Subject: BMJ - Decision on Manuscript ID BMJ.2014.024299

Body: 07-Feb-2015

Dear Dr. Park

Manuscript ID BMJ.2014.024299 entitled "Benzodiazepine prescribing patterns and drug overdose mortality among individuals receiving opioid analgesics: case-cohort study"

Thank you for sending us your paper, which we were pleased to have the chance to consider and enjoyed reading. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it. This is because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript committee meeting, so that we will be in a better position to understand your study and to decide whether The BMJ is the right journal for it.

Please respond point-by-point to the reviewer and editorial comments at the end of this letter.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a decision.

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

1. Deadline: Your revised manuscript should be returned within one month.

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Yours sincerely

Emma Parish
Editorial Registrar - The BMJ
eparish@bmj.com

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the committee were: Elizabeth Loder (chair), Julie Morris (statistician), Emma Parish (handling editor), Rubin Minhas, Tiago Villaneuva, Wim Weber, Jose Merino, Alison Tonks.

Decision: request revisions

Detailed comments from the meeting:

Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter.

Please also respond to these additional comments by the committee:

* 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 event the title)

* 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'.

* 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.

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

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

* 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.

* 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.

* 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.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at http://resources.bmj.com/bmj/authors/bmj-pico

d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis”

Abstract
structured abstract including key summary statistics, as explained below (also see http://resources.bmj.com/bmj/authors/types-of-article/research)

for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
Results
please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
• Sensitivity and specificity
• PPV and NPV (positive and negative predictive values)
one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system
Discussion
please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
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Footnotes and statements

What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
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for studies funded or sponsored by industry (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication
assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

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.

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.

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.

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.

Additional Questions:
Please enter your name: Michael Von Korff

Job Title: Senior Investigator

Institution: Group Health Research Institute

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:
I am PI of grants from Pfizer Inc. that concern use of natural language processing to identify problem opioid use, and to evaluate Group Health's opioid risk reduction initiative. I am also a co-investigator on pending FDA-mandated post-marketing surveillance studies that will be funded by the Campbell Alliance, a consortium of drug companies formed to respond to the FDA requirements for post-marketing surveillance research on the safety of extended release opioids.

Reviewer: 2

Recommendation:

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

References – no problems identified.

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

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.
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.

Additional Questions:
Please enter your name: Gregory Carter

Job Title: A/Director Dept. Consultation-Liaison Psychiatry

Institution: Clavary Mater Newcastle Hospital, NSW Australia

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: No competing interests.

END

Date Sent: 07-Feb-2015