Dear Dr. Parish,

We thank the editorial team and reviewers for their thoughtful comments regarding our manuscript, "Benzodiazepine prescribing patterns and drug overdose mortality among individuals receiving opioid analgesics: case-cohort study". We believe that the changes suggested by the editorial team and reviewers have improved the manuscript substantially by providing clarification to our methodology and interpretation of our research. In what follows, we re-state each editorial team and reviewer comment verbatim for convenience, followed by our response and, when applicable, with changes we have made to the paper.

Sincerely,

Tae Woo Park, MD
Assistant Professor, Warren Alpert School of Medicine of Brown University

Editorial team comments:

* Editorial staff feel this to be a timely and interesting research question.

* Overall reasonable statistical approach. Statistician team feel sensitivity analysis done is quite reasonable.

* The editorial team would like further recognition of the potential limitations in generalizability of these results to the general population. In particular, more emphasis that most of these participants are men and from the VHA (This should be in the abstract, or even the title).

Response: We thank the editorial team for the above comments and agree that further clarification of the study population would benefit the manuscript. We have changed the abstract and title to better reflect the cohort being studied. The title has been changed to "Benzodiazepine prescribing patterns and drug overdose mortality among US veterans receiving opioid analgesics: case-cohort study". Additionally, we have changed the word “individual” to “veteran” throughout the paper.

* The terminology used needs to be clear and consistent, in particular with regards to use of term 'overdose'. Do these deaths link to suicide or accidental overdose? Suggest perhaps using a more generic term if not suicide such as 'drug related deaths'.

Response: We thank the editorial team for this comment and agree that it requires more clarity. We have defined the term “drug overdose death” as “any intentional, unintentional or indeterminate poisoning death caused by any medication or drug” in the abstract and in the methods. In addition, we have made the term “overdose death” more consistent throughout the paper. We also added further clarification to nature of drug overdose deaths in the US by adding the following to the methods section:

“Of the 43,982 drug overdose deaths in the US in 2013, 81.1% were classified as unintentional, 12.4% were intentional, and 6.4% were indeterminate.”

* The authors use the word "associated" but could do more to caution that association is probably not causation. The last sentence of the abstract could be taken to imply causality.

Response: We agree with the editorial team and have removed the last sentence of both the abstract and the conclusions.

* Clarify assumptions made about medications. For example, were patients on PRN prescriptions considered to be taking maximum PRN dosing?

Response: We agree that more clarification regarding assumptions about medications is needed. The following was added to the methods:

“Both benzodiazepine and opioid analgesic dose were measured using an “as-prescribed” approach, which assumes that patients took their benzodiazepines and opioid analgesics according to the prescribers’ instructions. Patients were assumed to be taking the maximum

amount described in the prescription, including for "as-needed" prescriptions. Dose was calculated by adding all diazepam or morphine milligram (mg) equivalents in each prescription and dividing by the number of days supply. This dose represented the maximum daily dose prescribed and not necessarily the amount actually consumed. If there was an overlap between two prescriptions of the same drug at the same dose and schedule, it was assumed that the first prescription was finished before the second prescription was started rather than assuming a higher amount of medication was taken during the overlap. If the overlapping drugs were of a different type, dose or schedule, than the second fill was assumed to have started on the date it was filled."

* It would be important to clarify the indications for benzodiazepine prescription. In particular, were these medications for anxiety disorders or epilepsy for example?

Response: We agree that indications for benzodiazepine prescription would be useful information for this study. Unfortunately, the VHA administrative dataset does not include indications for medications prescribed. Therefore, we are unable to ascertain with certainty the reasons these medications were prescribed. We added the following to our limitations in the discussion section:

"Because VHA pharmacy data are not linked to indications or diagnoses, we were unable to ascertain the indications for which the benzodiazepines were prescribed. Thus, we are unable to know if the association between benzodiazepine prescription and overdose death differs by indication or draw inferences to patients with specific indications."

* Have the authors adequately controlled for other drugs in their analyses? Need to be sure any residual risk has been accounted for. Need to adjust for former users.

Response: We agreed that we could improve upon our control for other drugs in our original analysis. Therefore, we performed further analyses that included variables that assessed receipt of medications in the year prior to study entry of three categories: 1) antidepressants, 2) antiepileptic and anti-parkinsonism drugs, and 3) antipsychotic and neuroleptic drugs. These categories were the three most commonly identified classes of pharmaceuticals after benzodiazepines involved in opioid-related overdose deaths in the United States in 20101. We added the following to the methods:

"Use of other medications was assessed by examining the receipt of three categories of medications in the year prior to start of observation: 1) antidepressants, 2) antiepileptic and anti-parkinsonism drugs, and 3) antipsychotic and neuroleptic drugs. These categories were the three most commonly identified classes of pharmaceuticals after benzodiazepines involved in opioid-related overdose deaths in the United States in 2010."

In the revised paper, we report revised results with these covariates added to the analyses. Adding these variables slightly attenuated the increased risk of overdose death associated with benzodiazepine receipt. One change in the revised results was a non-statistically significant association between lorazepam and decreased risk of overdose death when compared to clonazepam. Thus, we modified the abstract, results, and discussion sections to remove mention that lorazepam was associated with decreased risk of overdose death.

* In some instances a group like VHA has prescribing restrictions. Need to identify clearly if there is any suggested drug formulary and whether any drugs are more commonly prescribed as a result within this population.

Response: We agree that this matter required further clarification. We added the following to the methods:

"Benzodiazepine types included in the study were alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, temazepam, estazolam, flurazepam, oxazepam, quazepam, and triazolam. The most commonly prescribed benzodiazepines were those on the VHA drug formulary which consisted of alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, and temazepam. The other benzodiazepines included in the study were prescribed during the study period but at lower rates."

* There needs to be more discussion about possible confounders. In particular, it is not clear which drug caused the 'overdose' death, and half of the deaths occurred in the absence of benzodiazepine intake. It is seen that higher doses of benzodiazepine are associated with higher

risk of death, but would that be true of more psychiatric co-morbidity too. This warrants further discussion.

Response: We agree that further discussion is necessary of possible confounders. We added the following to the discussion section:

"Because benzodiazepines were more likely to be prescribed to those with substance use and other psychiatric disorders, conditions which carry their own risk for overdose death, the association between receipt of benzodiazepines and overdose death may be partially explained by these underlying conditions or the severity of those conditions. We attempted to address this possibility in two ways. Baseline patient characteristics, including demographic information, medical and mental health diagnoses, and the daily opioid dose were adjusted for in a multivariable model. Additionally, by distinguishing between periods of current and former receipt of benzodiazepines, we addressed some unmeasured confounding. Nonetheless, because those with current receipt of benzodiazepines may have had more severe conditions for which benzodiazepines were prescribed than those with former receipt, some residual confounding may exist. Patients with greater substance use or psychiatric severity may be more likely to take any medication in greater quantities than prescribed, as well as illicit drugs, leading to an increased risk of overdose death. Additionally, it is unclear through our analysis the degree to which benzodiazepines contributed to the actual cause of overdose death. Half of the overdose deaths occurred during periods when benzodiazepines were not prescribed, and although the risk of overdose death increased in a benzodiazepine dose-response fashion, this may reflect an effect of greater psychiatric severity or other differences between patients who did and did not receive benzodiazepines, rather than the benzodiazepine itself. Thus it is important to note that within the present study, benzodiazepines might be better conceptualized as a marker of risk with unknown direct causal links to overdose death."

Reviewer #1 comments:

This is a timely and important paper. Concurrent prescribing of benzodiazpines is common among patients using opioids long-term for chronic pain even though it is consistently discouraged--with about one-quarter of chronic opioid therapy patients using sedatives on a chronic basis. Prior research has suggested increased risk of drug overdose with concurrent use of opioids and benzodiazapines, but there is not a large-scale observational study assessing these risks. There is growing interest in discouraging chronic use of benzodiazapines among patients using opioids long-term, so this paper is timely from a health care policy perspective.

This is a carefully conducted and clearly reported case cohort study of the fatal drug overdose risk in relation to benzodiazapine and opioid use. The complexities of the methods are explained efficiently and with remarkable clarity. The methods are rigorous, the conclusions are stated with appropriate caution, but this paper provides the strongest evidence to date regarding the risk of fatal overdose among patients using benzodiazapines and opioids concurrently. This is an important contribution to the literature on one of the leading causes of death in the United States--one of the few causes of death (drug overdose involving prescription medications) that has been increasing rapidly over the last 20 years in the United States.

The methods were generally rigorous. It is not clear why there was adjustment only for inpatient mental health and substance abuse episodes, rather than for the more common ambulatory mental health and substance abuse diagnoses that are reported as descriptors of the sample. While it is not likely to alter the results, it would be appropriate to control for mental disorder and substance abuse status using ambulatory care data, as both are risk factors for drug overdose, and both are associated with whether and how patients use opioids and benzodiazapines. The adjustment for socioeconomic status using ecological data is a nice feature of their methods.

Response: We thank the reviewer for his comments. In our original analysis, we adjusted for both inpatient mental health and substance abuse episodes and ambulatory mental health and substance use disorder diagnoses. We have clarified this in the statistical analysis section of the methods, in the discussion, and at the bottom of the tables involving Cox proportional hazards models.

Can the authors say anything about whether there is a greater than additive effect of concurrent use of opioids and benzodiazapines. Figure 1 suggests that this may be the case, but they do not evaluate interaction. The size of their sample provides a unqiue opportunity to evaluate

interaction.

Response: In response to the reviewer's suggestion, we added an interaction term for benzodiazepine prescription history and opioid dose to our primary analysis. We found that the interaction was not statistically significant. Thus, we removed the analysis stratified by opioid dose (Table 4) and removed mention of this analysis throughout the paper in order to avoid misleading readers into the belief that a statistically significant interaction exists. We also added the following to the methods section:

"In our primary analysis, we tested for an interaction between benzodiazepine prescription history and opioid dose. The results reported in the primary analysis do not include any interaction terms."

And in the results section:

"The interaction between benzodiazepine history and opioid dose was not statistically significant (p=0.60), indicating that the relationships between benzodiazepine prescription and opioid dose and overdose death were neither greater nor less than additive."

Also, it would be worth making clear that there is a large and significant effect of opioid dose among the patients who are not using benzodiazapines and among former users of benzodiazapines. The scaling of Figure 1 makes it appear that the differences in risk among the patients not using opioids are small, but the differences in relative risks among those patients appear to be large. It might be worth reporting the stratum-specific odds ratios by opioid dose so that there is no confusion on this point (perhaps this could be done in the text). The authors might have a better idea about how to handle this issue appropriately.

Response: We agree with the reviewer that it would be important to make clear that there is a significant effect of opioid dose during periods when patients are not receiving benzodiazepines, and thus the effect of opioid dose that has been observed in several studies is not explained by confounding with benzodiazepine use. In order to do this, we examined the association between opioid dose and overdose death stratified by benzodiazepine prescription history (current, former, none). We found that increasing opioid doses were associated with an increased risk of overdose death in each benzodiazepine prescription history stratum. We added a table displaying these results and the following was added to the methods section:

"Additionally, in order to demonstrate that any association between opioid dose and overdose death is not due to confounding by benzodiazepine prescription history, we examined the association between opioid dose and overdose stratified by benzodiazepine prescription history (Table 4)."

And the results section:

"After stratifying by benzodiazepine prescription history, compared to the lowest opioid dose category, higher opioid dose categories were associated with increasingly greater risk of overdose death during periods of no benzodiazepine receipt, former benzodiazepine receipt, and current benzodiazepine receipt (Table 4)."

And the discussion section:

"In this study, concurrent benzodiazepine prescribing was more common among those who died of an overdose. Benzodiazepines are often prescribed for patients also receiving high doses of opioid analgesics. Studies across a number of clinical samples and with varying methods (including the present sample) have now replicated a finding of an association between opioid dose and risk of overdose death. Our findings further demonstrate that this association is not due to confounding by benzodiazepine prescription history, or by several control covariates we included here that were not included in the prior study in this sample. The association of opioid dose with overdose death did not appear to differ by benzodiazepine prescription history."

The increase in risk among the "former" users of benzodiazapines suggests that unmeasured confounding could explain a non-trivial portion of the increased risk observed among the current benzodiazapine users. There are several alternative possibilities. Days supply estimated by pharmacists is often based on the maximum number of pills that can be taken per day, so it may underestimate the actual duration of use for some patients. It might be possible to do a

sensitivity analysis to see how much of the excess risk among the former users occurs in a time window when the patient may still have benzodiazpines on hand due to underestimation of actual days supply. It is also possible that "former" users are more likely to obtain benzodiazapines from non-VHA sources, so they may be exposed to medications not reflected in the VHA database. This limitation is already discussed, but they might want to point out the potential for a differential effect within the former benzodiazapine users as a possible explanation of the higher overdose risk in that group.

Response: In response to the reviewer's suggestions, we carried out a sensitivity analysis in which we expanded the periods during which patients were currently receiving benzodiazepines by 10% of the days supply (30 day prescriptions = 33 day prescriptions). We found that this had a negligible effect on the association between former or current benzodiazepine receipt on overdose death risk. The following was added to the methods section:

"Finally, since patients may not take all of their medications during the days supply described in the prescription, we expanded the periods during which patients were currently receiving benzodiazepines by 10% of the days supply (for example, a 30 day supply would be expanded to 33 days)."

And results section:

"We found that the exclusion of intentional overdose deaths, overdose deaths not related to opioids or benzodiazepines, people with cancer, and an expansion of the periods during which patients were currently prescribed benzodiazepines resulted in only minor differences in the degree of association between benzodiazepine prescription history and overdose death, and no substantive differences in the inferences drawn from analyses."

In addition, we added the following to the discussion section:

"We found that the risk of overdose death was increased during periods of former benzodiazepine receipt. In addition to having a greater risk of overdose death because of having the underlying conditions for which benzodiazepines are prescribed, the increased risk of overdose death in those formerly prescribed benzodiazepines may be explained by continued use of benzodiazepines obtained illicitly or through non-VHA providers. Additionally, although we found that expanding the period in which veterans were currently being prescribed benzodiazepines had a negligible impact on risk of overdose death, those formerly prescribed benzodiazepines may still have had leftover benzodiazepine medications that they continued to use well past the end date of their prescription."

Reviewer #2 comments:

Prescription opioid related mortality is a significant public health issue in the USA (which has no OTC opioids available, except for one codeine containing cough medicine) and population exposures have been generally increasing, except in some states e.g. Florida where prescription rates were recently reduced by governmental legislation.
This is an original study in that it accesses a national veterans' data set for drug prescriptions, fills, doses and dates linked to national mortality data, which in turn allows for the calculation of reasonably precise estimates for increased drug related mortality risk, after exposure to benzodiazepines in addition to opioid exposure. This data set allowed for an examination of the effect of dose on outcome, which is an original finding.

The issue is of general concern to consumers, clinicians, public health, policy and regulatory professionals.

The research questions are clearly articulated.
The study uses a case-cohort design and a series of Cox proportional hazard models (with control for several important confounders), which are appropriate to the research questions. The sensitivity analyses were appropriate.

Selection of cases and random sampling of the underlying cohort was well described. The exclusions were reasonable. The population is predominately male, older and veterans and so not a nationally representative sample, with implications for external validity. This point is acknowledged by the authors in the Discussion.

The study had appropriate ethical approval.
The primary outcome was "any intentional, unintentional or indeterminate overdose death caused by any medication or drug (X40-45, X60-65, Y10-15, without T-code specified)", which means that the death might have been associated with another co-prescription drug e.g. a TCA or a MAOI (not entered as a covariate in the models). This might introduced a degree of bias, which could be acknowledged in the limitations section.

Response: We thank the reviewer for his comments. As noted above, in response to the editorial team's comments, we have incorporated past prescription of the three categories of medications most commonly involved in opioid analgesic-related deaths in our analysis: 1) antidepressants, 2) antiepileptic and anti-parkinsonism drugs, and 3) antipsychotic and neuroleptic drugs.

It would be good to know something more about the accuracy of the data linkage procedure (if known).

Response: We agree with the reviewer's suggestion. We do know the accuracy of the data linkage procedure and added the following to the methods section:

"More than 99% of deaths among VHA patients had a full match on SSN."

The exposures to benzodiazepines and opioids were well done, with the prescription filled data being a good proxy for medication exposure on a day to day basis. There is of course some potential for bias in that patients may not have taken the medication as prescribed, may have had access to medications from non-VHA prescribers and may have additionally taken medications not prescribed for them but for someone else. This is acknowledged in the limitations.
The results are credible and succinctly presented in the text. The tabular results were clearly presented.

The increased risk for former (not current) benzodiazepines is interesting and perhaps worthy of more comment form the authors.

Response: Reviewer #1 had a similar suggestion, and we addressed it by adding the following to the discussion section:

"We found that the risk of overdose death was increased during periods of former benzodiazepine receipt. In addition to having a greater risk of overdose death because of having the underlying conditions for which benzodiazepines are prescribed, the increased risk of overdose death in those formerly prescribed benzodiazepines may be explained by continued use of benzodiazepines obtained illicitly or through non-VHA providers. Additionally, though we found that expanding the period in which veterans were currently being prescribed benzodiazepines had a negligible impact on risk of overdose death, those formerly prescribed benzodiazepines may still have had leftover benzodiazepine medications that they continued to use past the end date of their prescription."

References – no problems identified.

Abstract is fine except for the use of "overdose risk" when I believe the authors might mean overdose mortality risk.

Response: This issue was addressed in response to the editorial team's comments. "Overdose risk" was changed to "overdose death risk" in the abstract and throughout the paper.

Other Issues
Use of terminology "overdose"
The study is concerned with "overdose deaths" or "overdose mortality" as the primary outcome. At times the authors refer simply to "overdose" and it can be unclear that the authors probably mean overdose death or overdose mortality e.g. " The study generated the hypothesis that receipt of benzodiazepines may be associated with increased risk of overdose in patients receiving opioid analgesics." There are multiple examples of this usage throughout the text.

Response: The editorial team made a similar comment and in response we have changed the term throughout the paper from "overdose" to "overdose death".

The second point would be the use of the term "overdose", especially outside of the USA. This term tends to be associated with a deliberate self-poisoning or a suicide attempt (intentionality), although the concepts of chronic misuse and accidental overdoses are also accepted. Putting intention to one side, "overdose" is generally taken to mean taken in excess of the prescribed dose or the generally accepted dose range (at least outside of the USA).
The US national data shows that in 2013, 35,663 (81.1%) of the 43,982 drug overdose deaths in the United States were unintentional, 5,432 (12.4%) were of suicidal intent, and 2,801 (0.06%) were of undetermined intent (Centers for Disease Control and Prevention. National Vital Statistics System mortality data. (2015) Available from URL: http://www.cdc.gov/nchs/deaths.htm.) Since the vast majority of these deaths were unintentional, it raises the possibility that at least some of the patients in this classification were taking the prescribed dosage (and not more), which might not be considered as an "overdose" by some readers.
The solution is not so easy. The authors could use a more neutral term like "medication related mortality" or "drug poisoning deaths". Alternatively, they could make clear in the text (perhaps even as early on as the abstract or introduction) what the use of term "overdose death" might encompass for the purpose of this manuscript.
I should say that the classification of these deaths (on page 10) as the primary outcome is made quite explicit; it is the "overdose" connotations that might confuse or mislead some readers.

Response: We agree with the reviewer that further clarification is needed on this point. The editorial team commented similarly. As noted above, we addressed this issue by defining the term "drug overdose death" as "any intentional, unintentional or indeterminate poisoning death caused by any medication or drug" in the abstract and in the methods. We also added further clarification to nature of drug overdose deaths in the US by adding the following to the methods section:

"Of the 43,982 drug overdose deaths in the US in 2013, 81.1% were classified as unintentional, 12.4% were intentional, and 6.4% were indeterminate."

References

1) Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA. 2013;309(7):657-659.

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