Subject: BMJ - Decision on Manuscript ID BMJ.2015.026409

Body: 28-May-2015

Dear Dr. Gray

Manuscript ID BMJ.2015.026409 entitled "Benzodiazepine Use and Risk of Incident Dementia or Cognitive Decline: Prospective Population Based Study"

Thank you for sending us this 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 meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. Looking forward to hearing from you again and, we hope, to reaching a decision.

Deadline: Your revised manuscript should be submitted within 6 to 8 weeks

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Many thanks again. We look forward to seeing your revised article within 6 to 8 weeks.

Yours sincerely

Georg Roeggla
groggla@bmj.com

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.

MM 28 May 2015

Elizabeth Loder (Chair), Angela Wade (Statistics advisor), Rebecca Burch, Anita Jain, José Merino, Georg Röggla, Wim Weber.

Decision: Ask for revision

The committee was interested in the topic of your research. The following concerns were mentioned:

• The committee shared the reviewers concerns.
• The finding that low benzodiazepine use was associated with higher risk of dementia isn't easy to interpret.
• The reviewers raise important concerns over the measurement of exposure, in particular the use of seemingly arbitrary cut-offs. Whilst the authors state that the categories of low, medium and high benzodiazepine use were based on the distribution of exposure and clinically meaningful cut-points, there is no further information on the distribution and no references to support. Furthermore there are doubts over the appropriate assessment period to reduce the capacity for susceptibility bias in this observational study.
• To avoid the problems with arbitrary categorisation of exposure, we suggest modelling with TSDD as the continuum that it is, using non-linear models as appropriate to capture the changes.
• What is the rationale for treating only stroke and coronary heart disease as time-varying in the models? Updated information was also available for other covariates.
• About 3.7% appear to be excluded because of missing covariates. What information was missing? Is there any indication that this subgroup may be biased in any way associated with outcome? Does a sensitivity analysis using multiple imputation alter the findings?
• Re the covariates adjusted for – could these be associated with outcome and exposure, leading to over-correction. For example, is it valid to adjust for self-rated health and depressive symptoms? Whilst information is given pre-adjustment for dementia and AD (figure 3), for the CASI modelling there is none (table 6).

First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available below. Please also respond to the additional comments by the committee.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points. 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.

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

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
This is a carefully conducted study addressing an important question: does exposure to benzodiazepines increase the risk of dementia, Alzheimer's disease or cognitive decline?

The data is generally of good quality. Medication exposure relies on dispensing data, which may over-estimate the drugs taken by patients. Cognitive data uses a combination of an objective screening instrument and more detailed clinical diagnosis. Covariates are based on a combination of patient report, health care records, and dispensing records and appear to be an appropriate selection of variables likely to confound the association between benzodiazepine exposure and dementia/cognition.

The methods, results and discussion are very well and clearly presented.

The main issue that I believe requires clarification stems from the very low exposure of the population over a long period, which makes it difficult to determine meaningful comparison groups. If I understand the data correctly, the authors are comparing three relatively low levels of exposure over a long period to people with no exposure. The 'high exposure group' of 121 or more standard doses over 10 years, would equate to over about 4 months of daily exposure over 10 years. Therefore, it is not very surprising that there is not a dose response relationship with the 'low', 'medium' and 'high' exposures described. I wonder if the clinical message of this paper is predominantly about the risks of low exposure? Please justify the dose cut-offs investigated here further. The discussion does raise the issue that the exposure in this US study is lower than that in the Canadian study, which found an association with dementia for the highest exposure group.

Additional Questions:
Please enter your name: Sarah Hilmer

Job Title: Professor of Geriatric Pharmacology

Institution: Royal North Shore Hospital and University of Sydney, Australia

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
This study examines the issue of chronic benzodiazepine use and risk for AD, all-cause dementia and cognitive decline in the population-based ACT cohort. The article is well-written and the design is well-conceptualized and thorough in the inclusion of covariates. A particular strength is the use of electronic pharmacy records and integration of health history with self-report and medical records. Additionally, the examination of "reverse causality," where benzodiazepines may be prescribed for the treatment of prodromal symptoms (by modifying the exposure window relative to the diagnosis of dementia) is a strength. The authors acknowledge the limitations of the CASI, and employ an IRT approach. A minor suggestion is to add a sentence or two explaining how that approach might absolve a concern about ceiling effects or relative insensitivity of the CASI to detect cognitive decline in this relatively well-educated population. A comment in the Discussion related to this issue is also suggested.

Additional Questions:
Please enter your name: JoAnn Tschanz

Job Title: Professor

Institution: Utah State University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:
Review: Benzodiazepine use and risk of incident dementia or cognitive decline

This study focuses on the relationship between benzodiazepine use and the risk of dementia and benefits from well-documented data for both dementia diagnosis and benzodiazepine exposure as well as from quite a long follow-up. While the topic is not novel since several studies on this subject have already been published, the study provides interesting findings and opens up new perspectives about the nature of the relationship found by previous studies. The manuscript is quite well designed but should be altered and clarified since some parts of the design could be confusing. Moreover, some methodological choices, particularly those concerning the definition and measurement of exposure, require more precise explanations and/or supplementary analyses, since they may have led to underestimating the association. For example, the possibility of a depletion of susceptible bias should be discussed as well as the fact that the long-term user group, as defined by the authors, could have included a significant number of short-term users (see below). These points are crucial since the study concludes that there is no association between benzodiazepines and dementia in chronic users (the 30% increase in risk being explained by short-term users only), and therefore challenges the conclusions of the studies conducted so far on the same topic. Since the potential impact on public health is major, the appropriateness of the message delivered to prescribers is crucial. Indeed, some conclusions drawn from the study could go against current international recommendations. For example, one could conclude that no excess risk is to be feared with long-term treatments while short-term use is associated with a 30% increased risk. Finally, the authors conclude that their results "may alleviate concerns raised by prior studies", a claim that should be mitigated given the level of proof of the results of what is an observational study, and the high public health relevance of the topic.

MAIN COMMENTS

1. The study design should be clarified or more precisely explained. I assume the authors considered cumulative benzodiazepine exposure in the 1-to-10-year period prior to enrolment in the ATC cohort. However, several sentences in the manuscript are confusing and could suggest that the observation

period for ascertaining exposure started ten years before the event (and not before enrolment in the ATC cohort; see abstract and Figure 2) or lasted after enrolment in the ATC cohort (see. the legend of Table 3). For example:
- Abstract (page 2, lines 34-39) "Benzodiazepine exposure was defined as the total standardized daily doses dispensing in a rolling exposure window covering the prior 10 years…" It is unclear what "the prior 10 years" refers to: (1) the date of dementia (more evocative of a retrospective design) or (2) the date of enrolment in the cohort (more appropriate for a prospective design).
- In order to avoid this ambiguity, Figure 2 could provide the mean and maximum follow-up time after the observation period (during which the presence of dementia is investigated).
- Page 7, line 20 to 23: "... we summed the SDD for all benzodiazepine pharmacy fills during the exposure period (described below)". Again, in this part ("below"), the starting point for measuring exposure (ten year before dementia or enrolment in the cohort) is unclear.
Even if I am not fully grasping what the authors really did, the methodological choices should be justified more precisely.

2. Appropriateness of assessment period and definition of exposure. The 10-year event-free period used by the authors for measuring exposure before the index date (i.e. date of enrolment in the cohort, or the date of dementia) could be too conservative. Indeed, prevalent users, mostly those exposed at the beginning of the observation period (i.e. 5 to 10 years before the enrolment in the cohort), may have developed dementia before enrolment in the ACT cohort. This could result in a depletion of susceptible bias when estimating the association between benzodiazepines and dementia. The "prevalent user design" makes this bias more likely since it is likely that a significant proportion of users started their treatment before this observation period. It would make more sence to shorten the observation period (5 years before enrolment could be satisfactory) and to introduce a "new initiator design". This would partly reduce the likelihood of this bias. Moreover, doing so would probably reduce both the proportion of persons excluded for having fewer than 10 years before enrolment in the ACT cohort (N=674/4724) and the risk of selection bias.

3. Definition of chronic users does not seem optimal. The cut-off chosen to define exposure might not make it possible to highlight exposure profiles actually at risk of developing dementia. Indeed, the cut-off chosen by the authors to define chronic use (i.e. >120 TSDD cumulative use during the 10-year observation period) is likely to have mixed chronic users (supposed to be at risk) and sporadic users (not supposed to be at risk). This cut-off was adequately chosen by Olfson et al.1 in their recent study to define chronic use within a one-year observation period. However, keeping the same threshold for a 10-year period is questionable since >120 TSDD may also correspond to occasional uses.

4. Time measurement of confounders may be questionable. The period for measuring putative confounders should be more clearly mentioned in the text (this information seems only provided for age). Since exposure measurement started 10 years before study entry, measuring confounders at this date or one year before does not seem appropriate. The measurement should be made earlier, ideally at the start of exposure.

5. Points related to the discussion section:
- Comments about the representativeness of the ACT cohort are lacking.
- The long-term group as defined by the authors could include heterogeneous exposure patterns, so the ACT cohort might not make it possible to assess the risk of dementia in actual chronic users of benzodiazepines. This putative limitation should be mentioned in the discussion section since it could partly explain the absence of association found in the long-term group.
- Page 13 line 53-56: "This may alleviate concerns raised by prior studies for those people who have a long history of benzodiazepine use". As mentioned above, this sentence should be altered since the design was apparently not optimal for assessing the association in chronic users of benzodiazepines.

SPECIFIC COMMENTS

1. Abstract (Page 2, line 30). The sentence "The association between 10-year cumulative benzodiazepine exposure" introduces a confusion about the duration of benzodiazepine use in the exposed group and should be altered.

2. Introduction (Page 4, line 9-10). The authors should mention that the 9-12% benzodiazepine prevalence refers to the US community-dwelling elderly population. Indeed, the prevalence could be much higher in other developed countries.

3. Introduction (Page 5, line 6-11). The wording of the objective is somewhat confusing. One could deduce that the authors assessed the effect of benzodiazepine use over the 10 subsequent years. In fact, 10 years was the period used for observing exposure, which is quite different.

4. Methods. The ACT cohort focuses on dementia and relies on a robust diagnosis for dementia cases, which could be more emphasized in the text. For example, the authors should mention who actually made the diagnosis (a GP, a clinician, a neuropsychiatrist, etc.) and provide the criteria used.

1. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry 2015;72(2):136-42.

Additional Questions:
Please enter your name: Sophie Billioti de Gage

Job Title: PharmD, PhD

Institution: University of Bordeaux, France

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 4

Recommendation:

Comments:
The authors are commended for the analysis proposed and contribution to this field of research. The approach presented in this manuscript improves the knowledge of the relationship between benzodiazepines and dementia by using pharmacy dispensing data as a measure of exposure as well as a clinical diagnosis of dementia. The authors also design the study to address reverse causation, a known source of bias in pharmacoepidemiologic research. I believe this manuscript should be accepted with minor revisions and is of high importance to the area of aging brain pharmacoepidemiology.

I submit only two comments and suggestions for the editor and authors to consider:

1) There is potential for variability in the exposure calculation between this study and that of Billioti de Gage (2014), the most closely related literature describing the relationship between benzodiazepines and dementia. Suggest the authors add a comment about such differences between their approach and Billioti de Gage in the discussion (page 12, line 37-57). The authors note credible reasons for differences found between studies, but this particular difference should emphasized as the measurement of the exposure variable is critically important and this study represents a new method. The use of pharmacy dispensing/claims data is indeed novel, but with conflicting results published in using these data, future work will need to determine merits of the exposure definitions to reproduce or refute these results.

2) The authors approach to CASI scores with sensitivity analysis using IRT is commendable. However, CASI, as with other cognitive screening tests, is less reliable among those with higher cognitive function (sensitivity and specificity are established for diagnosis of dementia with very acceptable characteristics). The authors report in this study a population without cognitive impairment at baseline and use an outcome of dementia, with little validity to compare the intermediate phases of mild cognitive impairment. Certainly the CASI analysis is a credible attempt to address such changes, however the discussion section could be improved by an additional comment addressing limitations of cognitive screening measures in the transition from (and between) normal cognition, MCI, and mild dementia.

Additional Questions:
Please enter your name: Noll Campbell

Job Title: Research Assistant Professor

Institution: Purdue University

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

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If you have any competing interests (please see BMJ policy) please declare them here: I have received salary support from Astellas Pharma, US. for research related to the measurement of the adverse cognitive effects of medications.

END

Date Sent: 28-May-2015