PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Concurrent prescriptions for opioids and benzodiazepines and risk of opioid overdose: protocol for a retrospective cohort study using linked administrative data
AUTHORS	Liu, Erin; Tamblyn, Robyn; Filion, Kristian; Buckeridge, David

VERSION 1 – REVIEW

REVIEWER	Peter Kreiner Brandeis University USA
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	This is a detailed, thorough study protocol that addresses many of the limitations of previous studies of adverse outcomes of concurrent opioid and benzodiazepine prescriptions. Although I'm not a statistician, the use of a marginal structural Cox proportional hazards model would appear to addresses sources of bias identified in prior studies. A strength of the proposed study is its access to linked data for hospitalizations and ER visits as well as deaths. The study would advance our understanding of the adverse effects of these concurrent prescriptions, as well as extending this understanding to a Canadian population. I believe the manuscript would be improved if the following items were addressed. Two minor points: 1. P. 6, 1st paragraph. More recent data than 2015 on US opioid-related deaths are available. E.g., from https://www.cdc.gov/drugoverdose/epidemic/index.html 2. P. 6, 2nd paragraph. The first paragraph ends with data on opioid-related deaths in Canada. Data in the second paragraph, on the involvement of benzodiazepines, apparently switches back to US populations. Noting which country is being discussed would clarify these points. Less minor point: 1. P. 8, Outcome. The authors propose to identify outcomes using ICD-9 and -10 codes for opioid poisoning and acute effects of opioids. These codes would include poisoning and acute effects of illicit as well as prescription opioids. The possible involvement of illicit opioids is not addressed. There needs to be a discussion as to whether contextual data could be used, perhaps as part of the secondary analysis, to identify likely involvement of illicit opioids. And whether there is any evidence suggesting individuals with concurrent opioid and benzodiazepine prescriptions are more or less likely to be engaged in polydrug use including illicit opioids than individuals with opioid prescriptions only.

REVIEWER	Tae Woo Park Boston University School of Medicine, Boston, MA
REVIEW RETURNED	31-Aug-2020

GENERAL COMMENTS	Thank you for allowing me to review this research protocol involving the risk of concurrent prescribing of benzodiazepines and opioids. The use of a new user design and marginal structural models would advance the science of this field and help get us closer to answering the question: does concurrent benzodiazepine use cause overdose in people who use opioids? A couple of thoughts below: 1) Adding a new user design is helpful. It is possible that prevalent opioid users may have greater prevalence of substance use disorders and thus, a new user study may find a weaker association between concurrent benzodiazepines and overdose. It may be helpful to do both new user and prevalent user analyses in order to assess risk in these different populations. 2) It appears that overdose is the only outcome and includes both fatal and non-fatal overdoses. One might consider assessing these separately. Though overdose identified through ICD codes can be highly specific, overdose deaths may still be missed. Thus, adding all-cause mortality as an outcome could be informative. 3) Unfortunately, no study has assessed the potential benefits of benzodiazepine prescription in this patient population. They are effective treatments for anxiety and other conditions and some patients may have improvements that outweigh the risks. If data is available that can explore potential benefits from benzodiazepine prescribing, I would consider including them in this analysis. 4) It's unfortunate that this study does not do more to deal with residual confounding. You might consider a propensity score analysis. Additionally, as a sensitivity analysis, you might restrict the sample to those with an anxiety disorder and add a comparison treatment that includes non-benzodiazepine anxiolytics or receipt of psychotherapy. 5) Minor note: "To date, three epidemiologic studies conducted in population-based samples of adults have examined the risk of overdose associated with concurrent use of opioids and benzodiazepines". One might also include: Gressler LE, Martin BC, Hudson TJ, Painter JT. Relationship between concomitant benzodiazepine-opioid use and adverse outcomes among US veterans. Pain. 2018 Mar 1;159(3):451-9. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. bmj. 2015 Jun 10;350.

REVIEWER	Kara Stevens University of Plymouth, UK
REVIEW RETURNED	25-Sep-2020

GENERAL COMMENTS	General Comments An interesting topic that could help to inform clinicians on their prescribing behaviour. I would consider splitting some of the paragraphs, some of these are very long and might be easier to read and identify information if they were smaller. For example in the section "Statistical

	Analyses", sub-heading "Main Analysis", I would split up the second paragraph by the two models being used, and how the weights are calculated. Confounders 3rd paragraph - It might be worth having a little more detail on how the covariates measured every 30 days are derived for those who are not familiar with insurance data, e.g. do they check for a claim in the defined time period then use the codes to determine the type? Statistical Analyses There is no mention of any descriptive statistics which might be used. I would add a sentence or two to describe how the data will be summarised before inferential analysis (e.g. frequency an percentages, medians). Main Analysis - might be better to define this as primary analysis or change primary analysis under secondary analyses to be consistent with terminology. 2nd paragraph, line 28 - will all covariates be included in the model or will the model of best fit be used? 2nd paragraph, line 30 - it would be clearer to define what A and W represent, I am assuming exposure and covariates, but best to be explicit. Also what would authors plan to do if the weights were not robust? Secondary Analyses After reading the secondary analyses, I am little unclear whether the multinomial regression model used to calculate IPTWs in the primary analyses would be including all the proposed stratification variables or only for the secondary analyses. Also, if these are included in the model and the model indicated there was no association with the proposed stratification, would it be worth performing the stratification? Maybe a little more clarification on precisely what the secondary outcome analyses will involve, e.g. would you split the data into the different populations and fit the models to each population or include a covariate/interaction in the model, if not present. Sensitivity Analyses Try to splitting the paragraph into one for each sensitivity analysis. Patient and Public Involvement Not sure this is in the right location under statistical analyses. Maybe one sentence to say that there was no patient or public involvement in any aspect of the study to date or in the future. Also, as a protocol, there probably should not be any results.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Peter Kreiner

Institution and Country: Brandeis University, USA

Please state any competing interests or state ‘None declared’: None declared

This is a detailed, thorough study protocol that addresses many of the limitations of previous studies of adverse outcomes of concurrent opioid and benzodiazepine prescriptions. Although I’m not a statistician, the use of a marginal structural Cox proportional hazards model would appear to addresses sources of bias identified in prior studies. A strength of the proposed study is its access to linked data for hospitalizations and ER visits as well as deaths. The study would advance our understanding of the adverse effects of these concurrent prescriptions, as well as extending this understanding to a Canadian population. I believe the manuscript would be improved if the following items were addressed.

Two minor points:

1. P. 6, 1st paragraph. More recent data than 2015 on US opioid-related deaths are available. E.g., from https://www.cdc.gov/drugoverdose/epidemic/index.html

Thank you for the resource. In response to this comment, we have updated the first paragraph on page 6 with more recent statistics for opioid-related harms in both countries.

2. P. 6, 2nd paragraph. The first paragraph ends with data on opioid-related deaths in Canada. Data in the second paragraph, on the involvement of benzodiazepines, apparently switches back to US populations. Noting which country is being discussed would clarify these points.

Thank you for pointing out this inconsistency. We agree that it is important to explicitly state which country was involved in these studies and have done so in the revised manuscript.

Less minor point:

1. P. 8, Outcome. The authors propose to identify outcomes using ICD-9 and -10 codes for opioid poisoning and acute effects of opioids. These codes would include poisoning and acute effects of illicit as well as prescription opioids. The possible involvement of illicit opioids is not addressed. There needs to be a discussion as to whether contextual data could be used, perhaps as part of the secondary analysis, to identify likely involvement of illicit opioids. And whether there is any evidence suggesting individuals with concurrent opioid and benzodiazepine prescriptions are more or less likely to be engaged in polydrug use including illicit opioids than individuals with opioid prescriptions only.

You are right in pointing out that ICD-9 and -10 codes often do not distinguish the source (prescription or non-prescription) of the opioid involved. While this may result in differential misclassification if we were comparing non-users (who may actually be opioid users if they obtained them illicitly) to concurrent opioid and benzodiazepine users, our exposure contrast includes prescription opioid use in both the exposed and reference groups. Also, according to population-based surveys such as the Canadian Tobacco, Alcohol and Drugs Survey, in 2015, 2.3% of

Canadians aged 15 and older reported any non-cannabis, illicit drug use in the past year, and 0.3% had abused pharmaceutical pain relievers.[1] As such, we believe the impact of missing data on illicit opioid use will be minimal. As a final point, since our study period of 2000 to 2014 predates the rise of synthetic, illicit opioids (e.g. fentanyl) and their involvement in overdose deaths[2], we believe our study is less likely to suffer from misclassification bias as compared to more recent studies on this topic. We have included discussion of this potential limitation in the new *Strengths and Limitations* section on page 9.

We agree that concurrent opioid and benzodiazepine users could be more likely to engage in polydrug use. That is why our original analysis plan included subgroup analyses by patient characteristics indicative of potential polydrug use (i.e., substance use disorder, drug seeking behaviour).

Reviewer: 2

Reviewer Name: Tae Woo Park

Institution and Country: Boston University School of Medicine, Boston, MA, USA

Please state any competing interests or state 'None declared': None declared

Thank you for allowing me to review this research protocol involving the risk of concurrent prescribing of benzodiazepines and opioids. The use of a new user design and marginal structural models would advance the science of this field and help get us closer to answering the question: does concurrent benzodiazepine use cause overdose in people who use opioids? A couple of thoughts below:

1) Adding a new user design is helpful. It is possible that prevalent opioid users may have greater prevalence of substance use disorders and thus, a new user study may find a weaker association between concurrent benzodiazepines and overdose. It may be helpful to do both new user and prevalent user analyses in order to assess risk in these different populations.

We agree that the analysis should be separate for new vs prevalent opioid users and that it may be interesting to see how the association differs between these two groups. Our hypothesis is actually that new opioid users may be at higher risk since any early adverse events (including overdose) would likely result in discontinuation of use. This is in contrast to prevalent users, who tolerated the opioid enough to continue its use. Our current subgroup analysis stratifying the results by cumulative duration of opioid use (page 9, paragraph 1) will inform whether those who continued their opioid use have a higher association with overdose.

2) It appears that overdose is the only outcome and includes both fatal and non-fatal overdoses. One might consider assessing these separately. Though overdose identified through ICD codes can be highly specific, overdose deaths may still be missed. Thus, adding all-cause mortality as an outcome could be informative.

Thank you for the suggestion to assess fatal and non-fatal overdoses separately, and to add “all-cause mortality” as a secondary outcome. These are valid points and as such, we have added these analyses to our protocol. Please see the updated *Sensitivity analyses* section on page 9, paragraph 4.

3) Unfortunately, no study has assessed the potential benefits of benzodiazepine prescription in this patient population. They are effective treatments for anxiety and other conditions and some patients may have improvements that outweigh the risks. If data is available that can explore potential benefits from benzodiazepine prescribing, I would consider including them in this analysis.

We agree that it is important to assess the potential benefits of benzodiazepine prescriptions in the opioid-using population, given all drugs have benefits, risks, and uncertainty. It would be optimal to be able to provide data on effectiveness so that our safety study can be interpreted in the context of the risks and benefits of prescribing these medications. However, it is not possible using administrative claims data to measure symptom improvement for anxiety, insomnia, muscle pain and other indications commonly prescribed for benzodiazepines. We hope that future studies that can directly collect this information through patient-reported outcomes will be conducted.

4) It’s unfortunate that this study does not do more to deal with residual confounding. You might consider a propensity score analysis. Additionally, as a sensitivity analysis, you might restrict the sample to those with an anxiety disorder and add a comparison treatment that includes non-benzodiazepine anxiolytics or receipt of psychotherapy.

We agree that it is important to consider residual confounding in observational studies. We also agree that propensity scores can be useful for addressing this issue. In this study, we will be estimating propensity scores to calculate the inverse probability weights used in the marginal structural models. As for your point about restricting to those with an anxiety disorder, we have already planned to do this in our subgroup analysis stratifying by those with and without a history of mental health conditions (page 9, paragraph 1). While it would be interesting to compare the association between opioid use and concurrent non-benzodiazepine anxiolytic use, we feel it is beyond the scope of this study as it would necessitate a different research question, with different confounders under consideration. However, we may explore this in a future study, if our association differs substantially when we compare the effect adjusted and unadjusted for use of other CNS depressants (e.g., muscle relaxants, gabapentinoids, z-drugs).

5) Minor note: “To date, three epidemiologic studies conducted in population-based samples of adults have examined the risk of overdose associated with concurrent use of opioids and benzodiazepines”. One might also include:

Gressler LE, Martin BC, Hudson TJ, Painter JT. Relationship between concomitant benzodiazepine-opioid use and adverse outcomes among US veterans. Pain. 2018 Mar 1;159(3):451-9.

Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. bmj. 2015 Jun 10;350.

Thank you so much for providing references to these two additional studies. While we initially considered them in our literature review, we ultimately decided to only include populations similar to ours', which is health and drug-insured residents from the general population. As veteran and non-veteran populations often differ in their prevalence of mental health and other conditions, we did not think the two populations were comparable. However, we have added a sentence referring to these two studies and how the generalizability of these data is unclear (paragraph 4 on page 4).

Reviewer: 3

Reviewer Name: Kara Stevens

Institution and Country: University of Plymouth, UK

Please state any competing interests or state 'None declared': None declared

General Comments

An interesting topic that could help to inform clinicians on their prescribing behaviour.

I would consider splitting some of the paragraphs, some of these are very long and might be easier to read and identify information if they were smaller. For example in the section "Statistical Analyses", sub-heading "Main Analysis", I would split up the second paragraph by the two models being used, and how the weights are calculated.

We agree that some of the paragraphs were long and have split them into smaller paragraphs as suggested. In addition, we have reorganized the *Primary analysis* section on page 8, and hopefully it now communicates the information more effectively.

Confounders

3rd paragraph - It might be worth having a little more detail on how the covariates measured every 30 days are derived for those who are not familiar with insurance data, e.g. do they check for a claim in the defined time period then use the codes to determine the type?

You are correct that this is how we will identify participants as having a given medication, service, or diagnosis. We have updated paragraph 3 on page 7 to clarify this point.

Statistical Analyses

There is no mention of any descriptive statistics which might be used. I would add a sentence or two to describe how the data will be summarised before inferential analysis (e.g. frequency an percentages, medians).

We have now inserted a *Descriptive analysis* section, as suggested (page 8).

Main Analysis - might be better to define this as primary analysis or change primary analysis under secondary analyses to be consistent with terminology.

Thank you for pointing out the inconsistency in terminology. Throughout the text, we have replaced reference to the “main analysis” with “primary analysis.”

2nd paragraph, line 28 - will all covariates be included in the model or will the model of best fit be used?

All covariates will be included in the model, since statistics on model fit do not distinguish whether a variable is a confounder or not. Our reference to statistics of model fit (i.e., AIC) was for basing decisions on how best to model continuous covariates, as stated in paragraph 4 on page 8, which we have copy and pasted below:

“Indicator variables will be used for all categorical covariates and continuous covariates will be tested for non-linear effects using Akaike Information Criterion (AIC) to determine the optimal form.”

2nd paragraph, line 30 - it would be clearer to define what A and W represent, I am assuming exposure and covariates, but best to be explicit. Also what would authors plan to do if the weights were not robust?

We agree that A and W should be explicitly defined and have updated this paragraph to explicitly state that they represent exposure and covariates, respectively. In addition, we have modified the paragraph to explain how trimming our weights will ensure they remain robust.

Secondary Analyses

After reading the secondary analyses, I am little unclear whether the multinomial regression model used to calculate IPTWs in the primary analyses would be including all the proposed stratification variables or only for the secondary analyses.

Also, if these are included in the model and the model indicated there was no association with the proposed stratification, would it be worth performing the stratification?

Maybe a little more clarification on precisely what the secondary outcome analyses will involve, e.g. would you split the data into the different populations and fit the models to each population or include a covariate/interaction in the model, if not present.

The multinomial regression used to calculate IPTWs in the primary analysis will include the stratification variables if they are also confounders. Even if the proposed stratification variables may not be associated with the exposure, we will proceed with the stratified analyses. In these analyses, the stratification variables will not be included in the multinomial regression model used to calculate IPTWs. Instead, they will be used to separate the cohort (e.g. ever benzodiazepine users vs never benzodiazepine users at baseline) and each subgroup will be fit with their own Cox regression model to obtain strata-specific estimates (page 9, paragraph 3).

Sensitivity Analyses

Try to splitting the paragraph into one for each sensitivity analysis.

Thank you for this suggestion. We have added the sub-headings *i) Exposure measurement error, ii) Period of exposure*, and iii) *Outcome measurement error* to reflect what each sensitivity analysis will be addressing. Please see paragraphs 3-5 on page 9 for the updated section.

Patient and Public Involvement

Not sure this is in the right location under statistical analyses. Maybe one sentence to say that there was no patient or public involvement in any aspect of the study to date or in the future. Also, as a protocol, there probably should not be any results.

We have reformatted the *Patient and Public Involvement* section to be its own stand-alone section, separate from *Methods and analysis*. We are unsure what results you are referring to but assure you that the table and figure accompanying our manuscript do not contain results. Table 1 lists confounders and how they will be measured, while Figure 1 illustrates how exposure will be measured.

REFERENCES

1. Government of Canada. Canadian Tobacco Alcohol and Drugs (CTADS): 2015 supplementary tables - Canada.ca. https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2015-supplementary-tables.html#a12. Accessed October 20, 2020.

2. Centers for Disease Control and Prevention (CDC). Understanding the Epidemic | Drug Overdose | CDC Injury Center. https://www.cdc.gov/drugoverdose/epidemic/index.html. Accessed September 30, 2020.

VERSION 2 – REVIEW

REVIEWER	Peter W. Kreiner Brandeis University United States
REVIEW RETURNED	20-Nov-2020

GENERAL COMMENTS	I believe the authors have adequately addressed all of the reviewers' comments and feedback. I think the article will be an important contribution both to studies of the effects of concurrent opioid and benzodiazepine prescriptions and to studies that might partake of a similar methodological approach.

REVIEWER	Tae Woo Park Boston University School of Medicine
REVIEW RETURNED	25-Nov-2020

GENERAL COMMENTS	None