Author’s response to reviews

Title: Treatment patterns and burden of behavioral disturbances in patients with dementia in the United States: a claims database analysis

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Author’s response to reviews:

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Benjamin Ragen
Editor
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Dear Dr. Ragen,

On behalf of my fellow authors, thank you for considering a revised version of our manuscript "Treatment patterns and burden of behavioral disturbances in patients with dementia in the United States: a claims database analysis" (Manuscript ID#: NURL-D-18-00107R1) for publication in BMC Neurology.

In the second review of this manuscript, Shuying Zhang (Reviewer 1) and Qi-Hao Guo (Reviewer 2) had no further comments. The comments identified by the third reviewer, Dr. Stuart MacDonald were insightful and allowed us to further strengthen the manuscript. Point-by-point responses to his comments are detailed on the following pages of this letter. Changes to the manuscript based on comments have been highlighted in yellow.

We hope that you will find our revised manuscript to be improved and suitable for publication in BMC Neurology. If you have additional comments, please do not hesitate to contact me.

Sincerely,
Responses to Stuart MacDonald (Reviewer 3)

Comment 1: At several points in the manuscript, the authors clearly cite evidence demonstrating that patients with dementia and neuropsychiatric symptoms often require more medication, and typically transition earlier to subsequent levels of long-term care. Complementing Dr. Guo's earlier query re: dementia severity, to what extent might the well-documented issues of polypharmacy or multimorbidity influence the more complex clinical manifestations of dementia with BD?

Response to Comment 1: We appreciate Dr. MacDonald’s comment on including a discussion about polypharmacy and multimorbidities and agitation in patients with dementia. We have included the following text to the discussion on pages 14 to 15 (lines 320 to 329) to describe the published evidence to date on this topic and further research is needed to investigate how polypharmacy or multimorbidity might influence behavioral symptoms in patients with dementia with BD:

“Polypharmacy in patients with dementia is typically due to the significant comorbidity of medical and psychiatric conditions [29]. According to Desai and colleagues, polypharmacy increases the possibility of a “prescribing cascade”, in which side effects of drugs are misdiagnosed as symptoms of another medical condition resulting in further prescriptions and side effects [9]. Polypharmacy is also associated with a high incidence of drug-drug reactions and may manifest as BD [9]. Few studies have examined the association between polypharmacy and dementia [30, 31] and these studies did not evaluate how polypharmacy or multimorbidity might influence behavioral symptoms in patients with dementia. Therefore, further research is needed to elucidate how polypharmacy and comorbidities affect BD in patients with dementia.”

Comment 2: On page 14 of the discussion, and related to the issue of polypharmacy, the authors note that "The higher use of antipsychotics and antidepressants among the dementia patients with BD compared with patients without BD, in the current study, highlights potential off-label use of these medications for BD, underscoring the unmet need for a therapy with demonstrated effectiveness to treat BD in dementia". Given the risks of polypharmacy for older adults (particularly those with dementia), I wonder if the authors have (or can) reflect further on what these alternative therapies (or strategies) might be? For example, as implied in the discussion, might one of these approaches entail the stable presence of a caregiver who is actively involved in treatment? Going forward, it would be of great interest to evaluate whether patients with
dementia and BD had more limited access to a caregiver. Recent intervention evidence from various literatures (e.g., physical activity, social connectedness, music) suggests that key neuropsychiatric symptoms may be mitigated for those with dementia. Might such active engagement of caregivers, in concert with care providers, mitigate transition risk to subsequent levels of care (e.g., institutionalization)?

Accordingly, I wonder whether the authors can further augment their conclusion section (on page 16). For example, what are the authors’ suggestions regarding next steps for caregivers to contemplate when BD are manifest in addition to dementia? For example, relevant research and commentary over the past several decades (e.g., Silverstir et al., 2004) indicates widespread agreement that behavioral disturbances for those with dementia are effectively controlled with non-pharmacological support.

Responses to Comment 2: We thank Dr. MacDonald for sharing these important considerations for discussion, and we agree that strategies for treating BD in dementia should include behavioral and social care management and highlight recommendations from guidelines. Therefore, we have added a discussion on guideline recommendations including the use of non-pharmacological behavioral care strategies for the management of behavioral symptoms in patients with dementia. We also agree with that it would be of interest to evaluate whether patients with dementia and BD had more limited access to a caregiver in future analyses thus the following paragraphs on page 15 (lines 330 to 347) have been added:

“Given the risks of polypharmacy for older patients, particularly those with dementia [32], numerous behavioral care strategies have been studied as potential treatment for BD in dementia. Recent research suggests that use of behavioral care strategies that focus on preserved capabilities and interests in the patient with dementia and engagement of caregivers as promising approaches for reducing NPS in dementia [33]. These activities are thought to engage patients in a positive manner, potentially minimizing agitation or other NPS. In addition, instructions to caregivers to involve patients with dementia in activities may minimize their time spent caregiving and may enhance their own well-being [33].

American, British and Canadian guidelines recommend alternative clinical approaches as a first-line intervention including ruling out underlying causes and initiating and attempting non-pharmacological interventions such as behavioral interventions [34]. The most recently 2016 APA Practice Guidelines recommended a comprehensive, person-centered non-pharmacological approach prior to initiating the use of pharmacological treatment [21]. Although a range of behavioral techniques are available, notably they have a limited evidence base. Because behavioral care strategies that include the engagement of caregivers have been shown to potentially minimize agitation or other NPS [33], it would also be of interest to evaluate whether patients with dementia and BD have more limited access to caregivers in future analyses.”

Comment 3: The authors have focused their analysis on all-cause dementia with BD. Do the authors anticipate distinct patterns if the focus was restricted to those with Alzheimer Disease with BD?
Response to Comment 3: We appreciate Dr. MacDonald’s comment regarding whether we might anticipate distinct patterns if the focus of the study analyses were restricted to patients with AD with BD. However, Alzheimer’s disease accounts for 60%-80% of dementia cases in general thus we do not expect to see a significant change in results if the sample was restricted to those with Alzheimer’s disease only. It is worth noting that certain dementias such as Parkinson’s disease with dementia or dementia with Lewy bodies were not included in the sample and may indeed lead to different results. We have added the following discussion points on page 17 (lines 383 to 388):

“Different neurodegenerative diseases may be associated with certain NPS; however, few studies have examined differences in NPS between dementia subtypes and the results of such studies have been equivocal [36-39], making it difficult to establish a pattern of NPS in different subtypes of dementia. In the current study, analyses were conducted in patients with all-cause dementia. Further analyses are needed to determine if distinct patterns would emerge by dementia subtypes.”

Comment 4: I have no qualms per se with the statistical analyses performed. The techniques employed for the comparisons made were appropriate, with patterns of significance always in the expected direction. However, I do have a minor comment regarding the presentation of the results. Given the population, the authors have ample statistical power to detect group differences; I wonder whether it might also be useful to quantify the magnitude of such differences? Have the authors also considered including a suitable estimate of effect size to formally quantify the magnitude of group differences between BD vs non-BD? Alternatively, the authors could include further comment in the discussion that addresses the practical implications of observed differences between those with vs. without BD.

Response to Comment 4: Thank you as well for this comment. As correctly mentioned, observed differences between BD vs non-BD populations could have been statistically detected given the statistical power. When summarizing the study measures for the selected sample, the focus was not on testing statistical hypothesis but instead confirming the relevance of the measures selected and potential differences. We believe that the heterogeneity of these two subgroups are fully characterized with respect to the most relevant patient characteristics and the data presented in the analysis. Estimates of the effect size in terms of both point estimates and interval estimates are indeed useful for interpreting the magnitude of difference in certain analyses. Thus, we have added corresponding 95% confidence intervals to some of the key outcome measures including healthcare resource utilization and healthcare costs in the results section on pages 12-13 and in Table 4.