**Author's response to reviews**

**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.

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BMC Editorial team

Dear Editor,

Thank you for reviewing our manuscript manuscript “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” by Fred Andersen, Matti Viitanen, Dag S. Halvorsen, Bjørn Straume, Tom Wilsaard and Torgeir A. Engstad. Please find enclosed a detailed list of revisions according to the reviewers’ comments. Revised/new text is underlined.

Reviewer 1, Asa K. Wallin
Major compulsory revisions.

1) Stimulation therapy. A more detailed description of the stimulation therapy is now given on page 9 as the first paragraph under “Intervention.” The text has been rewritten; “A program of stimulation therapy including physical activities, cognitive, sensory and social stimulation was developed and adjusted to each participant taking cognitive and physical function, educational level and professional background into consideration. The program included systematically performed and intensified daily activities like walking, domestic work, regular reading of books and papers, training in fitness rooms, dancing, crossword puzzles, listening to music, and regular participation in the social life of the community. A few more sophisticated activities such as reminiscence groups, Sudoku, aroma therapy and sensory garden were added, between which the participants could move freely. This stimulation therapy was carried out for a minimum of 30 minutes 5 days a week for one year (maximum 250 sessions a year) in close co-operation with the participant and his/her family or trained health providers. Each session of stimulation therapy was described in a log which was submitted to the study site weekly. These were then compared to the pre-planned individual stimulation program and assessed consecutively, approved or rejected by the study staff. In nursing homes the employee conducted the stimulation therapy while community nurses or other caregivers (family members or even neighbors) guided by the nurses were responsible for the stimulation therapy of community dwellers not regularly receiving community health care. The stimulation program was monitored and adjusted according to functional abilities and interests of the participants during the period of intervention. Nursing home residents and community dwellers received the same stimulation program with an exception for the individual adjustment. Participants living in municipalities allocated to standard care did not receive organized stimulation”.


2. **Drug.** Donepezil dosing and how the drugs were provided to the study participants is given on page 10, as the second paragraph under “Intervention.” The following text has been added: “Having received the randomization codes the pharmacy at the hospital in Bodø distributed the drugs to the patient or the caregiver according to a prescription from the family physician. All participants were prescribed donepezil or placebo once daily. Passing four weeks the dosage was increased from 5 mg to 10 mg. Adverse events were recorded consecutively.

3. **MMSE.** It is well known that the cognitive deterioration slope in AD varies across disease stage. The baseline mean MMSE sum score in the present study was 23.2 which are in accordance with mild disease stage. Inclusion criteria were MMSE 10 points or more. At entry 43 participants tested less than 21 MMSE points, 92 participants tested 21 to 25 MMSE points and 52 tested 26 MMSE points or more. Even the most cognitively impaired group (MMSE<21) retained cognitive performance during follow-up. As the main outcome in the present study was changes in MMSE sum score, we agree to your comments and have omitted the sentence “Based on the calculation of power we found that a sample size of 64 in each group was necessary to detect a 2 point differences in change of mean MMSE sum score using 80% power, a standard deviation of 4 and a two-sided significance level of 5%” from the paragraph under “Statistics” on page 11. In the paragraph “Participants” on page 6 the following text has been added: “At entry 43 participants tested between 10 and 20 MMSE points, 92 participants tested between 21 and 25 points and 52 participants tested 26 MMSE points or more. In the paragraph “Strength and weakness” on page 16 new text has been added: “However, a stratified analysis of a subgroup obtaining a MMSE score less than 21 points at entry (n=43) showed no differences, and the results were consistent for all three cognitive tests (data not shown)”. The results were consistent for three cognitive tests. No cognitive deterioration during follow-up was found. The following paragraph under “Strength and weakness” on page 16-17 has therefore been revised: “Furthermore, the stratified samples in the two-by-two factorial analysis could be prone to type II errors due to relatively small sample sizes, especially subgroup analyses of participants with MMSE<21. However, the differences between all groups were consistent for all three tests.

4. **Medication.** The description of donepezil dosing was given in point 2. The following sentence has been added under “Strength and weakness” (on page16): “None of the participants used memantin or other ChEI. Although 23% of the participants used anticholinergic drugs for co-morbidities [32] inappropriate drugs were equally distributed between groups and could hardly explain the results”.

5. **MMSE protocol.** The following sentence has been added under “Participants” (on page 6):” A standard MMSE protocol translated into Norwegian was used and the protocol was not changed during the study period”. In our opinion it is less likely that there has been a learning effect and we have added the following sentence under “Strength and weakness” (on page 17): “It is therefore unlikely that a MMSE learning effect has occurred”.


6. **Adverse events.** The following sentence has been added under “Results” (on page 13): “22 participants (25%) dropped out from the donepezil group due to adverse reactions compared to 8 (10%) in the placebo group, p= 0.008 (data not shown). 17 participants in the donepezil group reported gastrointestinal reactions, especially anorexia, diarrhoea and nausea compared to 6 in the placebo group. Other participants using donepezil reported depression, dizziness, nightmare and headache whereas these symptoms were uncommon in the placebo group. In two cases the adverse reactions were temporarily and the medication could be resumed. In the other cases the symptoms remained and the drug treatment had to be interrupted”.

7. **Medication.** Please see our reply to point 4.

8. **Dropouts.** The following sentence has been added under “Results” (on page 12): “The dropouts were equally distributed between subgroups. At entry the dropouts were older (82.5 ± 7.1 versus 80.4 ± 6.9 years), and more cognitively impaired (MMSE 21.17 ± 4.1 versus 23.48 ± 3.7) compared to those completing the study period”. Further new text is added under “Strength and weakness” (on page 16): “…and the dropouts were equally distributed among subgroups. A possible weakness is that lower MMSE score among dropouts could have influenced mean cognitive deterioration during follow-up. However, repeated measure analyses confirmed the main result of the study”.

Discretionary revisions.

9. **Restructure results.** The results section has been rewritten and restructured.

10. The language in the Discussion section has been revised.

11. Table 5 is revised

12. The following sentence was added under “Diagnosing Alzheimer’s disease” (on page 8): “…testing AD participants with a MMSE sum score exceeding 21 points”.

Reviewer 2, Carina Wattmo

Major compulsory revisions.

1. **Methods.** The following sentence has been added under “Methods, Participants” (on page 6): “At baseline no significant differences between subgroups were found with respect to age, gender, cognitive function, neuropsychiatric symptoms, activities of daily living, drug consumption, number of co-morbidities or education level (Table 5 and Table 6)”.

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2. Methods. Dropouts. Please see our answer to point number 8 referee 1.

3. Methods. Clock drawing test was coded 0-4. The coding has well defined levels: 0= Not able to draw the circle. 1= Draw the circle, but not able to place the figures on the right place in the circle. 2= Draw the circle, place the figure correctly, but not able to draw the hands in the circle. 3= Draw the circle, place the figure and draw and place the hands correctly in the circle, but not able to place the hands at a defined time. 4= Draw the clock and place the hands in a correct time position. The sample size exceeded 30 in all groups. Mann-Whitney U test and independent sample t-test were used with similar results. We decided to present the results from the independent sample t-test.

4. Methods. Barthel Index (Scale 0—20, better function with increasing score). This is an informant based scale including basic activities of daily living. The information is provided by close relatives, a spouse or a caregiver.

5. Methods. Stimulation therapy. Please see our reply to point number 1 referee 1. In addition the following sentence is inserted under “Results” (on page 12): ”The education level was significantly lower in the donepezil group compared to placebo (Table 2)” and under “Strength and weakness” (on page 16): Another possible weakness is that despite randomisation, participants in the donepezil group had a lower educational level compared to the placebo group. Less education is associated with an increased risk of AD [2] but it is questionable whether this risk factor has an influence on the cognitive trajectory in AD in any way.

6. Drug dosing. Please see our reply to point number 2 Referee 1

7. Methods. Statistics: Please see our reply to point number 4 Referee 1.

8. Methods Statistics. The drug arm of the factorial design was a double blinded RCT. As a consequence we initially decided not to use baseline values as covariance in the analyses of differences between drug groups. As the participating municipalities were not randomised to stimulation therapy or standard care we included municipality as random effect in the linear mixed models in order to control for possible clustering of data within the municipalities. To increase the reliability of the results we now have included several new analyses as recommended by reviewer. The mixed model analyses have been done over again using baseline cognitive function as covariate. The new p-values\(^2\) is inserted in Table 3, 5 and 6. Table 4 is new and shows the effect differences between each time point with confidence interval and p-values using baseline cognitive function as covariate. MMSE, CDT and ADAS-Cog are the dependent variables of the patients’ cognitive score at each time point. The dose of donepezil was increased from 5 to 10 mg after 4 weeks in all AD participants.
Donepezil dose is therefore not a random factor. The slope of cognitive decline depends upon baseline cognitive performance. AD participants in the present study had mild to moderate AD. However, 43 participants tested MMSE<21 at entry, but even this group retained cognitive function during one year follow-up. The following sentence has been inserted under “Strength and weakness” (on page 16): “It is therefore unlikely that a MMSE test learning effect has occurred”. We have introduced a covariance analysis adjusting for the correlation structure within subjects. As a consequence of few time points we have chosen an unstructured covariance matrix as this type of structure will fit the data best. If a compound symmetry had been chosen, it would have been identical with a random intercept but this presuppose a compound symmetric structure of the covariance matrix. This assumption would not be valid. It is unsuitable to include a model predicting changes in cognitive performance (explained variance) on an individual level, as biological variations is possible fairly significant. The following sentence has been inserted under “Statistics” (on page 11): “Repeated measures analyses assessed differences in time-trends between groups of participants completing one-year follow-up” and under “Results” (on page 12); “Repeated measures analyses were consistent with the Linear mixed model analyses”.

9. Discussion. The following sentence is inserted under “Discussion” (on page 14): “The differences could be due to smaller sample size and greater variation in cognitive function among participants in the Requena et al study compared to the present study. Differences in baseline cognitive function between mild and moderate AD may also give different cognitive deterioration slopes.” The following sentence is inserted under “Discussion” (on page 15): “The Hawthorn effect has to our knowledge only been addressed in one single AD study [30].”

10. Discussion. New reference: The following sentence has been inserted under “Discussion” (on page 14): In a recent systematic review, Olazarán et al [27] has evaluated the best effect of nonpharmacological therapies. Evidence of potential grade A treatment recommendation was found for the effect of multicomponent intervention in delaying institutionalisation and grade B treatment recommendation for improved cognition and activity of daily living. The intervention program of the present study is in accordance with these recommendations.

11. A new Table 2 has been inserted.

12. Table 1-6. Standard deviation is added in Table 1, 3, 4, 5 and 6, and 95% confidence interval is added in Table 2. P-values for equal time trend between groups adjusted for baseline cognitive function is added in Table 1, 3 and 4.
Minor essential revisions.

13. **Background, paragraph 2.** “Three” is changed to “several”


15. **Background.** Typographical error is corrected.

We hope that our comments and revisions have clarified the text and are in accordance with your request. Should there be anything missing or misunderstood, please contact me immediately.

Kind regards

Fred Andersen, MD, PhD