Reviewer’s report

Title: Treatment of chronic insomnia in patients abusing hypnotics of 3rd generation

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Reviewer: Michael Perlis

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MS: 3171429181582410

Title: Antidepressant improves the results of cognitive-behaviour therapy of chronic insomnia in non-depressed patients

Authors: Lucie Zavesicka, Martin Brunovsky, Milos Matousek and Peter Sos

Preliminary Remark
This is the 2nd of two papers we were assigned to evaluate. While this paper shares several problems with the first manuscript, the aim of the project is truly novel. The authors should be encouraged to undertake the necessary revisions to make the paper suitable for publication. If they elect to do so, we are very confident that this study will make a significant contribution to the insomnia literature.

Review (Questions posed by BMC Psychiatry)

1. Is the question posed by the authors well defined?
Yes and No. The stated aim in the abstract is clear. The necessary “inverted pyramid” style introduction is lacking (brief review of the issues and literature ….. statement of the aim or hypothesis for the present study). Further, the point of departure, it seems to us, is not ideal. The Introduction contains the following assertions and logic (the items below in italics are implicit in the authors formulation).

CBT-I doesn’t work for everyone
Alternative therapies are needed
Medical adjunctive/combination treatment may be useful (?? for Tx non-responders ??)
BZs or BZRAs are not ideal as they are not indicated for long term Tx
Antidepressants are indicated for long term Tx
Some antidepressants have positive effects on sleep (meaning sleep architecture)
Trazodone represents an ideal medication
It can be used long term
It has positive effects on sleep architecture
It has a low abuse potential

Hence CBT +/- Trazodone was evaluated for its effects in patients with Primary Insomnia

The primary problem with the structure for the Introduction is that it lends itself to a project where the relative effects of CBT +/- Trazodone are assessed in patients with Primary Insomnia who are treatment refractory to CBT. Further, there is no argument about why combined treatment is likely to work better than either of the constituent treatments as monotherapy.

We believe a better platform/rationale for the investigation is as follows:

“While CBT has been shown to be effective and is roundly considered the first line treatment for Primary Insomnia, the treatment is not curative; instead it produces approximately 30-50% reductions in illness severity during acute treatment. The lack of “cure” has prompted several investigators to assess whether combined treatment (CBT + a medical intervention) might produce larger and/or more durable clinical effects. To date, there have been two kinds of “augmentation” studies including CBT + BZs/BZRAs (see Morin et al; Jacobs et al; Sivertsen et al.) and CBT + modafinil (Perlis et al). The findings from these studies suggest, by and large, that combination therapy does not produce larger sleep continuity effects nor more durable clinical outcomes. To date no investigators have reported the effects of combined therapy on sleep architecture, although two studies have noted that CBT alone produces 2-6% increase in Slow Wave sleep (Cervena et al; Sivertsen et al.). A third possible avenue for augmentation, which to our knowledge has not been explored, is via the combination of CBT with sedating antidepressants. In the present study… Trazodone was selected because… The hypotheses for the present study were…

2. Are the methods appropriate and well described?
Yes and No. In the abstract the authors adequately defines the two treatment conditions. They do not, however, adequately describe the study design or the components of CBTi. In the case of the latter, the authors simply list the therapies used (i.e., Sleep Hygiene, Relaxation, etc.). Each treatment component needs to be described (treatments by the same name often vary significantly in how they are conducted) and their inclusion (or exclusion) rationalized. Note: The investigators appear to not use Stimulus Control Instructions. This is roundly considered a central ingredient of CBTi… Its exclusion needs to be explained.

3. Are the data (presentation) sound?
Yes & No. We are confident that the data acquired are, for the most part, sound (i.e., the continuous sleep diary data and the pre-post ISI, ESS, BDI, etc. data). The exception to this is the PSG data. Very little information is provided on the
methods of acquisition, on scoring conventions, and the definition of the various sleep continuity and sleep architecture variables. The authors do note that their EEG montage is bi-polar (e.g., Fz-Cz). Rechtschaffen and Kales scoring standards require that the EEG montages be monopolar (e.g., C1/A2). This is not a fatal flaw... It simply needs to be acknowledged and explained.

The presentation of the data could be improved. The article should not rely so heavily on the data presented in the tables. The results should be organized around the study’s central questions and the reader should be told how the data in the table answer the various questions.

Finally, while others may disagree, we believe that the inclusion of self reported sleep continuity (subjective SL, NOA, WASO, and TST) data are essential. Insomnia is a subjectively defined disorder and as such treatment outcome also needs to be assessed in subjective terms.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes. Conventional headers are used. The manuscript would benefit from additional formatting and careful attention to a separation between the Methods and Results.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Given that the study’s instruction was not well framed and the results were not well explicated, it follows that the discussion was not adequate. The Discussion should have several sections (labeled or not) including a re-statement of the goals of the study, a re-statement of the findings, explication re: the study findings, a statement about the strengths and limitations of the study, recommendations for future research.

6. Are limitations of the work clearly stated?
Yes.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
No. As noted above.

8. Do the title and abstract accurately convey what has been found?
Yes but it may be more useful to refer to the patients with insomnia as patients with “Primary Insomnia”.

9. Is the writing acceptable?
Yes and No. If the author is a non-native English speaker, the prose is excellent. This said, for the purposes of a published article, review by a native English speaker is advisable.

9. Recommendation
Requires a Major Revision.