MJ - Decision on
Manuscript ID
BMJ.2015.026409.R2

Body: 21-Nov-2015

Dear Dr. Gray

Manuscript ID BMJ.2015.026409.R2 entitled "Benzodiazepine Use and Risk of Incident Dementia or Cognitive Decline: Prospective Population Based Study"

Our reviewer still has concerns. Please address these queries.

Yours sincerely,

Georg Roeggla
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** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

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

The present study by Gray et al. provides interesting findings and new perspectives about the relationship between benzodiazepines and the risk of dementia. It also provides estimations of the risk of cognitive decline associated with benzodiazepine use outside the dementia process. The study benefits from valid data for dementia, cognitive decline and benzodiazepine exposure and a long follow-up. Exposure definition has been altered and the design is much clearer now. The discussion section has been extended to explore further limitations of the study. Nevertheless, concerning the benzodiazepines-dementia analysis I still believe that the exposure definition is not optimal to capture true "long term users", since the highest exposure category can include a significant part of short-term users or, at least, of "regular" short-term. In my opinion more caution should be introduced when concluding to no association between chronic use of benzodiazepines and dementia taking into account that (i) putative limitations of the study could explain a significant part of the results (ii) the results of this study challenge those of most of the studies dealing with the topic and (iii) the results appear to be in contradiction with current prescribing guidelines recommending short-term exposure to benzodiazepines. Considering that the public health impact of this topic is potentially high, the appropriateness of the message delivered to prescribers is crucial.

My remaining remarks are detailed below:

1) Definition of chronic users still does not seem optimal.
I maintain the comment from my previous review as this point could potentially explain the absence of association found in the group defined as "chronic users". I am aware of the limitations of the database to capture true "long term users", which may not be very prevalent. Nevertheless I still believe that the cut-off chosen to define exposure might not capture or focus on exposure profiles suspected to be at risk of developing a 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 too low and likely to mix 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 but it was within a one-year and not a 10-year observation period. Keeping the same threshold for a 10-year period is questionable since >120 TSDDs may also correspond to sporadic uses. For example, an above suspicion use of 2 weeks per year during 10 years would exceed this threshold.

2) More balanced statement should be considered when concluding to no association in chronic users.
I keep thinking that the final sentence, conclusion section page 18 line 39 to 46: "Although benzodiazepines have been associated with many adverse health outcomes in older adults, our findings from a study using detailed pharmacy data and rigorous outcome assessment suggest that increased dementia risk may not be one of them" should be toned down regarding remaining limitations which are well mentioned in the discussion section and precluding clear-cut conclusions:
- Limitation of the database to capture "true" users at risk (see point 1 and discussion section page 16, lines 53-56: "our participants may have had lower levels of exposure than in some other studies").
- Possible exclusion of an unknown part of benzodiazepine users with an excess risk of dementia (see discussion section page 17 lines 13-20: "We are unable to exclude the possibility

that within the source population, the most susceptible users of benzodiazepines may have developed dementia at a younger age and therefore been ineligible for study enrolment, which may have biased our findings toward not finding an association").
- Concerns about the appropriateness of adjustment, patient characteristics being assessed after exposure measurement (see discussion section page 16 line 32-39: "no data on these characteristics are available prior to study enrolment, and thus in some cases, covariates were assessed after the start of exposure. If these confounders lie in the causal pathway, this could result in overadjustment").
- Concerns about extrapolation of the results (see discussion section page 18 line 17-20: "most participants were white and relatively well-educated, and so our results may not be generalisable to other groups").

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

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