Reviewer's report

**Title:** Modern Hypnotics Cause Depression

**Version:** 4  **Date:** 11 April 2007

**Reviewer:** Malcolm Lader

**Reviewer's report:**

General
1. This is an attempt at semantic legerdemain concerning the various meanings of the word “depression”.
2. The data comprise listings of the incidence of “depression” in the FDA databases for 4 newer drugs. The author does not explain why he has limited his analysis only to newer hypnotics. He should look at the incidences for, say, triazolam and flurazepam as older benzodiazepine-type drugs.
3. I believe that the FDA reporting system uses COSTART headings for depression, for which there are over 20 sub-headings, some for physical and some for psychological types of depression. The author should confine his analysis to psychiatric depression, essentially the well-defined (DSM-IV) Major Depressive Disorder (MDD).
4. He should also confine his analysis to the incidences of treatment-emergent MDD, in which the investigator made clear attributions of causality with the hypnotic medication. I doubt if this can be done and is an intrinsic limitation of the data.
5. The data are suspect anyway. If they were comparable, the placebo incidences of “depression” should be reasonably similar. In fact the incidences in the table are 0.26%, 1.02%, 2.17%, and 0.8%. The ratio of the greatest to the least is 8.3, much more than the Risk Ratio for the pooled hypnotic/placebo. Assuming the studies were run to similar protocols and used similar populations of primary insomniacs, this suggests that the criteria for depression were unreliable.
6. Further, I suspect that the term “depression” is picking up general depressant effects such as psychomotor and cognitive impairment. One would expect this to be greater in hypnotics with longer half-lives where the effects are more likely to persist into the next day. Analysing the data in table 1 in terms of % incidences and then as drug minus placebo incidences, one arrives at 3.05 - 2.17 (0.88) for zaleplon, 1.4 - 0.26 (1.14) for zolpidem, and 4 - 1.02 (2.98) for eszopiclone. This exactly in line with their half-lives (roughly, 1-2, 2-4, 4-8 hours). Ramelteon is not a depressant drug and has the lowest differential of all three – 1.34 - 0.8 (0.54). I think it likely that the term “depression” is being used in a non-psychiatric way.
7. There are pathetically few references.

My firm advice is to send these comments to the author and ask him to refute them, if he can, with further analyses and better data.

I would be prepared to referee a revised version of this paper.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)