PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hypnotics' association with mortality or cancer: a matched cohort study
AUTHORS	Daniel F. Kripke, Robert D. Langer and Lawrence E. Kline

VERSION 1 - REVIEW

REVIEWER	Barbara Phillips Division of Pulmonary, Critical Care and Sleep Medicine University of Kentucky College of Medicine Lexington, KY US I have no competing interests with the topic of this paper.

GENERAL COMMENTS	This manuscript is the result of a retrospective review of more than 10,000 patients who received hypnotic prescriptions and about twice as many matched controls who were followed for about 2 ½ years. The authors report a "dose response" relationship between numbers of prescribed hypnotic doses and increased risk of death, although even those in the lowest tertile of hypnotic prescription had a significantly increased HR for death. This work is highly original, and is likely to affect clinical practice significantly. Because it is highly and immediately relevant to so many different groups of people, including clinicians, patients, educators and policy makers, it belongs in a general, widely-read journal with a high impact factor. The hypothesis is clearly stated, and the methods are well-described and are probably the best that could have been applied to this particular hard-to-access dataset. Matching variables and controlled factors are extensive and appropriate. The discussion is understated and well written. In the US, pharmaceutical funding for authorship, speaking, journal advertising, and research is a significant issue that biases publication. This is an important paper that may help to balance the discussion a bit! Questions/Comments/Queries- 1. In the abstract, is there room to say which risk factors were controlled for? 2. In the abstract, results section, the second sentence is difficult to wade through. Can this be stated more clearly, and also give the reader some idea of the dose ranges? 3. In the abstract, conclusions section, consider changing "Hypnotics" to "receiving a prescription for hypnotics" and better define "low levels of use."

	4. In the methods section, describe how hypnotics were defined and identified in the records. Drugs "recognized as hypnotics" means different things to different people. Exactly which drugs are included here? And how many were taking each kind? This needs to be included in the Methods section, and maybe as a table. Were "off label" agents, such as trazodone, included? 5. Table 1 includes specific data for only zolpidem and temazepam. I think that "users" refers to ALL hypnotics, but this needs to be clearer in the heading, not just the footnote. Mabye "Any Hypnotic"? 6. In Results, do we know what KIND of cancers were increased? The discussion mentions lymphoma, lung, colon, and prostate; are these increased compared to controls in this sample? 7. The conclusion should start right away with the main finding.

REVIEWER	Justin Stebbing, Imperial

GENERAL COMMENTS	This is potentially a hugely important study with the potential to change clinical practice. The authors demonstrated a 4.6x hazard of dying over a relatively short observation period of 2.5 years, compared to non-users, though it would be relevant to note how reliable their data collection system is. To me, the most striking finding is the dose response though I am surprised that their strategies to elucidate bias revealed no bias. The authors discuss potential limitations The major limitation of this excellent paper is the lack of any validation cohort. Given the potential importance of these data I do think some kind of external validation, in any dataset would be useful. A European dataset would be outstanding. The supp info is excellent too. This was an absolute pleasure to review. It should have a statistical reviewer though re matching too. It must have an editorial with it and would be delighted to write one.

REVIEWER	Jorma Panula, Pori City Hospital

GENERAL COMMENTS	This is a well-planned study of a subject, which is globally urgent. Its message on the association between excess mortality and even low doses of sedative-hypnotics is very important for clinicians, policymakers, and patients. The authors add their results adequately into the context with the previous knowledge of this issue. Furthermore, their replies to JAMA reviews are valid and improve the text. I agree with the authors on the study setting; there might be ethical problems with RCTs in this field. The style and most importantly the universal value of the results make this report suitable for a general medical journal. The balance between the core message in the text and the very comprehensive web material is appropriate. There are, however, some aspects, which might need revision: Introduction: Omitting the cancer topic may make the manuscript more focused on the core message – mortality and taking sedative-hypnotics. At least, the aim to study also cancer association should

be mentioned in the Introduction.

Methods: The authors report that the population is mostly of low socio-economic status and less than one-third are insured under the Geisinger Health Plan. How do these patients differ from the others; are they 'the frailest of frail' and might this cause some selection bias?

Methods: How are the accuracy and completeness of death register in this study validated? Were cause-of-death data available? The authors debate about accidents and falls as possible causes for mortality.

Conclusion: 2nd and 3rd paragraph would be more appropriate in the Discussion.

Supplementary Table 4: The prevalence of dementia is surprisingly low both among nonusers and users. What might be the reason for that (mean age of 54y? There are, however, 6586 nonusers +65y and 2966 users +65y)?

VERSION 1 – AUTHOR RESPONSE

The author addressed the minor revisions highlighted in the above reviews and then re-submitted the manuscript to BMJ Open, where it was re-reviewed by two of the original reviewers.

VERSION 2 – REVIEW

REVIEWER	Barbara Phillips Division of Pulmonary, Critical Care and Sleep Medicine University of Kentucky College of Medicine Lexington, KY US I have no competing interests with the topic of this paper.
REVIEW RETURNED	13/01/2012

The reviewer completed the checklist but made no further comments.

REVIEWER	Justin Stebbing, Professor of Medicine and Oncology, Imperial College, London no competing interests
REVIEW RETURNED	18/01/2012

GENERAL COMMENTS	Superb- massively enjoyed. Irritated it was not accepted in the BMJ where I reviewed it .