Reviewer’s report

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

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Reviewer: Edmond Teng

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In their manuscript, “Behavioral symptoms in patients with Alzheimer’s disease and their association with cognitive impairment,” Martinez and colleagues seek to further explore the role of non-cognitive symptoms in Alzheimer’s disease. The strengths of their contribution lie in the inclusion of a large and well-characterized sample recruited from multiple centers across Spain. They evaluated non-cognitive symptoms with a Spanish-language version of an established and validated scale, the ADAS-Noncog, and obtained further information about additional neuropsychiatric symptoms by clinical interview, including apathy, anxiety, agitation, and delirium. There has been a substantial amount of previous work in this field, and Martinez et al.’s results are largely consistent with this prior work. However, there are a number of issues that may need to be addressed before this manuscript should be accepted for publication.

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.

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.

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.

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.

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.

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.

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.

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

**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.