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: 21 March 2012

Reviewer: Asa K Wallin

Reviewer’s report:

- Major Compulsory Revisions

The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.

1. A thorough description of how the stimulation therapy was organized and of its content seems to be missing. The authors mentioned the frequency of stimulation but did not describe the degree to which the stimulus was physical, cognitive, or sensory. The authors stated that the stimulation was monitored and adjusted during the period of intervention; however the manner via which it was adjusted was not explained. Adjusted to what? What was the standard stimulation that the study aimed to provide? Was it provided and to what extent? Another concern is the need for a better description of whether there was a difference in the stimulation between patients living at home and patients in nursing homes.

2. A very essential point that the authors did not mention is the dose of donepezil that was used in the treatment arm of the study (5 or 10 mg?). Was the dose standardized? In what way? The fact that “the drugs were sent to the patient or the caregiver according to national guidelines for primary health care”, is not sufficiently explanatory, as the readers are not familiar with the Norwegian guidelines. Furthermore, how was the dose adjusted throughout the study? How many patients dropped out of the study because of side effects? As higher doses of ChEI have been shown to yield a better effect in cognitive tests, this is vital for the interpretation of the results.

3. The detection of a two-point difference in MMSE score in a population of mild AD could be a too high goal in a cohort of very mild AD patients. MMSE is less sensitive to decline in the early and late stages of AD.
I would not expect to see a deterioration of two points in MMSE in a very mild AD population even without treatment over 1 year. The mean MMSE level was 23, which is in the mild range. However, information was lacking regarding the number of patients in the cohort who had very mild, mild /moderate, and severe disease. The authors mentioned that a subgroup analysis of a cohort with MMSE score < 21 was performed.

How many patients were included in this group? Was this subgroup sufficiently large to render power to this calculation? Is it possible that differences between treatment arms could be detected if a larger cohort was used? This was mentioned in the paper, but the manuscript would be improved if these matters were discussed better.

4. It is intriguing to note that there were no differences in outcome between the donepezil -treated and the placebo-treated patients because such differences were detected in other studies. This could be due to low doses of donepezil, the use of other medications, or other factors. This was not discussed in the paper, which was an omission.

5. What MMSE protocol was used in the study? Did the authors change the words learned or the calculus section used? The test was carried out every 4 months: could there be a learning effect involved? This should be discussed.

6. A section describing the adverse events or possible side effects of treatment seems to be missing. In addition, how did the authors deal with the possible side effects of treatment?

7. It would be advisable to include a description of other medications used by the patients. For example, was treatment with memantine allowed? How could this affect the results?

8. The description of the population that dropped out during the study (22% of the patients) is missing. Was this cohort different from the remainder of the patients at baseline regarding age, MMSE level, treatment received, etc.? Why did they drop out?

- Discretionary Revisions

These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.
9. The Results section needs to be better structured.

10. The Discussion section, especially page 13, needs language revision.

11. In table 1, it is not stated whether the values are mean values.

12. The authors state that MADRAS was used, but not how it was used?

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

Quality of written English: Needs some language corrections before being published

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.