the Methods, in the paragraph “Collating, summarizing and reporting results”, the authors report that “an abstract meeting was held to outline the process and model how to characterize intervention functions to establish consistency among seven members”. In Table S1 team members seem to be four people (AP, AM, DG, JB). Please clarify.

Response: This inconsistency stems from assistance we received from some of the additional collaborators listed in the acknowledgment section of the manuscript. We realize now that this creates confusion for potential readers, so we have 1) replaced the word “seven” with “team” at line 179 in the text and 2) added “(n = 7)” and “additional team members” to the appropriate cells in Table S1.

7) In the Results, the authors report that “only three studies exclusively examined strategies for stopping Z-drugs. The remaining...” but it is not clear which is the total amount of papers they are referring to. Please, specify it.

Response: The sentence refers to original research trials. This has been specified and the sentence has been amended to (starting at line 210):

“Only three (4%) of 74 original studies exclusively examined strategies for stopping Z-drugs. The remaining...”

8) In the Results, please clarify that effectiveness of the interventions has been evaluated regardless the type of the intervention.
Response: This has been clarified at line 214:

“The general direction of effect for the endpoint of discontinuation of benzodiazepine or Z-drug therapy was noted for each research trial, regardless of the type of intervention studied.”

9) In the paragraph “Deprescribing strategies”, authors should consider to insert three different subheadings such as “Pharmacological interventions”; “Psychological therapies”; “Mixed interventions”.

Response: Headings have been inserted in this section as suggested.

10) In the Results, in the paragraph “Deprescribing strategies”, the allocation of identified studies among “Pharmacological interventions”, “Psychological therapies” or “Mixed interventions”, is not clear. The authors should report another box in the flow-chart, indicating the number of studies for each category. Actually, the global amount of papers (and its percentage) is of 64 studies (percentage 87%), but the authors analyzed 139 papers, grouped in 74 original studies and 65 non-original studies. The authors should clarify it and consider to summarize such results in a figure or in a table.

Response: This suggestion has been noted and we have developed a Table 2 titled “Benzodiazepine and Z-drug deprescribing strategies studied or discussed in publications” (inserted after the references section). We have outlined clearly the allocation of studies into different categories and provided denominators to show how percentages were derived. The table has been cited throughout the paragraph ‘Deprescribing strategies’.

11) In the paragraph “Intervention functions”, Table S2 should be cited. Moreover, the description of each kind of intervention should not be reported in the results and should be moved to the methodology section.

Response: Additional file 2 (Table S2) has been cited at line 267. The description of the various intervention functions has been moved to the methods section (starting line 165).

12) In the Discussion, the sentence “Pharmacological interventions were the primary discontinuation strategy in the majority of the studies within meta-analyses” deals with a very important finding of the present scoping review and should be stressed and commented on. I would suggest the authors to comment the different analytic approach adopted. Subsequently, they should discuss the finding that pharmacological strategies were the most frequently endorsed strategies.

Response: This feedback has been addressed by expanding on the discussion of findings about pharmacologic interventions from our review (starting line 290):

“Pharmacologic interventions have been the primary discontinuation strategy reported on in the majority of studies within previous meta-analyses (Parr 2009, Oude 2006, Mugun 2011). Likewise, our scoping review found that the addition of pharmacologic agents to facilitate discontinuation has been the most commonly studied type of intervention in RCTs (31 trials, totaling 2273 patients). This method of discontinuation may be counterintuitive to both prescribers and patients as risks for different adverse events and increased costs are inherent within this approach. Despite the majority of trials studying this method, non-original review articles and guidelines included in our scoping review did not discuss this approach as frequently. This is especially important to consider given the large degree of variability and tensions that can exist with the use of different forms of evidence in clinical decision-making (Lewis 2009, Swennen 2013, Murphy 2006).
Depending on the practitioner, guidelines and narrative reviews may be significantly influential in decision-making. Patients will also inherently use various forms of information about medications in their decision-making, much of which will not necessarily include information from clinical trials but that is readily accessible on the internet (Kravitz 2013).”

13) In the Discussion, second paragraph, as regards the sentence “estimates of effect were mixed, with 47% positive, 41% negative, and 12% undetermined, resulting in a lack of clarity for how to best deprescribe benzodiazepines and Z-drugs”, the authors should describe and comment on their finding more extensively. It should be highlighted that the global estimate of the effects is not referred to a specific intervention.

Response: The sentence beginning at line 304 has been amended to clarify that the estimate of effect direction does not refer to a specific type of intervention:

“Estimates of effect size direction, while not attributable to a specific intervention or intervention type, were mixed, with 47% of trials being positive, 41% negative, and 12% undetermined, resulting in a lack of clarity regarding how to best deprescribe benzodiazepines and Z-drugs.”

14) In the Discussion, the authors should stress the importance to carry out real-world studies in order to assess the impact of long-term use of BDZs on patients with several comorbidities.

Response: The suggestion has been noted and incorporated into the discussion at line 335:

“Future research should determine the specific harms associated with long term sedative use, especially in vulnerable groups (e.g., frail adults, patients with multiple comorbidities), and aim to identify which patients benefit from benzodiazepine and Z-drug discontinuation in terms of quality of life, morbidity, and mortality.”

15) In the Discussion, fourth paragraph, the authors should include some references regarding the fact that existing studies did not assess the impact of BDZs discontinuation on quality of life.

Response: Thank you for this comment. We agree with the revision and have altered the sentence structure and added a reference. The statement originated from our impression of the literature as a whole that was captured in our scoping review. We have subsequently found two relevant studies by Curran et al. (2003) and Lopez-Peig et al. (2012) that did evaluate quality of life related outcomes in elderly patients after stopping benzodiazepine therapy. Starting line 333:

“To date, the outcome of interest in benzodiazepine and Z-drug deprescribing research has largely been whether or not treatment was successfully stopped. Clinical outcomes such as impact on reducing falls, fractures, quality of life, and mortality have been evaluated less frequently (Curran 2003, Lopez-Peig 2012).”

16) I would suggest authors to replace figure 2 with another figure or table, since it is not very useful for the manuscript. In particular, it is not clear the reason why on vertical axis only RCT are reported as well as why each column is subdivided according to group age. Moreover, in figure 1 the caption should be provided.

Response: Figure 2 has been removed and we feel that the new Table 2 is a suitable replacement as it outlines the types of interventions and number of studies. Figure 2 was intended to show the disproportionate number of relatively small RCTs investigating pharmacologic deprescribing strategies compared to other intervention types. The caption for Figure 1 is provided at line 833 near the end of the manuscript.