Reviewer's report

Title: The clinical meaningfulness of ADAS-Cog changes in Alzheimer's disease patients treated with donepezil in an open-label trial

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Reviewer: Michael WOODWARD

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REVIEW : Rockwood et al

TITLE : Meaningfulness of ADAS-Cog changes in Alzheimer's disease patients treated with donepezil in an open-label trial.

REVIEWER : Associate Professor Michael Woodward

This open-label study addresses an issue important to clinicians, regulatory authorities and the pharmaceutical industry – now meaningful is the ADAS-Cog and does it correlate with other outcome/response measures?

In some countries (eg Australia), the ADAS-Cog is required to achieve ongoing subsidisation of an acetylcholinesterase inhibitor (AchEI) for an individual and in most countries improvement on the ADAS-Cog, averaged across the trial population, has been used as evidence of efficacy in regulatory submissions. However, the ADAS-Cog is routinely used on individual patients in only a few specialist centres around the world (or where required by regulatory authorities) and generally an individual clinician and patient does not have pre and post AChEI treatment scores available to them.

The article addresses the question posed well, within the limits of the open-label design. It would have been more rigorous to utilise data from double blind randomised placebo controlled trials (DBRCT), and it is surprising that an analysis of the ADAS-Cog's correlations has not been published using these data bases. However, the ADAS-Cog is routinely used on individual patients in only a few specialist centres around the world (or where required by regulatory authorities) and generally an individual clinician and patient does not have pre and post AChEI treatment scores available to them.

The methods in this paper have been well described and are appropriate. There is sufficient information in this article, including the references, to allow others to duplicate the work. The data is sound, but there is no control group in this open label study. Data is reported in an acceptable way and statistical analyses seem appropriate (although this reviewer does not have a complete knowledge of correct statistical methods in trials such as these).

The discussion section is sound, and openly acknowledges both the strengths and weaknesses of the paper. Many clinicians, and possibly regulatory authorities, would find this information useful in assessing their use of AChEIs as a whole and for an individual patient.

The title and abstract accurately reflect the content of the paper and the writing style including grammar and spelling is exemplary. Specific comments follow, and where indicated should, I feel, be addressed by the authors:

1. A brief description of the clinical correlations of other outcome measures (eg the CIBIC) where DBRCT data is available would have been useful either in the introduction or in the discussion. Do the authors feel their statement that the CIBIC better correlated than the ADAS-Cog with most outcome measures (bottom paragraph, page 8) is reflected in other published work on the CIBIC?

2. Utilising only the data from those who completed 6 months of treatment (ie a per protocol, observed cases analysis) does not reasonably allow comparisons with DBRCT data as the better trials often utilise ITT analysis. Thus, the statement at the top of page 4 should be qualified.
3. The statement on page 5 (top paragraph) that patients would have some idea of how they performed on the ADAS-Cog is puzzling. Correctly administered, no feedback is given to the patient on their progressive or final performance and, as a clinician and researcher who has administered the ADAS-Cog over 1,000 times, I doubt patients do know how they performed. This statement should thus be qualified.

4. The setting of + 3 to – 3 as ‘no change’ on the ADAS-Cog is reasonable and reflects other trials/papers.

5. Getting 95 of an initial 100 patients to 6 months is almost incredible. Many real-world data bases suggest less than 50% of initiated patients reach 6 months, but this study was not entirely standard clinical practice, and a lack of subsidisation of donepezil outside of trial enrolment could have been a factor influencing retention. Perhaps the high retention rate could be commented on.

6. The analysis of GAS – cognition goals to attempt to better understand the degree of correlation with the ADAS-Cog is valid and most interesting. It is not clear however what proportion of goals set were in the cognitive domain – this information should be included, at least in summary form.

7. The main finding of the paper – that ADAS-Cog improvement at 6 months is more clinically meaningful than ADAS-Cog decline (whether set at 4 or 3 points) is a very strong and clinically useful conclusion when assessing individual’s response to an AChEI. However, it may still be valid in analysis of trial populations (rather than individuals) to take account of ADAS-Cog declines. This difference between individual and trial population responses (the latter often used in regulatory decisions) should be addressed.

8. The statement (page 10) that the changes seen over 6 months in the open-label trial cannot necessarily be attributed to the donepezil treatment is an important and very valid point. If word limits allow, this, and the fact that only completers were analysed, would be better also stated in the abstract.

9. The small number of women in the study is unusual, and perhaps reflects Dr Rockwood’s base is a Veteran hospital. This somewhat limits the generability of the results and should be briefly included in the discussion.

10. The references are a strength – comprehensive and contemporary.

11. The tables are detailed and although many will not spend much time on them, they are necessary to support the results and discussion sections.

12. The graphs (figures) are clear and most useful.