Author's response to reviews

Title: Behavioral symptoms in patients with Alzheimer's disease and their association with cognitive impairment.

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Author's response to reviews: see over
Dear editor and reviewers:

We appreciate the effort you have undertaken in reviewing the article entitled “Behavioral symptoms in patients with Alzheimer's disease and their association with cognitive impairment”.

Please find enclosed the responses to the comments you have made. We have also added the suggestions you proposed, which will undoubtedly improve the quality of the manuscript.

Reviewer: Edmond Teng
Version: 1
Date: 21 April 2009

Major Compulsory Revisions:

1. The sample population is relatively arbitrarily segmented into those with ADAS-Noncog scores # 25 and >25, and indeed, subject recruiting was based on this cut-off, to ensure relatively even recruitment of subjects with less and more severe BPSD. The group with scores #25 is described as “without BPSD.” However, as it is clear from the data from Table 1, the vast majority of subjects “with BPSD” and “without BPSD” had behavioral symptoms both over the past year and at time of study inclusion (#90% in both groups). Therefore, it seems a bit of a misnomer to call either group “without BPSD,” particularly because both the overall incidence of any symptoms and the incidence of many individual symptoms were similar between groups. What would seem to be different between the “with BPSD” and “without BPSD” groups would appear to be the severity of such symptoms as measured by the ADAS-Noncog scale rather than just their presence or absence. The manuscript would therefore benefit from a clearer articulation of why the cut-point on the ADAS-Noncog was chosen and what additional information can be abstracted from using such a cut-point.

As far as we know, there are not previous publications to clarify this issue. We established an intermediate cut point (values above and below 25) to ensure a relatively
satisfactory distribution of patients, those with more BPS or those with less BPS. We completely agree with the reviewer, but this stratification allows us to avoid the bias of having analyzed a sample of patients with major or minor behavior disorders as it is likely that patients attending consultation are those with more behavior problems. Stratification is likely to allow the sample being more heterogeneous.

We agree with this assessment, in the sense that all patients have BPS, and it is therefore not correct to use the terms “without BPS ”and ”with BPS”. It is probably more correct to use the terms “lower and higher BPSD scores”, terms that we will use throughout the entire manuscript instead of "without BPSD" and "with BPSD, which would not be correct.

2. The authors make clear that there are different patterns of symptoms between the “with BPSD” and “without BPSD” groups. This is consistent with prior work. The authors used multiple correlation analyses to demonstrate associations between specific symptoms. However, prior work has focused on factor, cluster, and principal components analysis to unravel the different behavior syndromes seen in different subsets of patients, and such a statistical approach may be more fruitful and statistically robust than the current approach.

Certainly in this study we use multiple correlation analyses to demonstrate different associations between specific symptoms. In addition to it and according to your suggestion we conducted a factor analysis of the ADAS-Noncog. Results are included in the manuscript. Two new tables (5 and 6) have been added.

3. On the bottom of page 8, the authors indicate a significant negative correlation between MMSE and ADAS-Noncog scores. This would suggest that MMSE scores decrease as ADAS-Noncog scores increase and the conclusion that could be drawn from this finding is that BPSD symptoms should get worse with decreasing cognition. However, at the top of page 9, the authors draw the opposite conclusion. Looking at the data from Table 1, I would have to tend to agree with the authors conclusions, since the BPSD- group is slightly skewed towards more severe disease. I suspect that the authors likely ran the correlation between ADAS-Noncog scores and the 3 levels of stratification of AD severity. If so, this point should be more clearly stated.
Also unclear is the statement on page 8: “Nevertheless, the presence of BPSD seems to be associated to a poorer cognitive function in the last two years,” since the sentence preceding it states that there were no statistical differences in MMSE scores, and then the subsequent paragraph asserts that BPSD were more common in subjects with milder dementia. The authors also note in their discussion (page 14) that other studies have intermittently found an association between the severity of cognitive and behavioral symptoms in AD. However, much of this work has suggested worsening of behavioral symptoms with increased dementia severity (at least until end-stage dementia is reached), which would seem to be the opposite of the findings reported here (see Mega et al, Neurology 46:130-135, 1996 and Reisberg et al, Bull Clin Neurosci, 1989 54:95-112). Perhaps a more detailed exploration of the current findings relative to prior findings would be helpful.

Regarding the statement “Nevertheless, the presence of BPSD seems to be associated to a poorer cognitive function in the last two years (MMSE1)”, the justification is that some of these data are retrospective and must be taken with caution. The retrospective MMSE and behavioral symptoms correlation probably has less validity, since the only objective collected measure is the MMSE.

In any case, in the manuscript discussion we insist on cross-sectional aspects of the study, which we believe are more valuable.

We ran the correlation between ADAS-Noncog scores and the present MMSE score. There were not significant correlations item to item between the current MMSE score and each item of the ADAS-Noncog scale, but there was a significant correlation between the current MMSE score and the global ADAS-Noncog score. It is the combination of all items which can find out a significant correlation between both scales.

4. In the current form of the manuscript, the data regarding AD treatments does not seem to add much to the interpretation of the data. The authors could consider more tightly integrating it with the rest of the paper, or eliminating it entirely.

We integrate AD treatment data, mainly risperidone data, to explain the increased presence of extrapyramidal symptoms in the patient group with higher scores on the ADAS-Noncog scale.
5. The frequency of hallucinations (around 30%) is somewhat higher than that reported with the NPI in both epidemiological and clinical populations (ranging from 10-15%). Given the high prevalence of other extrapyramidal symptoms in this cohort, it does raise the possibility that there may have been a significant number of DLB patients included in the study population, particularly since many DLB patients could meet DSM-IV criteria for AD. Were specific criteria applied to exclude such patients? If so, it would be helpful if they were more completely described in the methods.

Certainly, the frequency of hallucinations (around 30%) suggests that it is likely that there may have been a significant number of DLB patients included in our study population.

The use of DSM-IV criteria is probably a limitation in our study, and it is a point that we will introduce in the discussion to explain the possibility of having included DLB patients by using only these inclusion criteria. One limitation of our work is not having included other inclusion and exclusion criteria. But according to recent publications using the NPI, hallucinations and pacing are highly prevalent in patients with AD, and moreover, the frequency of 30% concerns about their presence in the last year (sometime during last year).

6. As noted elsewhere in this review, there has been a lot of previous work examining BPSD in AD patients. The introduction could certainly benefit from a greater mention of the previous work and be more explicit regarding the additional knowledge that the current contribution adds to the field.

We increased the content of the introduction, mentioning other previous works. In addition, we are more explicit regarding the additional knowledge that the current contribution adds to the field.

**Minor Essential Revisions:**

1. The ADAS-Noncog is typically scored by the examiner based upon both patient and caregiver interview and examiner impression regarding symptoms exhibited over the past week. The methods section could benefit from more explicit description of the task
administration, and the discussion could benefit from an inclusion of potential limitations of this approach—namely that the examiner may be overly influenced by their snapshot impression of the patient at the time of the visit— that may not be representative of behaviors present during typical daily routines.

In the methods section we add a more explicit description of the task administration. We are also more explicit in explaining the limitations of this approach, and we add your comment.

2. There are a scattered grammatical errors (mostly subject/verb mismatches) throughout the article which should be addressed.

We have corrected grammatical errors.

**Reviewer:** Robert Perneczky  
**Version:** 1  
**Date:** 26 August 2009

**Major Compulsory Revisions:**

1. **Introduction:** The introduction is quite short. I would suggest giving some more detailed information on the nature of BPSD in AD and elaborating on the rationale for the study. How could the enhanced understanding of BPSD improve the diagnostic and treatment of dementia? In my opinion, results of previous studies using the ADAS-noncog or the NPI scales to rate BPSD in AD (and their association with cognitive impairment) should also be referenced. The main aim of the study should be stated more precisely. Please use, “patients with AD” instead of, “AD patients” throughout the manuscript.

   We extend the introduction and elaborating on the rationale for the study, detailing the nature of BPSD in Alzheimer's disease in order to justify the objective of the study, and how understanding of BPSD can improve the diagnosis and treatment of these patients. We state more precisely the main and secondary objectives of the study. Previous studies using the NPI or Behave-AD scales are referenced.
We write “patients with AD” instead of, “AD patients” throughout the manuscript.

2. Methods (patient population): Was every eligible patient included in the study or where there any reasons for exclusion? How was the cut-off value for having or not having BPSD according to the ADAS-noncog defined?

This was an incidental sample of patients; recruitment was conducted simultaneously with the arrival of the patient to the consultation. The inclusion of patients in the study was conducted consecutively. 161 patients were excluded and the reasons were several; they either did not have an ADAS score, or some of the scale items were missing, or because they did not meet DSM IV criteria for dementia, or some demographic, clinical or treatment data were missing.

Due to the lack of any data, comparisons between both groups, patients included or not, have not been able to perform.

As far as we know, there are not previous publications to clarify this issue. We established an intermediate cut point (values above and below 25) to ensure a relatively satisfactory distribution of patients, those with more BPS or those with less BPS. This stratification allows us to avoid the bias of having analyzed a sample of patients with major or minor behavior disorders as it is likely that patients attending consultation are those with more behavior problems.

We have changed throughout the entire manuscript the expressions "without BPSD" for “lower BPSD scores”, and "with BPSD" for “higher BPSD scores”.

Methods (Variables): Where the MMSE and ADAS-noncog scales applied at the same visit? If not, this could be a significant bias due to the alternating nature of BPSD. It is not entirely clear to me, why and when the three mentioned MMSE scores were obtained. How where the cut-off values on the MMSE defined? A value of 27 as the upper limit for AD seems quite high.

Yes, the MMSE and ADAS-noncog were applied at the same visit (inclusion visit). This would be the cross-sectional part of the study. Collecting data in the same visit avoids selection bias. Thus correlations can be made without bias.
In addition to the current MMSE score, the last two MMSE scores available from medical records were collected. We also collected simultaneously in that first visit other retrospective data using the ADAS-noncog scale itself: what behavioral symptoms the patient had presented in the last year?

On the other hand, we recorded behavioral and psychological symptoms of dementia (BPSD) according to the International Psychogeriatric Association consensus conference (1996). These symptoms were collected at the time of inclusion, and retrospectively those that patient had suffered during last year.

We agree with the reviewer, probably a value of 27 as the upper limit seems quite high, but it has been based on previous studies. The inclusion of patients with a high score on the MMSE allows us including patients with a high cultural level that meet criteria for dementia.

3. Results (population description): Did the group of patients who were excluded from the study due to missing ADAS-noncog scores differ from the population used for the statistical analyses? In my opinion, only between-group differences that survive a correction for multiple testing should be reported as significant. This is a major concern. There are definitely correlations between the reported BPSD (as shown in table 4).

Due to the lack of any data, comparisons between both groups, patients included or not, have not been able to perform.

Table 4 provides the correlation analysis between ADAS-Noncog items according to both evaluable groups, those with lower and higher scores.

4. Result (AD treatment): I am not sure how to interpret the last sentence of this section. Does it imply that there were no significant differences in medication use between the two study groups (with and ‘without’ BPSD). I am not entirely convinced that this suffices to exclude medication effects on BPSD frequencies and severities. This limitation should at least be discussed in more detail.
There were no significant differences in treatment use of cholinesterase inhibitors and memantine among subjects with lower and higher BPSD scores. We clarify it in the results section. In contrast, there were differences in treatment use of neuroleptics. In the discussion we include as a study's limitation that may lead to bias the presence of previous treatment for BPS. We discuss this limitation in the discussion section.

5. Discussion: In my opinion, the limitation section should be expanded (no correction for multiple testing, probable medication effects, …)

We expand the discussion section including study's limitations as suggested by the reviewer (no correction for multiple testing, probable medication effects) that can bias the results.

Sincerely yours

M. Fernandez on behalf of all authors.