PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Patterns of benzodiazepine prescription among older adults in Switzerland: a cross-sectional analysis of claims data
AUTHORS	Luta, Xhyljeta; Bagnoud, Christophe; Lambiris, Mark; Decollogny, Anne; Eggli, Yves; Le Pogam, Marie-Annick; Marques-Vidal, Pedro; Marti, Joachim

VERSION 1 – REVIEW

REVIEWER	Michael Schoenbaum National Institute of Mental Health
REVIEW RETURNED	04-Jun-2019

GENERAL COMMENTS	This paper examines an issue of clinical and public health importance, patterns of use - and possible misuse - of benzodiazepine medications in Switzerland. As the authors describe, research elsewhere has documented high rates of benzodiazepine prescribing, especially among women; and various ways in which benzodiazepine prescribing is likely to be inappropriate at a population level, including that prescribing rates rise consistently with age (although risks of adverse cognitive and physical effects of benzodiazepines also rise with age), and of high-volume and/or long-term prescribing (although, with the possible exception of treatment for seizure disorders, benzodiazepines are only appropriate for short-term or occasional/as-needed use). Documenting patterns of benzodiazepine prescribing in Switzerland could help inform clinical quality improvement efforts there, and, as the authors describe, perhaps also generalize to certain other high-income settings. That said, I have several concerns about the current paper, which I think the authors can and should address. Most fundamentally, although the title and text focus specifically on benzodiazepines, in fact the analyses cover not just benzodiazepines but also non-benzodiazepine hypnotics. I find this problematic, both for the exposition (the first place where the authors mention that their scope includes non-benzo hypnotics is at the end of the "data sources" section of Methods, at the top of page 6 - after literally dozens of uses of the term "benzodiazepine," beginning with the title), and in terms of substance (while the clinical indications for benzodiazepines and non-benzo hypnotics, respectively, overlap to some extent - since some benzos are indicated or used for sleep - they mainly do not, since patients modally use benzodiazepines while they are awake, and non-benzo hypnotics in order to sleep). Empirically, per supplemental file 2, the single most commonly prescribed drug in the current scope of this study is zolpidem - accounting for 1/3 of *all* prescriptions considered here - and of course this drug is not a benzodiazepine.

	In my view, the primary analyses here should separate benzodiazepines from non-benzo hypnotics, respectively. Given the current content, simply excluding non-benzo hypnotics would require the fewest changes to the text, because nearly all of the current background & discussion - and the associated references - focus on benzodiazepines. (I do recognize that non-benzo hypnotics account for approximately 40% of all the prescriptions examined here, so the benzodiazepine-only dataset will be smaller. But that's just the way it is here.) If the authors also want to present information about non-benzo hypnotics, I think they need to add some additional background & motivation, since again I think nearly all the current supporting text focuses on benzodiazepines. More specific comments: Abstract, Participants - listing "Adults >= 65 years" is not sufficient information. Also, why does this study look only at patients 65+, vs. some wider age range (e.g., 50+, 20+, etc)? Abstract, Results (and throughout the paper) - In my view, reporting odds ratios (i.e., exponentiated coefficients from multivariate logistic regression) is not sufficient. In my view, I think it's important (also) to provide information on standardized rates, e.g., the estimated % with benzodiazepine use for individuals with high vs. low deductibles, all else equal, or for different Swiss cantons, etc. The authors can compute this, since they have access to the data and to the regression output, whereas readers can't calculate this themselves, and can't even readily approximate it. Introduction, framing about appropriate benzodiazepine use - the authors mention the inappropriateness of use "for a long period of time," and of guidelines discouraging "prolonged" use. In my view, I think this may understate the threshold for misuse: as above, my understanding is that anything beyond short (e.g., a few weeks) or occasional use is associated with high risk of habituation, at which point continued use provides reduced or even no clinical benefits while withdrawal/discontinuation is difficult and potentially risky. In the same sense, stating that "benzo use for >120 days or at dose levels more than 2x recommended may be potentially problematic" strikes me as too mild; as I understand it, such use is contraindicated, and risky in various ways. Methods, data sources - Do I understand correctly that the health plan studied here has a national market share of 1.4 million / 8.4 million = 17%? And that the study cohort is: all, i.e., a census, of members of this one health plan who were 65+ in 2017 and lived in the 9 cantons that do not permit clinician-dispensing of prescriptions? Methods, ethics - is "anonymous" patient data accurate? Or might the data be "de-identified"? Results, Table 1 - I recommend adding a column for "All enrollees," alongside the N and % columns, that reports [% with any benzodiazepine prescription in 2017]. This is the univariate information corresponding to the information on standardized % from the multivariate logistic regression that I requested above. Also, please add a row for "Male" (it isn't currently needed, but will

	be necessary once one adds the column for [% with any benzo Rx]. Finally, the authors need to use a chi-squared test to examine whether the distribution of beneficiaries between categories of a given domain (e.g., age group, canton, insurance plan, deductible, etc - in short, any domain that involves more than 2 options) differ statistically between users vs. non-users. Except for dichotomous characteristics, such as gender, It is inappropriate to use a t-test for each each individual row, as the table currently presents. Results, "In all cantons, prescription rates increased with age..." - per the Figure, there is actually one canton of these nine where this pattern does not hold. Results, "Among users, 36% had at least one Rx of antidepressant or antipsychotics during the same calendar year." - I think this warrants elaboration. Benzodiazepines are contraindicated as a treatment for depression (although antidepressants are also indicated for anxiety, which I expect is the modal use for benzodiazepines). Both benzodiazepines and antipsychotics are contraindicated among older adults with dementia, although the use of both these drug classes is unfortunately common among dementia patients as a kind of chemical restraint. Discussion, "Latin speaking cantons" (this is used in two places) - I actually have no idea what this refers to! I don't recognize German, French, Italian or Romansch as "Latin." Discussion, "higher Rx rates among women, which may be explained by a higher prevalence of anxiety disorders in women." I'm uncomfortable with this wording, since I think there are (many!) possible alternative explanations, and the current paper doesn't include any findings that support one more than others. Discussion, "Is it driven by patient demand or by physician supply, with a minority of doctors initiating such treatments?" First, I think the issue in the second part of this sentence is distinct from the issue in the first part. Second, I'd think that the dataset the authors use here - or anyway, health care claims data - could be used to examine the 2nd part of this sentence (although not the first). In which case, perhaps the authors could do this?

REVIEWER	E. McDonald McGill University Health Centre Canada
REVIEW RETURNED	24-Jun-2019

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript. This is an important topic and you have a great wealth of data to analyze here and to tell an interesting story about prescribing patterns of sedatives in Switzerland. I have some concerns about the the statistics and how the data are displayed. The results section is in need of a review as I think there are several calculation errors, the denominators are not appropriately selected and the the results are difficult to interpret and questionable as presented. Abstract: For the objective, could you have it match more with the outcomes? Participants: include that they are outpatients please (not

	hospitalized/community dwelling) What is highest deductible level of CHF? (not common term for all readers/avoid acronyms) Add to the conclusions that use is high, is associated with trauma and healthcare expenditures, with variability across cantons, suggesting regional/prescriber directed interventions could address overuse. Introduction: I would remove this qualifier: Despite proven beneficial effects Would remove “problems associated with discontinuation” (stated already with withdrawal symptoms) and include problems related to dependency, traumatic falls and fracture, remove confusion (already stated with problems with cognition), and add in death/hospitalization (these are reasons for healthcare expenditures directly related to the drug). Add a reference for this statement: Despite the lack of evidence supporting their use beyond short periods, benzodiazepines are often prescribed for longer periods than recommended, particularly among those aged ≥65 If including these studies in the introduction: In 2017, Bietry et al. examined the association between prior benzodiazepine use and the risk of developing Alzheimer disease in the Swiss population 22. Another qualitative study examined high-dose benzodiazepine users’ perceptions and experiences of anterograde amnesia. 23 Could you include what the studies found? Otherwise would remove them. Would include the statement from choosing wisely Switzerland “don’t use…” For the objective of the study, please add the “why” we looked at variation in prescribing patterns in Switzerland to inform a future intervention directed at prescribers (for example) or, in order to identify regions in need of concerted efforts for deprescribing etc… Methods: What are: gatekeeping or managed care arrangements Are the nine selected cantons the only states that do not have direct physician dispensing or are they just a subset? If so, how were they selected. And why do they differ? Which non-benzo sedatives were included in the analysis? (could you list them) Change gender to sex Rates or prevalence? Why did you look at number of active ingredients? Why look at number of pills if looking at defined daily doses? Could remove number of pills (no necessary to include I think) Which co-morbidities were accounted for? Could also add the median number of drugs the patient takes (a marker of polypharmacy) but I don’t think this is absolutely required Should sex be a variable in the model? I don’t see it listed Ethics: don’t you still need a waiver of ethics to analyze the data

	even if it is anonymous? Results: In the methods, could you define what the deductible CHF levels correspond given they are discussed in the results? Could you consider putting the order of the columns in the results as follows from left to right: Users, Non-users, all enrollees Is there an error in the results table: 80+ 16859 24 11118 22 5741 30 The number of users and non-users do not add up to the total enrollees and the percentages of users and non-users do not add to 100 (is there a third option other than user and non-user)? And the percentages are not correct e.g. 5741/16859 is 34% and not 30% I didn't check all the lines in the table so I'm not sure if the error carries through everywhere or where it originates What is the denominator for all enrollees? Include in heading of the table? You say the study population is 69005 individuals but when I add of the three age groups in the table I get 106331 Either I am missing something or the table needs better explanation with clearer descriptions of the denominators In table 1 what is PCG? The legend for figure 1 currently appears under table 1 and there is no legend for table 1 Table 2 needs a better description/definition of the different components please: What does number of prescriptions mean? How to interpret this? E.g. in one year I had 20 different prescriptions- does this mean, three doctors prescribing 2 benzos for 1 month duration or one doctor prescribing 1 benzo for 2 months duration etc… How did you calculate DDD I don't think you need to include number of pills or number of active ingredients there is no clinical reason to display this to the reader. Or if there is, then please explain it. I think this is a typo: prescriptiodates Is min/max the correct statistic to display for median or should it be interquartile range? It's strange that 56% of users had zero co-morbidities but 19% had a hospitalization. We need to see what co-morbidities are included. Are all the components of the CHarlson comorbidity index included? It seems like co-morbidities may not be properly captured.

	Wow that's a lot of Zolpidem!!! We consider this to be a non-benzodiazepine sedative hypotic though. I see you have included it as a benzodiazepine. A total of 125,832 benzodiazepines prescriptions were filled in 2017. The most commonly prescribed products were Zolpidem (35.8%), Lorazepam (23.8%), Oxazepam (9.7%) and Bromazepam (7.8%) I think Table 2 would be more interesting if you included the breakdown of what types of benzos and non-benzo sedatives are prescribed In table 1, I would order the cantons by highest proportion to lowest proportion of prevalence of use (e.g. VD, VS, GE etc…) Why are there p-value comparisons this list? The denominator for the prevalence of use by canton should be the total enrollees per canton. E.g. For canton AG users should be 461/3986 (12.3% use). And I don't think you need the proportion of non-users. It is just the opposite of the users. Where you might include p-values is when you compare the demographics and the deductible of the users and non-users and that is where you need both columns. E.g. Co-morbidity Users Non-users N=1000 N=4000 1 100 (0.1) 800 (0.2) p= xxx 2 For the logistic regression, why is the age range cut for the OR given as the example of 75-78? Did you look at Odds for each 3 year increment? Is so, why? As in the rest of the paper you use different age cuts; come to think of it, in table 1, it is also strange to use, 10 year, 5 year and then 80 plus. More standard would be 65-69, 70-74, 75-80 and over 80 and then to keep these same cuts for the logistic regression (or display continuous with odds for each additional year) In table three, is benzo use the only significant finding from the regression? Would include the findings for all of the variables included. Discussion: In the first sentence would include the range of prevalence across cantons (the overall prevalence was x, but it ranged from y-z). I think the discussion could do a better job of discussing the results of the study and how they compare to prior studies, as well as the implications. For example, I would like to see more discussion about the variability across cantons and some insights into why this might be. Are there differences in socioeconomic status between cantons that explains this? Is it that there are heavy prescribers working in some regions? How might this be addressed in a future intervention?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Michael Schoenbaum
Institution and Country: National Institute of Mental Health
Please state any competing interests or state 'None declared': No competing interests, to my knowledge.

Please leave your comments for the authors below

1. This paper examines an issue of clinical and public health importance, patterns of use - and possible misuse - of benzodiazepine medications in Switzerland. As the authors describe, research elsewhere has documented high rates of benzodiazepine prescribing, especially among women; and various ways in which benzodiazepine prescribing is likely to be inappropriate at a population level, including that prescribing rates rise consistently with age (although risks of adverse cognitive and physical effects of benzodiazepines also rise with age), and of high-volume and/or long-term prescribing (although, with the possible exception of treatment for seizure disorders, benzodiazepines are only appropriate for short-term or occasional/as-needed use). Documenting patterns of benzodiazepine prescribing in Switzerland could help inform clinical quality improvement efforts there, and, as the authors describe, perhaps also generalize to certain other high-income settings.

That said, I have several concerns about the current paper, which I think the authors can and should address. Most fundamentally, although the title and text focus specifically on benzodiazepines, in fact the analyses cover not just benzodiazepines but also non-benzodiazepine hypnotics. I find this problematic, both for the exposition (the first place where the authors mention that their scope includes non-benzo hypnotics is at the end of the "data sources" section of Methods, at the top of page 6 - after literally dozens of uses of the term "benzodiazepine," beginning with the title), and in terms of substance (while the clinical indications for benzodiazepines and non-benzo hypnotics, respectively, overlap to some extent - since some benzos are indicated or used for sleep - they mainly do not, since patients modally use benzodiazepines while they are awake, and non-benzo hypnotics in order to sleep). Empirically, per supplemental file 2, the single most commonly prescribed drug in the current scope of this study is zolpidem - accounting for 1/3 of *all* prescriptions considered here - and of course this drug is not a benzodiazepine.

In my view, the primary analyses here should separate benzodiazepines from non-benzo hypnotics, respectively. Given the current content, simply excluding non-benzo hypnotics would require the fewest changes to the text, because nearly all of the current background & discussion - and the associated references - focus on benzodiazepines. (I do recognize that non-benzo hypnotics account for approximately 40% of all the prescriptions examined here, so the benzodiazepine-only dataset will be smaller. But that's just the way it is here.) If the authors also want to present information about non-benzo hypnotics, I think they need to add some additional background & motivation, since again I think nearly all the current supporting text focuses on benzodiazepines.
We thank the reviewer for this important feedback. Indeed, in our analysis we included both benzodiazepines and non-benzodiazepine hypnotics. As suggested by both reviewers, we have amended the analysis by focusing on benzodiazepines only. We made changes throughout the text accordingly.

More specific comments:

2. Abstract, Participants - listing "Adults >= 65 years" is not sufficient information. Also, why does this study look only at patients 65+, vs. some wider age range (e.g., 50+, 20+, etc.)?

The sentence has been changed to “Older adults aged 65 years and older enrolled with a large Swiss health insurance company”

We focused only on the population 65 and over considering that guidelines discourage prolonged use of benzodiazepines particularly among older people due to several issues associated with risk of cognitive impairment, delirium, falls, fractures, and accidents (motor vehicle crashes).

References:
American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 2015. 63(11): p. 2227-4.
Markota, M., et al., Benzodiazepine Use in Older Adults: Dangers, Management, and Alternative Therapies. Mayo Clin Proc, 2016. 91(11): p. 1632-1639.

3. Abstract, Results (and throughout the paper) - In my view, reporting odds ratios (i.e., exponentiated coefficients from multivariate logistic regression) is not sufficient. In my view, I think it's important (also) to provide information on standardized rates, e.g., the estimated % with benzodiazepine use for individuals with high vs. low deductibles, all else equal, or for different Swiss cantons, etc. The authors can compute this, since they have access to the data and to the regression output, whereas readers can't calculate this themselves, and can't even readily approximate it.
We agree with the reviewer and added estimated % throughout the paper including in the abstract, the main text and in Table 1.

4. Introduction, framing about appropriate benzodiazepine use - the authors mention the inappropriateness of use "for a long period of time," and of guidelines, discouraging "prolonged" use. In my view, I think this may understate the threshold for misuse: as above, my understanding is that anything beyond short (e.g., a few weeks) or occasional use is associated with high risk of habituation, at which point continued use provides reduced or even no clinical benefits while withdrawal/discontinuation is difficult and potentially risky. In the same sense, stating that "benzo use for >120 days or at dose levels more than 2x recommended may be potentially problematic" strikes me as too mild; as I understand it, such use is contraindicated, and risky in various ways.
Thank you for this suggestion. We have made the following changes in this paragraph and included a new reference to address this comment: “In 2019 The American Geriatrics Society (AGS)8 published an update of the Beers Criteria to guide prescription in the elderly population. It recommends avoiding use of benzodiazepines in elderly patients due to increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents. Moreover, benzodiazepine use for longer than 4 weeks may be potentially problematic.”

In addition, we have added a new sentence and reference in the introduction “Benzodiazepines have been ranked among the most abused drugs, particularly for dependence.”

5. Methods, data sources - Do I understand correctly that the health plan studied here has a national market share of 1.4 million / 8.4 million = 17%? And that the study cohort is: all, i.e., a census, of members of this one health plan who were 65+ in 2017 and lived in the 9 cantons that do not permit clinician-dispensing of prescriptions?
Yes, this is correct. However, the updated numbers regarding national market are slightly different. We apologize for this. The sentence now reads “We obtained data from Groupe Mutuel, which is one of the largest health insurance companies in Switzerland, covering some 981,160 individuals with mandatory health insurance in 2019.” So, in summary, our sample of 69,005 enrolees are all enrolees from this health plan living in the 9 cantons and who are 65+ in 2017.

6. Methods, ethics - is "anonymous" patient data accurate. Or might the data be "de-identified"?
Yes, we agree with the reviewer. The sentence has been changed to “Ethical approval was not

required for this study since we used de-identified patient data."

7. Results, Table 1 - I recommend adding a column for "All enrollees," alongside the N and % columns, that reports [% with any benzodiazepine prescription in 2017]. This is the univariate information corresponding to the information on standardized % from the multivariate logistic regression that I requested above. Also, please add a row for "Male" (it isn't currently needed, but will be necessary once one adds the column for [% with any benzo Rx].
We agree with the reviewer and we have made the suggested changes in Table 1.

8. Finally, the authors need to use a chi-squared test to examine whether the distribution of beneficiaries between categories of a given domain (e.g., age group, canton, insurance plan, deductible, etc - in short, any domain that involves more than 2 options) differ statistically between users vs. non-users. Except for dichotomous characteristics, such as gender, It is inappropriate to use a t-test for each each individual row, as the table currently presents.
Following suggestions by both reviewers, we have now fully reorganized Table 1. It now focuses on the objectives of the study, which is to show % with any prescription and association between individual characteristics and use (both unadjusted and adjusted). We are no longer comparing the distribution of beneficiaries between categories of the various domains between those with and without any benzo prescription.

9. Results, "In all cantons, prescription rates increased with age..." - per the Figure, there is actually one canton of these nine where this pattern does not hold.
We have updated the sentence to" In all cantons, except in canton of Fribourg where prescription rate dropped in older enrolees, prescription rates increased steadily with age to reach about 30% for the oldest age group in some cantons"

10. Results, "Among users, 36% had at least one Rx of antidepressant or antipsychotics during the same calendar year." - I think this warrants elaboration. Benzodiazepines are contraindicated as a treatment for depression (although antidepressants are also indicated for anxiety, which I expect is the modal use for benzodiazepines). Both benzodiazepines and antipsychotics are contraindicated among older adults with dementia, although the use of both these drug classes is unfortunately common among dementia patients as a kind of chemical restraint.
We have decided to no longer report this specific combined use, as it is challenging to elaborate on the finding without more information on specific indication.

11. Discussion, "Latin speaking cantons" (this is used in two places) - I actually have no idea what this refers to! I don't recognize German, French, Italian or Romansch as "Latin."
We have changed Latin speaking cantons to non-German speaking cantons throughout the text.

12. Discussion, "higher Rx rates among women, which may be explained by a higher prevalence of anxiety disorders in women." I'm uncomfortable with this wording, since I think there are (many!) possible alternative explanations and the current paper doesn't include any findings that support one more than others.
This sentence has been removed.

13. Discussion, "Is it driven by patient demand or by physician supply, with a minority of doctors initiating such treatments?" First, I think the issue in the second part of this sentence is distinct from the issue in the first part. Second, I'd think that the dataset the authors use here - or anyway, health care claims data - could be used to examine the 2nd part of this sentence (although not the first). In which case, perhaps the authors could do this?
We have planned to analyze the second part of the question in a separate longitudinal study on benzodiazepines initiation and have therefore decided not to conduct such analysis in this cross-

sectional study.

Reviewer: 2
Reviewer Name: E. McDonald
Institution and Country: McGill University Health Centre, Canada
Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below Thank you for the opportunity to review the manuscript. This is an important topic and you have a great wealth of data to analyze here and to tell an interesting story about prescribing patterns of sedatives in Switzerland. I have some concerns about the the statistics and how the data are displayed. The results section is in need of a review as I think there are several calculation errors, the denominators are not appropriately selected and the the results are difficult to interpret and questionable as presented.
We agree with the reviewer that the formulation of the research question was not clear. We have updated the statistical analysis and the tables in the results section. We have separated the analysis by focusing on benzodiazepines only.

Abstract:
1. For the objective, could you have it match more with the outcomes?
We have updated the abstract to match the outcomes as suggested by the reviewer. We have changed the sentence to "To examine prevalence and determinants of benzodiazepine prescriptions among older adults in Switzerland, and analyse its association with hospitalisation and costs"

2. Participants: include that they are outpatients please (not hospitalized/community dwelling)
In fact, as we are focussing on enrolees, our dataset includes community-dwelling individuals, and also institutionalised ones, we therefore have changed the sentence to "Older adults aged 65 years and older enrolled with a large Swiss health insurance company"

3. What is highest deductible level of CHF? (not common term for all readers/avoid acronyms)
We now indicate this in the text "Enrollees with the highest deductible level of Swiss Franc (CHF) 2,500 were 70% less likely to receive a prescription than enrollees with the lowest deductible level of CHF 300 (Adjusted OR=0.29, 95% CI: 0.24-0.35)"

4. Add to the conclusions that use is high, is associated with trauma and healthcare expenditures, with variability across cantons, suggesting regional/prescriber directed interventions could address overuse.
Thank you for this suggestion. We have added the following text to the conclusions: "The proportion of older adults with at least one benzodiazepine prescription is high in Switzerland, and these enrollees are more likely to be hospitalized for trauma and have higher health care expenditures. Important differences in prescription rates across cantons were observed, suggesting high rates of potential overuse. Further research is needed to understand the drivers of regional variation, patterns of prescription across provider type and trends of use over time"

Introduction:
5. I would remove this qualifier: Despite proven beneficial effects
We have removed this sentence.

6. Would remove "problems associated with discontinuation" (stated already with withdrawal symptoms) and include problems related to dependency, traumatic falls and fracture, remove confusion (already stated with problems with cognition), and add in death/hospitalization (these are reasons for healthcare expenditures directly related to the drug).

We have changed the sentence to “Indeed, when used for long periods, benzodiazepines may lead problems related to dependency, traumatic falls and fracture, death/hospitalization leading to increased health care costs”

We also added two new references to support the sentence:
• Peel NM. Epidemiology of Falls in Older Age. Canadian Journal on Aging / La Revue canadienne du vieillissement 2011;30(1):7-19. doi: 10.1017/S071498081000070X [published Online First: 2011/03/15]
• Ballokova A, Peel N, Fialová D, et al. Use of Benzodiazepines and Association with Falls in Older People Admitted to Hospital: A Prospective Cohort Study2014

7. Add a reference for this statement: Despite the lack of evidence supporting their use beyond short periods, benzodiazepines are often prescribed for longer periods than recommended, particularly among those aged ≥65
We have added the following reference as suggested:
• Gerlach LB, Maust DT, Leong SH, et al. Factors Associated With Long-term Benzodiazepine Use Among Older Adults Letters. JAMA Internal Medicine 2018;178(11):1560-62. doi: 10.1001/jamainternmed.2018.2413

8. If including these studies in the introduction: In 2017, Bietry et al. examined the association between prior benzodiazepine use and the risk of developing Alzheimer disease in the Swiss population 22. Another qualitative study examined high-dose benzodiazepine users’ perceptions and experiences of anterograde amnesia. 23
Could you include what the studies found? Otherwise would remove them.
We have removed these studies from the introduction part since the findings are reported in the discussion.

9. Would include the statement from choosing wisely Switzerland “don’t use…”
We have updated the sentence and included the statement from Choosing Wisely Switzerland “In Switzerland, the Choosing Wisely Switzerland (“smarter medicine”) top-5 list of low-value interventions for geriatrics includes benzodiazepines (https://www.smartermedicine.ch), and makes the following recommendation: “Don’t use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium and avoid prescription at discharge”.20 Use of benzodiazepines is, however, recommended for alcohol withdrawal symptoms/delirium tremens or severe generalized anxiety disorder unresponsive to other therapies”

10. For the objective of the study, please add the “why” we looked at variation in prescribing patterns in Switzerland to inform a future intervention directed at prescribers (for example) or, in order to identify regions in need of concerted efforts for deprescribing etc…
A new sentence was included: “In addition, we study differences in prescription rates across cantons to assess potential unwarranted variation, and identify regions in need of concerted de-prescribing efforts”

Methods:
11. What are: gatekeeping or managed care arrangements
We have clarified this in the text “The standard plan offers freedom of provider choice and direct access to secondary care. Enrolees can choose their deductible level (options range from CHF 300 to 2,500) and, in return for a lower premium, they can choose alternative healthcare plans (HCPs), with either a general practitioner (GP) or a medical call centre acting as gatekeeper.27 Gatekeeping plans require enrolees to see a general practitioner for referral to specialists, and manage care plans typically restrict access to a list of providers”

Reference:
• Keizer, E., et al., Impact of alternative healthcare plans on out-of-hours help-seeking intentions in Switzerland. Swiss Med Wkly, 2018. 148: p. w14686

12. Are the nine selected cantons the only states that do not have direct physician dispensing or are they just a subset? If so, how were they selected. And why do they differ?
These are all the 9 out of 26 Swiss cantons in which direct physician dispensing is not allowed.

13. Which non-benzo sedatives were included in the analysis? (could you list them)
No longer relevant as we now focus on benzodiazepines.

14. Change gender to sex
We have changed gender to sex throughout the text and tables.

15. Rates or prevalence?
We report % with any use (i.e. prevalence).

16. Why did you look at number of active ingredients?
This is no longer included in the analysis.

17. Why look at number of pills if looking at defined daily doses? Could remove number of pills (no necessary to include I think)
Thank you for this suggestion. We have removed number of pills and we now focus on DDD.

18. Which co-morbidities were accounted for?
The following co-morbidities were included: ADHS, asthma, autoimmune diseases, cystic fibrosis/pancreatic enzyme, high cholesterol, COPD/severe asthma, Crohn's disease/ulcerative colitis, depression, diabetes, type 2 diabetes, epilepsy, glaucoma, heart disease, hiv/aids, hormone-sensitive cancer, hypertension, cancer, kidney disease, brain or spinal cord diseases, neuropathic pain, Parkinson's disease, psychosis, Alzheimer, and addiction, rheumatism, thyroid disease, transplantation. We have added this information in methods section (footnote)

19. Could also add the median number of drugs the patient takes (a marker of polypharmacy) but I don't think this is absolutely required Should sex be a variable in the model? I don't see it listed
We have added median number of drugs in Table 1 and included sex as variable in Tables 1 and 3.

20. Ethics: don't you still need a waiver of ethics to analyze the data even if it is anonymous?
Ethical approval is not required with this data.

Results:
21. In the methods, could you define what the deductible CHF levels correspond given they are discussed in the results?
We added this information in the text: "Enrolees can choose their deductible level (options range from CHF 300 to 2,500) and, in return for a lower premium, they can choose alternative healthcare plans (HCPs), with either a general practitioner (GP) or a medical call centre acting as gatekeeper"

22. Could you consider putting the order of the columns in the results as follows from left to right: Users, Non-users, all enrollees
Is there an error in the results table:
80+ 16859 24 11118 22 5741 30
The number of users and non-users do not add up to the total enrollees and the percentages of users and non-users do not add to 100 (is there a third option other than user and non-user)? And the

percentages are not correct e.g. 5741/16859 is 34% and not 30%. I didn't check all the lines in the table so I'm not sure if the error carries through everywhere or where it originates. What is the denominator for all enrollees? Include in heading of the table? You say the study population is 69005 individuals but when I add of the three age groups in the table I get 106331. Either I am missing something or the table needs better explanation with clearer descriptions of the denominators
We agree with the reviewer's remarks. We have now fully reorganized Table 1 following both reviewers' advice.

23. In table 1 what is PCG?
PCG stands for "Pharmacy Cost Groups" co-morbidities. This has been clarified in Table 1 and Table 3

24. The legend for figure 1 currently appears under table 1 and there is no legend for table 1
This has been updated.

25. Table 2 needs a better description/definition of the different components please: What does number of prescriptions mean? How to interpret this? E.g. in one year I had 20 different prescriptions- does this mean, three doctors prescribing 2 benzos for 1 month duration or one doctor prescribing 1 benzo for 2 months duration etc…
Table 2 has been updated and number of prescriptions have been clarified within the table.

26. How did you calculate DDD
DDD were obtained from WHO ATC/DDD Index 2018 (https://www.whocc.no/atc_ddd_index/)

27. I don't think you need to include number of pills or number of active ingredients there is no clinical reason to display this to the reader. Or if there is, then please explain it.
We agree with the reviewer and we have excluded both the number of pills and the number of active ingredients from the analysis.

28. I think this is a typo: prescript iodates
Thank you. We have corrected this.

29. Is min/max the correct statistic to display for median or should it be interquartile range?
Thank you for this suggestion. We now provide the median and interquartile range in Table 2.

30. It's strange that 56% of users had zero co-morbidities but 19% had a hospitalization. We need to see what co-morbidities are included. Are all the components of the Charlson comorbidity index included? It seems like co-morbidities may not be properly captured.
Our co-morbidity information is not standard as it is derived from medication use (PCG method, as described in the paper referenced in the text). It is the best information we can get regarding conditions with our data.

31. Wow that's a lot of Zolpidem!!! We consider this a non-benzodiazepine sedative hypotic though. I see you have included it as a benzodiazepine.
We have now excluded non-benzodiazepine sedatives from the analysis.

32. A total of 125,832 benzodiazepines prescriptions were filled in 2017. The most commonly prescribed products were Zolpidem (35.8%), Lorazepam (23.8%), Oxazepam (9.7%) and Bromazepam (7.8%). I think Table 2 would be more interesting if you included the breakdown of what types of benzos and non-benzo sedatives are prescribed
Thank you for the suggestion, Table 2 has been updated accordingly.

33. In table 1, I would order the cantons by highest proportion to lowest proportion of prevalence of use (e.g. VD, VS, GE etc…)
This has been changed accordingly.

34. Why are there p-value comparisons this list? The denominator for the prevalence of use by canton should be the total enrollees per canton. E.g. For canton AG users should be 461/3986 (12.3% use). And I don't think you need the proportion of non-users. It is just the opposite of the users. Where you might include p-values is when you compare the demographics and the deductible of the users and non-users and that is where you need both columns.
E.g.
Co-morbidity Users Non-users
N=1000 N=4000
1 100 (0.1) 800 (0.2) p= xxx
2
We have updated the table as suggested. P-values and non-users are no longer shown in the table.

35. For the logistic regression, why is the age range cut for the OR given as the example of 75-78? Did you look at Odds for each 3 year increment? Is so, why? As in the rest of the paper you use different age cuts; come to think of it, in table 1, it is also strange to use, 10 year, 5 year and then 80 plus. More standard would be 65-69, 70-74, 75-80 and over 80 and then to keep these same cuts for the logistic regression (or display continuous with odds for each additional year)
The age groups have been changed to 65-69, 70-74, 75-80 and over 80 in the whole paper as suggested by the reviewer.

36. In table three, is benzo use the only significant finding from the regression? Would include the findings for all of the variables included.
We have updated the table and included findings for all variables.

Discussion:
37. In the first sentence would include the range of prevalence across cantons (the overall prevalence was x, but it ranged from y-z).
This sentence has been added in the discussion part " We also found important variation in prescription rates across cantons, with rates ranging from 16% to 31%"

38. I think the discussion could do a better job of discussing the results of the study and how they compare to prior studies, as well as the implications. For example, I would like to see more discussion about the variability across cantons and some insights into why this might be. Are there differences in socioeconomic status between cantons that explains this? Is it that there are heavy prescribers working in some regions? How might this be addressed in a future intervention?
Thank you for the suggestion. A new paragraph on comparison with other studies has been included as well as an explanation about possible causes of variation and implications

VERSION 2 – REVIEW

REVIEWER	Michael Schoenbaum National Institute of Mental Health, USA
REVIEW RETURNED	04-Sep-2019

GENERAL COMMENTS	The authors have addressed the comments in my initial review, with one main exception.

	The exception: In my original review, I expressed the view that reporting odds ratios from logistic regression is not sufficient; I think it's important (also) to provide information on standardized rates, i.e., the estimated outcome - % with trauma hospitalization, from Table 3 - for individuals with different values of particular variables, all else equal. There are various conventions for calculating study predicted rates from logistic regression output; my preference is to use to the vector of estimated parameters to calculate multiple values of the predicted dependent variable for each individual, using the individuals' actual data for all variables except the one being evaluated; so, for instance, one would calculate predicted hospitalization with their own data plus deductible=300, then deductible=500, etc. Then one calculates the mean of predicted Y across the sample for each of the respective values of "deductible", and the difference between mean predicted Y with deductible=300 vs. deductible=500 represents a measure of the effect size of changing the deductible in this way. Regarding the second panel of Table 3, for health care expenditures, there is a fairly large literature on the appropriate functional form of regressions when the dependent variable is very skewed, as is often the case for total health expenditures. The authors' citation for this seems appropriate - but they might provide a little more justification on the choice of using a log-linear approach (which is problematic when a non-trivial fraction of the sample Y=0 - which I strongly assume is not the case here). A few additional comments: In Table 1, the authors should be explicit that "any prescription" means "any benzodiazepine prescription" The authors explain that they focus on individuals aged 65+ because "guidelines discourage prolonged use of benzodiazepines particularly among older people." While I agree that older adults are especially at risk from inappropriate benzodiazepine use, I think there is also reason for concern in younger individuals - e.g., age 50+, if not the full adult age range - including because benzodiazepine misuse at older ages may reflect misuse and consequent habituation at younger ages. My opinion in this is reinforced by the Discussion, which appropriately highlights concerns about the high and, perhaps especially, prolonged use of benzodiazepines in the study population. I really think this suggests it would be valuable to examine patterns of benzodiazepine use in adjacent younger ages, to get a better sense for how much of the problematic use patterns in older ages may be a result of problematic use patterns in younger ages, vs. being newly initiated at older ages. So I think this study would be enhanced by including additional age categories, but will defer to the authors and editors about this.

REVIEWER	Emily McDonald McGill University Health Centre CANADA
REVIEW RETURNED	02-Sep-2019

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript. Abstract:

	There is a typo in one of the OR and another OR is still in beta (not log transformed) I think: (1.31OR=, 95% CI: 1. 20-1.1.44,) (β=0.72, 95% CI: 0. 67- 58 0.77) In the conclusion change suggest being more accurate: change "Switzerland" to "one large Swiss health insurance company" Manuscript: Introduction: Change "abused" to "misused" From what I understand, researchers cannot decide if ethics is approval is required or not- only the research ethics board or IRB can decide that. I believe the study still needs to receive a waiver of ethics from a responsible body and not from the researchers themselves. Methods: Can you comment on how you associated the trauma with the start of the benzodiazepine? What was the timing of benzodiazepine use and subsequent trauma? Results: In the table with the adjusted odds ratios (table 1) could you add to the table (at the bottom) what was adjusted for? Discussion/conclusion: Is a lower deductible a marker of lower socio-economic status? And could this be a factor for overuse of benzodiazepines? Would definitely emphasize that prescriber variation may be driving this. There may be a number of prescribers who could be intervened on in cantons that are outliers. Future directions should really focus on an intervention now that you know where the highest users are. And you can also use this study to set a national benchmark. Perhaps the country should aim for <8-9% use in adults age 65 and older as you know that this achievable in one of the cantons. Would also be good to look into why this canton is able to achieve such low prevalence.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Abstract:

There is a typo in one of the OR and another OR is still in beta (not log transformed) I think:

(1.31OR=, 95% CI: 1. 20-1.1.44,)
(β=0.72, 95% CI: 0. 67- 58 0.77)

Thank you for noting this. We have made the correction accordingly.

In the conclusion change suggest being more accurate: change “Switzerland” to “one large Swiss health insurance company”

We have made the suggested changes.

Manuscript:

Introduction:

Change “abused” to “misused”

We have changed “abused” to “misused”

From what I understand, researchers cannot decide if ethics is approval is required or not- only the research ethics board or IRB can decide that. I believe the study still needs to receive a waiver of ethics from a responsible body and not from the researchers themselves.

In our analysis we used routinely collected anonymous data; therefore, ethical approval was not required according to the Swiss law for research on humans.

References:

Junod, V. and B. Elger, Retrospective research: What are the ethical and legal requirements? Swiss medical weekly, 2010. 140: p. w13041.

https://www.admin.ch/opc/en/classified-compilation/20061313/index.html

Methods:

Can you comment on how you associated the trauma with the start of the benzodiazepine? What was the timing of benzodiazepine use and subsequent trauma?

We simply examined the association between hospitalization for trauma and any benzodiazepine use in the year, without finer consideration of timing. This will be done in future work exploiting longitudinal data.

Results:

In the table with the adjusted odds ratios (table 1) could you add to the table (at the bottom) what was adjusted for?

We have clarified this in table 1.

Discussion/conclusion:

Is a lower deductible a marker of lower socio-economic status? And could this be a factor for overuse of benzodiazepines?

The choice of deductible in Switzerland is indeed related to socio-economic status, but not necessarily in this direction. On the one hand, a lower deductible is often a marker of poorer health, which is often associated with lower socioeconomic status. On the other hand, low-income individuals tend to choose a higher deductible to benefit from a premium reduction. These two effects are challenging to disentangle.

Would definitely emphasize that prescriber variation may be driving this. There may be a number of prescribers who could be intervened on in cantons that are outliers. Future directions should really focus on an intervention now that you know where the highest users are. And you can also use this study to set a national benchmark. Perhaps the country should aim for <8-9% use in adults age 65 and older as you know that this achievable in one of the cantons. Would also be good to look into why this canton is able to achieve such low prevalence.

Thank you for this suggestion. We have added the following text to the discussion: “As overuse may be driven by variation in prescribing practice, future interventions could target prescribers in cantons with highest prescribing rates. Results shown in this study could also be used to set a national benchmark. For instance, authorities could aim for a target of use in adults age 65 and older, which would be realistic and reflect what is achievable in some cantons (e.g. <10% in use). Future research should also look into why some cantons are able to achieve such low prevalence compared to others.”

Reviewer: 1

The exception: In my original review, I expressed the view that reporting odds ratios from logistic regression is not sufficient; I think it's important (also) to provide information on standardized rates, i.e., the estimated outcome - % with trauma hospitalization, from Table 3 - for individuals with different values of particular variables, all else equal. There are various conventions for calculating study predicted rates from logistic regression output; my preference is to use to the vector of estimated parameters to calculate multiple values of the predicted dependent variable for each individual, using the individuals' actual data for all variables except the one being evaluated; so, for instance, one would calculate predicted hospitalization with their own data plus deductible=300, then deductible=500, etc. Then one calculates the mean of predicted Y across the sample for each of the respective values of "deductible", and the difference between mean predicted Y with deductible=300 vs. deductible=500 represents a measure of the effect size of changing the deductible in this way.

Thanks for this comment. As suggested, we now report predicted outcomes in Table 3 in addition to odds ratios and regression coefficients. These were calculated following the method described above and the methods section was updated accordingly.

Regarding the second panel of Table 3, for health care expenditures, there is a fairly large literature on the appropriate functional form of regressions when the dependent variable is very skewed, as is often the case for total health expenditures. The authors' citation for this seems appropriate - but they might provide a little more justification on the choice of using a log-linear approach (which is problematic when a non-trivial fraction of the sample Y=0 - which I strongly assume is not the case

here).

Thanks for this remark. In fact, we have less than 5% of Y=0 in our cost data and the log-linear model had the best fit and is fairly easy to interpret (as opposed to e.g. glm with log link). We have added a sentence on this in the text.

A few additional comments:

In Table 1, the authors should be explicit that "any prescription" means "any benzodiazepine prescription"

We have changed “any prescription” to “any benzodiazepine prescription”.

The authors explain that they focus on individuals aged 65+ because "guidelines discourage prolonged use of benzodiazepines particularly among older people." While I agree that older adults are especially at risk from inappropriate benzodiazepine use, I think there is also reason for concern in younger individuals - e.g., age 50+, if not the full adult age range - including because benzodiazepine misuse at older ages may reflect misuse and consequent habituation at younger ages.

My opinion in this is reinforced by the Discussion, which appropriately highlights concerns about the high and, perhaps especially, prolonged use of benzodiazepines in the study population. I really think this suggests it would be valuable to examine patterns of benzodiazepine use in adjacent younger ages, to get a better sense for how much of the problematic use patterns in older ages may be a result of problematic use patterns in younger ages, vs. being newly initiated at older ages. So I think this study would be enhanced by including additional age categories, but will defer to the authors and editors about this.

Thank you for this suggestion. Unfortunately, with the data at hand, we were not able to investigate use in younger populations. However, we have added a sentence on this issue in the discussion:

“Also, as benzodiazepine misuse at older ages may reflect misuse and consequent habituation at younger ages, focusing on the population aged 65 and over is a limitation. Future studies should examine patterns and initiation of problematic use in different age groups, and persistence of misuse over time.”

VERSION 3 – REVIEW

REVIEWER	Michael Schoenbaum National Institute of Mental Health, USA
REVIEW RETURNED	21-Oct-2019

GENERAL COMMENTS	The authors have addressed the concerns from my prior reviews.

REVIEWER	Emily McDonald McGill University Health Centre, Canada I own a software for deprescribing called MedSafer but derive no personal financial gains from it
REVIEW RETURNED	26-Sep-2019

GENERAL COMMENTS	Overall the manuscript is much improved and the authors have worked hard to address the comments by the reviewer.

	I think it will benefit from reading by a copy editor for grammar and clarity (there are several minor adjustments that need to made regarding tense and grammar). With regards to reporting of the results, there are still two instances where the beta coefficient is not transformed to odds ratio (I think this should be done as the readers will not be familiar with interpreting beta coefficients). In one place the the result is report as 70% increase, based on the beta coefficient, but I think it should be 30% increased odds (based on the OR) The result for women should be reported as twice as high only if men are used as the reference. In this case women were the reference and the OR is 0.5 and so should be reported as men were 50% less likely to be prescribed... In several instances the term rate is used and should be replaced by prevalence. I would temper the strengths related to the section where it says there is individual patient data; I think would be more appropriate to say, select data from individuals was available. Overall a very nice paper that tells the story of overuse based on regional variability and that describes the state of overuse in the country. Thanks for the opportunity to review.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Emily McDonald
Institution and Country: McGill University Health Centre, Canada
Please state any competing interests or state 'None declared': I own a software for deprescribing called MedSafer but derive no personal financial gains from it

Please leave your comments for the authors below
Overall the manuscript is much improved and the authors have worked hard to address the comments by the reviewer.

I think it will benefit from reading by a copy editor for grammar and clarity (there are several minor adjustments that need to made regarding tense and grammar).

Thank you for this suggestion. The manuscript has been edited and proofread. We hope this has improved the clarity.

With regards to reporting of the results, there are still two instances where the beta coefficient is not transformed to odds ratio (I think this should be done as the readers will not be familiar with interpreting beta coefficients).

In our analysis of costs, we used using a linear regression with log transformation of the outcome

variables (i.e. costs). The beta coefficient is therefore interpreted as a semi-elasticity (i.e. % of variation in costs following one unit of change in the variable of interest – in our case from 0 to 1 for the variable “any prescription”). We have added a note under table 3 to clarify this for the reader.

In one place the result is report as 70% increase, based on the beta coefficient, but I think it should be 30% increased odds (based on the OR)

See answer above. A semi-elasticity of 0.7 indicates a 70% increase in costs following an increase in one unit of the variable of interest.

The result for women should be reported as twice as high only if men are used as the reference. In this case women were the reference and the OR is 0.5 and so should be reported as men were 50% less likely to be prescribed...

We have changed the sentence to “Men were 50% less likely to be prescribed benzodiazepines as women (adjusted OR=0.53 95% CI: 0.51-0.55)”

In several instances the term rate is used and should be replaced by prevalence.

We have amended the text accordingly.

I would temper the strengths related to the section where it says there is individual patient data; I think would be more appropriate to say, select data from individuals was available.

We have changed the sentence to “First, select data from individuals was available with detailed patient-level information to provide recent evidence on benzodiazepine prescription in older people in Switzerland”

Overall a very nice paper that tells the story of overuse based on regional variability and that describes the state of overuse in the country.

Thanks for the opportunity to review.

Reviewer: 1
Reviewer Name: Michael Schoenbaum
Institution and Country: National Institute of Mental Health, USA
Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below
The authors have addressed the concerns from my prior reviews.