Reviewer's report

Title: Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer’s disease

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Reviewer: Gregory Jicha

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The authors present detailed safety data from the recently published trial of high-dose donepezil (23mg) and further expand the safety evaluation to include two additional 5 & 10 mg trials safety data. While less than the most exciting breakthrough in therapeutics for AD, the manuscript expands on the data published in the original trial report (Farlow et al, 2010) and so serves a useful purpose as an addition to the present literature. The manuscript is well written and I have few comments as outlined below that I consider “minor essential revisions” according to BMC reviewer policy:

1) References begin at #3? What happened to #1 & 2? References should be renumbered.

2) The ‘Treatment-emergent laboratory abnormalities, ECG, or vital signs’ section in Results states that there were no differences between groups, and yet clinically significant differences in bradycardia are noted above? This needs to be clarified, as bradycardia is an ECG finding. I assume the authors meant “ECG findings other than bradycardia”? This should be clarified.

3) The analysis of Age-effects is confusing. The groups represent different time spans 20 years, 10 years, 10 years, and 15 years? How were the cutoffs for these groups determined? How was the analysis performed? Why wasn’t age simply used as a continuous variable? What are the relative frequencies in these age groups?

4) Likewise for the weight group analysis, essentially no details were shared on the grouping or the analysis? This limits the usefulness of this data for clinicians evaluating individual subject risks. I recommend providing more detail and establishing some sort of clinically relevant framework for the analysis.

5) The first paragraph of the discussion states that ‘Overall, age and gender had a minor effect on a small number of AEs’ which is not supported by the data presented that demonstrate significant effects on diarrhea, urinary tract infection, fatigue, somnolence and urinary incontinence, anorexia, and weight decrease. Either delete this sentence which is misleading or expand on why the age and gender effects should be so casually dismissed.

Level of interest: An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests