Reviewer's report

Title: Modern Hypnotics Cause Depression

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Reviewer: Rafael Pelayo

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The study reports an association of depression with hypnotics, but jumps the gun by stating hypnotics caused the depression. Causality can not be determined with the methods used in this study. In light of this reality the title and conclusions should be changed.

The title refers to modern hypnotics, but does not define them. Would an analysis of older hypnotics fare differently?

The methods section consists of only one sentence. This is probably the shortest method section on a research article for a long time. Given the conclusion reached, could the methods section please be further elaborated? There are far-reaching conclusions, but the methodology is essentially undescribed and one cannot assess the validity of the presentation and can only deduct from the write-up here and there what was done as shown below.

The clinical trials used were designed to look at longitudinal changes in the insomnia pattern not the depression patterns. So this is the wrong approach to answer the author's question. People with insomnia who volunteer for research trials do not volunteer in order to receive a placebo. They want the active agent. Research subjects receiving placebo tend to drop out of the trials more so than subjects receiving the active agent. Did the author factor in the differing drop-out rates or completion rates between groups when doing the statistical analysis? This is important and may influence the results. For example, patients with depression who received the placebo may have dropped out of the trial and could have skewed the results.

The author reports an increased risk ratio of 2.2 for the use of hypnotics. However looking at Table 1 the overall incidence of depression in the hypnotic group was 2% (109 out of 5535) while the incidence of depression in the placebo group was 1% (21 out of 2318). A one percent difference may not be clinically sufficient to warrant the concerns raised in the author's conclusions. Specific statistical analyses have to be performed taking into consideration the number of subjects.

The author mentions the antidepressant properties of sleep deprivation as a possible reason why hypnotics could worsen depression. This is fallacious argument since the antidepressant effects of sleep deprivation are more closely associated with REM sleep deprivation. None of the hypnotics under review alters REM sleep at the prescribed doses. The author's conclusion would be analogous to arguing against the use of anti-pyretics to lower the fever in someone with sepsis. The anti-pyretics do not worsen the sepsis they simply improve the patients comfort as an adjunct to the overall management. The patient can feel better while waiting for the antibiotics to work. In the same way the hypnotics may give symptomatic relief to the patient from their insomnia while the depression is being simultaneously addressed. By quickly improving one of the depressions cardinal symptoms the patient may obtain some hope that they will get better someday. Would the author agree that hope has antidepressant properties?

The author suggests medications such as nefazadone would be more suitable, yet does not present any references for large randomized trials with nefazadone for the treatment of insomnia.