Author's response to reviews

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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Author's response to reviews: see over
June 7, 2007

Dear Dr. Le:

My colleagues and I were very glad for the opportunity to revise and resubmit our manuscript, entitled 'The clinical meaningfulness of ADAS-Cog changes in Alzheimer’s disease patients treated with donepezil in an open-label trial' (MS: 1654385463120670). We are grateful for the careful attention paid to our work by the reviewers, and we believe that the result is a much better paper.

We have provided a detailed point-by-point response below. Each set of comments was particularly helpful, and the paper should be much easier to read as a consequence.

I am respectful of the peer review process, and of the volunteer nature of reviewing. Consequently, I am grateful for opportunities like this to improve work that I hope can impact on both clinical practice and clinical research.

My colleagues have signed off on the revisions documented below. I look forward to hearing from you about the disposition of our manuscript.

Yours sincerely,

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C1. It would have been more rigorous to utilize data from double-blind randomized placebo controlled trials (DBRCT), and it is surprising that an analysis of the ADAS-Cog correlations has not been published using these data bases.

We agree. We have begun by working with the data to hand.

C2. The range of outcomes in this trial differ from those in most DBRCTs, as Ken Rockwood’s Goal Attainment Scaling (GAS) tool is not yet widely utilized, and may more accurately reflect true clinical meaningfulness of response to an AChEI.

We agree and hope that these data lend some insight into what ADAS-Cog change scores might mean.

1. A brief description of the clinical correlation 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 that their statement that the CIBIC better correlated than the ADAS-Cog with most outcome measures is reflected in other published work on the CIBIC?

Despite their widespread use, there are surprisingly little published data on the correlation between the ADAS-Cog and the CIBIC+.

2. Utilizing only the data from those who completed 6 months of treatment (ie a per protocol, observed case analysis) does not reasonably allow comparisons with DBRCT data as the better trials often utilize ITT analysis. Thus, the statement at the top of page 4 should be qualified.

The Reviewer is correct that the question of imputation is fraught. In antibiotic trials, it is clearly most conservative to maintain the original group assignment in the analyses and then to carry forward the last observation. In an open-label study, there is only one treatment group assignment, so the question becomes what to do about withdrawals. Withdrawals are often informative with balance due to inefficacy and intolerance. In either case, however, early withdrawal, before the opportunity to decline, favours the earlier, higher-functioning state.

While this was the strategy we followed in the original report, here, we are more interested in the question of what true change looks like, it seems to us more appropriate to only study people in whom the ADAS-Cog was actually changed. We have now expanded on this in the Methods section.

The statement on page 4 that originally read, “Here, for better comparison with the 6-month double-blinded trials, we included only those patients who received treatment for a minimum of six months, with no imputation,” has now been changed to, “Here, for better comparison with the 6-month double-blinded trials, we included only those patients who received treatment for a minimum of six months. To ensure that we would address only the meaningfulness of true change, we did not impute in the case of missing data.”
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 research who has administered the ADAS-Cog over 1,000 times, I doubt patients do know how they performed. This statement should thus be qualified.

Even so, patients in our experience often have some idea about whether they knew all the answers or struggled. The statement is meant to acknowledge that the patients were not truly blinded to their own ADAS-Cog performance and has been amended as such.

The original statement was, “The ADAS-Cog was completed independently of the CGAS. Patients would have some idea on how they performed on the ADAS-Cog, but neither they nor their caregivers were told of the ADAS-Cog scores,” but has now been changed to “The ADAS-Cog was completed independently of the CGAS, and although patients might have had some idea as to how they performed on the ADAS-Cog, neither they nor their caregivers were told of the ADAS-Cog scores.”

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

Agreed

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 practice, and a lack of subsidization of donepezil outside of trial enrolment could have been a factor influencing retention. Perhaps the high retention rate could be commented on.

We agree. The study took place at a time when government subsidization for treatment was not otherwise available. Treatment was new and widely advertised. People were keen to try. The GAS interviews were undoubtedly empowering and the field interviews in people’s own homes made it clear that we were interested in what people had to say. The local culture, at least in those days, reckoned that doctors knew what they were doing. All that, plus the open label design seems to have very much worked in our favour.

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.

Our thanks to the reviewer for bringing this omission to our attention. We have added the following data to Table 1 (page 19) to allow readers to interpret the GAS data in context.

<table>
<thead>
<tr>
<th>Treatment goals set at baseline</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PGAS-total, mean (sd)</td>
<td>8.6 (3.3)</td>
<td>8.2 (2.7)</td>
<td>8.7 (3.3)</td>
<td>8.6 (3.8)</td>
</tr>
<tr>
<td>PGAS-cognition, mean (sd)</td>
<td>1.2 (0.8)</td>
<td>1.1 (0.7)</td>
<td>1.2 (0.8)</td>
<td>1.2 (0.7)</td>
</tr>
<tr>
<td>CGAS-total, mean (sd)</td>
<td>3.4 (1.3)</td>
<td>3.1 (0.8)</td>
<td>3.5 (1.4)</td>
<td>3.3 (1.2)</td>
</tr>
<tr>
<td>CGAS-cognition, mean (sd)</td>
<td>2.1 (1.8)</td>
<td>2.5 (2.3)</td>
<td>2.2 (1.7)</td>
<td>1.8 (1.4)</td>
</tr>
</tbody>
</table>

81/95 patients/caregivers set cognition goals: respectively 16/19, 45/53 and, 20/23

81/95 clinicians set cognition goals, respectively 17/19, 45/53 and 19/23

7. The main finding of the paper – that the 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.

Agreed. We indicated that “a 4-point ADAS-Cog change at 6 months might help discriminate between patient groups”. This has been amended to indicate its potential regulatory usefulness.

That statement now reads, “In consequence, it appears that while such a 4-point ADAS-Cog change at 6 months might help regulators discriminate treatment effects between patient groups, a 4-point decline has little inherent clinical meaning for individual patient or physician decision-making.”

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.

The abstract has been changed accordingly.

The second sentence in the Methods section of the abstract now reads: “We studied the observed case, 6-month change from baseline on the ADAS-Cog, the Clinician’s Interview Based Impression of Change-Plus Caregiver Input (CIBIC-Plus), patient-Goal Attainment Scaling (PGAS) and clinician-GAS (CGAS).”

The following sentence was added at the end of the Conclusions section of the abstract: “The open-label design of this study does not allow us to know whether this is a treatment effect, which requires further investigation.”

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.

We feel the reviewer may have misread the data in Table 1, which indicates that most of the patients in the sample were women – overall 68/95 (72%). We have revised the table such that the type of data displayed – e.g., n (%), mean (sd) – is more clearly defined.

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

We thank the Reviewer for this endorsement.
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.

We thank the Reviewer for this endorsement.

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

We thank the Reviewer for this endorsement. Please note that we have amended the graphs in the revised paper, in the hope that, by plotting the ADAS-Cog response on the x-axis, these will be even clearer and to allow for easier comparisons across measures.

Response to Reviewer 2 (Dr. Farlow)

1. The general lack of concordance is not surprising as general global measures tend to focus on domains involving executive functioning, which in particular is a major factor characterizing deterioration through mild to moderate stages of AD, while ADAS-Cog does not assess executive functioning and thus ADAS-Cog is not really a ‘global’ assessment of cognitive functioning.

We agree, although we note that the use of only the cognitive goals did not make concordance substantially better. So some part of the reason for the differing impressions between the ADAS-Cog and the patent-centred measures appears to be responsiveness, and not just comprehensiveness.

2. It would be interesting to know, at least generally which domains were targeted in the global measures and what cognitive functions would be recognized for their performance (i.e., for a chosen domain would memory or orientation or executive functioning be required?) These data might better inform the reasons behind observed differences.

Thank you for this suggestion. We have amended the Methods section as follows:

“Examples of the types of goals that were set for each domain include: cognition – a decrease in repetitive questioning, improved word finding, improvement in recent memory, less misplacing of objects; function – performing various IADL and ADL tasks with less dependence; behaviour - less irritability, more initiative; social activities - outings, especially to scheduled activities such as church, bingo, card games; leisure - more interest in or effective performance of hobbies and pastime activities.”

Additional Revisions to the Manuscript:

- The manuscript has been reformatted in accordance with the online manuscript template provided on the BMC web site. Specific changes include:
  - e-mail addresses for all authors were added to the title page;
  - reference numbers are now cited before the full stop;
  - all unnecessary capitalization has been removed;
o figures were removed from the manuscript and will be submitted as individual files; and
  o a figure legend was added.
- Descriptive characteristics of the ACADIE population were added to the first sentence on page 3 (“71% women; average age=76 years, sd=8”) and to the second line of the first paragraph on page 4 (“mild=75%).
- The second last sentence on the bottom of page 4 was changed from “Goals can then be weighted or ranked in order of their relative importance (the most important goal receives the highest weight),” to “Goals can then be weighted or ranked in order of their relative importance (the most important goal receives the highest numerical rank).”
- For consistency, all references to carers were changed to caregivers.
- CIBIC+ was changed to CIBIC-Plus