Reviewer’s report

Title: Modern Hypnotics Cause Depression

Version: 4 Date: 11 April 2007

Reviewer: Michael T Smith

Reviewer’s report:

General

This is a provocative manuscript on multiple levels. The author compiled data from a newly available public database maintained by the FDA, which is comprised of randomized clinical trial data used to support new drug applications in the US. The author conducted a comparative meta-analysis of sorts, to evaluate whether modern hypnotics (benzodiazepine receptor agonists and a melatonin receptor agonist) are associated with the increased side effect of “depression.” To accomplish this, the author compared the frequencies of reported incident depression in 5535 subjects randomized to placebo versus 2318 subjects randomized to sedative hypnotics. The analysis showed higher incidence of “depression” in subjects receiving each of the hypnotic agents compared to those receiving placebo.

The major strengths of this paper are that it is succinct, the argument elegant, and the data involved randomization. The fact that the data are randomized causes inherent pause and I think provides this manuscript the legs needed for it make a very significant and timely contribution to the literature. This finding needs to be investigated further and raises important questions about how psychiatric side-effects are defined and reported in the FDA system. Depression is a potentially life threatening illness. At the population level, any agent that might double the risk of depression should be of concern.

With this said, this paper, does not provide conclusive evidence of this interpretation as suggested by the title. This is due in part to the lack of key procedural information, which may or may not be available.

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

1) The one sentence “Methods” section should be expanded to provide more information needed to fully understand what this finding means (details below).

Two major issues potentially threaten the validity of the conclusion and require elaboration and discussion. They are: a) the lack of definition of “incident depression” and how it was assessed within these studies and b) the lack of information on dropout by condition.

2) With respect to the former, no information is provided as to how incident depression was assessed or defined across studies. Is incident depression measured the same way in each study? How many studies is this data derived from? The author should discuss whether the FDA has formal definitions of CNS side-effects and guidelines with respect to how they are assessed, monitored and graded for severity. If this data is available, it should be reported and analyzed. If this data is not available it should be recognized as a cause for concern. The issue of definitions of important adverse events and guidelines for their monitoring, is particularly salient for psychiatric diseases, such as depression, which do not have an agreed upon objective test defining the presence of the pathologic state(s).

3) It is unclear due to lack of detail, whether one can take on face value that incident depression means formally diagnosed (DSM-IV) cases of emergent depression, made by a qualified mental health professional. If this were the case, then the argument would be substantially strengthened. Many emergent CNS side-effects, however, are monitored via patient self-report without any agreed upon definition between participant and researcher as to what “depression” means. It is unclear whether a case classified as “depression,” truly reflects the disease, which sits on an extreme end of a spectrum of mood alterations or whether it was a relatively mild side-effect of depressed mood that might disappear after a week with little to any consequence. In the cost benefit analysis this side effect might be outweighed by the drug’s primary effect. Without knowing the measurement details, one wonders whether expected residual daytime side-effects such as morning sedation, fatigue, transient depressed affect are simply being captured here.

4) Many industry and after market trials of psychotropic medications use psychometrically valid measures of
depressive symptoms. The potential contribution of a systematic analysis of these data, is largely ignored and this might lead to a biased conclusion that is an artifact of an inadequate CNS side-effect reporting system or the database itself. If these after market data were analyzed, might they tell a different story? This data may even be included within the new drug application documents, but not reported in the abbreviated database used to draw the conclusion of this report.

5) More information about what is included in this FDA database and its purpose is needed. For example, does the FDA database report the duration of the trial? Reporting the mean time frame studied for each agent including placebo would be very helpful information. If this basic information is lacking, it points to major shortcomings for the use of this database to draw firm conclusions and this should be recognized.

6) The author mentions only one study that appears to be somewhat in conflict with the finding (Fave et al, 2006). Did the author conduct a systematic review of the post-marketing literature? If so, reporting the databases and search strategies used would bolster the argument. There might be more instances within the published literature that are seemingly at odds with the author’s conclusion [e.g., Soares et al. (2006), Obstetrics and Gynecology, 108(6), 1402-1410.]

7) The other major caveat threatening the conclusion is that there is no analysis of whether there was differential drop out by placebo or active drug. Subjects receiving placebo often drop out of clinical trials early due to lack of the desired therapeutic effects. Perhaps, this present finding is a function of duration of participation within the trial? Did subjects receiving drug participate longer and therefore, have a greater chance of developing incident depression? This would be expected whether or not primary insomnia represents a true independent risk factor for depression or whether it is simply a prodromal symptom of depression.

8) This paper would be substantially enhanced by having a limitations section in which major threats to validity are discussed.

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

9) The title, while provocative, does not reflect the tentative nature of the conclusion. This paper does not present enough evidence to support this conclusion as fact, but it does raise legitimate cause for further investigation. Perhaps, rephrasing the title as a question, “Do modern hypnotic cause depression?,” would be a more appropriate, albeit less dramatic title.

10) The statistical analyses do not adjust for error due to multiple comparisons.

Discretionary Revisions (which the author can choose to ignore)

11) In the table, it would be helpful if in addition to the frequency of incidence the % values (Incidence / N) were listed.

In sum, this paper is quite provocative, in some respects more so for what it doesn’t say than what it does. It will undoubtedly raise debate, hopefully prompt further research, and possibly highlight short-comings in the reporting of CNS / psychiatric side-effects. In the final analysis, the data are what they are and the findings can not simply be dismissed--too much is at stake.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

Johns Hopkins University has received funds from Sepracor, Inc. to conduct a Principle Investigator Initiated Clinical Trial conceived and led by Dr. Smith.