Reviewer’s report

Title: The effect of stimulation therapy and donepezil on cognitive function in Alzheimer’s disease. A community based RCT with a two-by-two factorial design.

Version: 1 Date: 28 March 2012

Reviewer: Carina Wattmo

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The aim of the present manuscript was to study the effect of stimulation therapy on cognitive function after one year in community-dwelling Alzheimer patients. Strengths of the work are the systematically and prospectively collected dataset with wide inclusion and few exclusion criteria. In particular, the potential combination effect of donepezil and stimulation therapy is an interesting aim (comparisons of the 4 subgroups).

Major compulsory revisions

1. Methods, paragraph 2: Information about socio-demographic characteristics of the patients in the current paper is missing. In the previous paper the authors are referring to, level of education and co-morbidities are, for example, not reported. To better understand the findings it would be useful to have such information easily accessible.

2. Methods, paragraph 2: The overall drop out rate was 22% after 1 year. Was there any difference in baseline characteristics between the patients that completed the study and those who dropped? Was the percentage of individuals who discontinued equal among the subgroups, so that differential dropout was not driving some of the findings? Please discuss the possible influence in your analysis from the drop out rate (especially due to “worsening”), or how is this dropout accounted for in the analyses?

3. Methods, paragraph “Diagnosing Alzheimer’s disease”: How was Clock Drawing Test coded? If this scale has few levels and/or a skewed distribution, a non-parametric test (Mann-Whitney U test) would be more appropriate for comparisons between the groups than the parametric independent samples t test.

4. Methods, paragraph “Outcome measures”: How was Barthel Index coded? Please, give some information about this scale. Is it an informant-based measure? Did the caregivers provide information about the patients’ ADL status?

5. Methods, paragraph “Stimulation Therapy”: Please, give a more thorough description of the intervention cognitive stimulation. The authors state that the “Stimulation Therapy Program” was different for each participant taking functional status and professional background into consideration. Could this affect the result (for example, if level of education differed among the subgroups)? It is
described in the “Results section” that “All subgroups were well balanced at study entry with respect to age, gender, drug consumption and co-morbidities”. But educational level was not mentioned, please discuss.

In community-dwellers not regularly using community health care, community nurses or other caregivers guided by the nurses were responsible for the stimulation therapy. Were these “other caregivers” formal caregivers or family members? Please, clarify. If they were family members, could this affect the result (i.e. if there was unequal distribution of formal and informal caregivers among the subgroups)? Was the percentage of nursing home residents equal among the subgroups?

6. Methods, paragraph “Drug”: The dose of donepezil during the study was not reported.

7. Methods, paragraph “Statistics”: The authors correctly found that a sample size of 64 patients in each group was necessary to detect a 2 MMSE point difference in change. However, there were fewer participants than 64 in the 4 subgroups (Table 1, n=53, 40, 50, 37, respectively). This implies that the study might not be powered to detect the potential interaction effect between donepezil treatment and stimulation therapy (Aim 2).

8. Methods, paragraph “Statistics”: Please, clarify the following points regarding Linear mixed models. Doing the multivariate modelling as suggested below would more effectively address the authors’ aims of examine whether donepezil increased the effect of stimulation therapy on cognition, and better quantify the nature of the rate of the decline in the groups.

Are the dependent variables the patients’ cognitive scores (MMSE, CDT, ADAS-cog, respectively) from 4 months and onwards? (baseline values should not be used as the dependent variable)

Did you include any relevant independent variables (predictors), such as gender, age, level of education, co-morbidities, and cognitive severity at baseline (MMSE, CDT, ADAS-cog, respectively) in the models? The authors might also consider using dose of donepezil as a visit level predictor. It is important to mention the magnitude of effect and the uncertainty in it from each predictor, so that the reader can understand the clinical meanings of parameter estimates together with the “time trend” outcome.

How was the “time trend” variable expressed in the models? Time in months and the interaction effect “baseline cognitive status with time in months” would be preferable. Not only is baseline level of cognition an important predictor, but that there may be an interaction between baseline level and time (baseline MMSE (CDT or ADAS-cog) × t). This variable expresses the possible change in slope across time.

Was “subject” used as a hierarchical variable, i.e., to avoid correlation within subjects?

Were random intercept and random slope considered? That is, individual paths assumed to follow the path of the group except for the random effects, which
cause baseline level of disease severity to be higher or lower (random difference in intercept) and rate of decline to be faster or slower (random difference in slope) over time.

Did you perform a comparison among the 4 subgroups in the mixed models, for example, using dummy variables with the “placebo – standard care” group as the reference? (Aim 2)

How much of the variance was explained regarding the fixed predictors in the model?

9. Discussion, paragraphs 2 and 3: Potential areas of support and discrepancies in results need to be discussed including whether and how, for example, demographic characteristics, disease severity at baseline, methodological differences and various types of stimulation therapy might affect the outcome of different studies.

10. Discussion: A recent meta-analysis of Nonpharmacological Therapies including cognitive stimulation in AD has been published: Olazaran et al. 2010. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord 30: 161-78. This review might be a relevant reference for the current manuscript to further improve the discussion.

11. Table 1: A statistical analysis comparing the 4 subgroups regarding the clinical characteristics at baseline would be preferred. In addition, a comparison of socio-demographic characteristics at baseline among the 4 subgroups, please see point 1.

12. Tables 2 to 4: A measure of dispersion, for example standard deviation (SD) is missing in the tables. Due to the dropout, there is probably less certainty in the values (larger SD) for outcomes that are farther out in time from baseline. Please, clarify how the time trend statistic was obtained.

Minor Essential revisions


14. Discussion, paragraph 1: “an increase of 5-12 ADAS-cog points”. The described expected annual decline of 12 point is large, considering the reported mean of 5.5 ADAS-cog points (95% confidence interval up to 8.1 points) deterioration reported in the stated reference.

15. Background, paragraph 2, line 12: Typographical error, reference 3

**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.