Author's response to reviews

Title: A prospective study of symptoms, function, and medication use during acute illness in nursing home residents: design, rationale and cohort description

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Author's response to reviews: see over
Thank you very much for the thoughtful and detailed reviews from the reviewers. The following is a point by point response to the reviews:

Reviewer: Dr. McCann

Major compulsory revisions:
1. Comment: “I was unable to replicate the first power calculation on the basis of a logistic regression model with the characteristics described. This makes me think the calculation used may not have been appropriate. I replicated the second calculation based on an independent samples t-test; however this is not the appropriate test for this data. If 75 people are surveyed once when healthy and once when ill, then a paired t-test would be appropriate.

In the current design it appears some individuals may be surveyed more than twice, and individuals are considered in separate healthy and sick groups (of approx 113 people). For this data I think a multi-level approach to change in characteristics over time within individuals would be necessary. In all cases, I am very worried about the current calculations and feel the study may be underpowered. I would encourage the authors to look into this and seek advice on sample size and appropriate statistical methodology for the study.”

**Response:** The first power calculation is based upon sample size calculation comparing two proportions. We assumed that among the 200 episode of acute illness (AI), 20% would have an interruption of CNS medications. Assuming that the proportion who would have withdrawal symptoms without interruption of CNS medications (due to other causes such as the acute illness itself) to be 15%, a sample size of 200 will provide 83% power (with an alpha of 0.05) to detect an absolute difference of 25% in the proportion with interruption of CNS medications who develops withdrawal symptoms (with a proportion of 40%). Based on the rate of medication interruption, we may be able to include other factors in a multivariable regression model; otherwise we may only be able to model bivariate effects of other factors in medication withdrawal symptoms. We have clarified that calculation in the following text:

On page 11 paragraph 2:
“For the outcome of withdrawal symptoms, we plan to compare proportions of patients who developed withdrawal symptoms if they had medication interruption to those who did not have medication interruption. For the sample size of 200 AI episodes, we estimated that 20% of them would have an interruption of CNS medications. Assuming that the proportion who would have withdrawal symptoms without interruption of CNS medications (due to other causes such as the acute illness itself) to be 15%, this will provide 83% power (with an alpha of 0.05) to detect an absolute difference of 25% in the proportion with interruption of CNS medications who develops withdrawal symptoms (with a proportion of 40%).”
In limitations, we have also included the following text to describe the potential difficulties with examining multiple factors.

On page 14 paragraph 3:
“A limitation of our study is that our examination of different levels of factors affecting medication interruption is limited by the proportion of AI with medication interruption. The analysis of the effects of multiple factors may require a larger sample size. However, we will likely be able to observe clinically important effects which are likely to be of larger magnitude.”

Regarding the analyses on functional status, we would like to thank Dr. McCann for the suggestions regarding the second sample size calculation. We agree that a multilevel approach is likely to be more appropriate—perhaps using a linear mixed effects model. Functional status data were collected at the time of enrollment, subsequently at 3 month intervals and at the time of illness onset and 14 days after illness. We plan to use a linear mixed model to estimate the effect of acute illness on function with functional status score as the outcome measure. We plan to include potential covariates, including patient demographics, chronic disease burden, symptom level and medication use, in the model if they were found to be associated with both acute illness and functional decline in bivariate analyses. However, considering that we do not currently know the within-person level correlation, we do not know to what extent this correlation will affect our power estimates. In this regard we view our analysis using this multilevel approach as exploratory. However, as mentioned above, we believe we will be able to observe effects of larger magnitude that are the most clinically important. The following text is added to reflect this plan:

On page 11 paragraph 2:
“For the outcome of functional decline, we collected functional status data at the time of enrollment, subsequently at 3 month intervals, and at the time of illness onset and 14 days after illness. We plan to use a linear mixed model to account for repeated measurements, to estimate the effect of acute illness on function with functional status score as the outcome measure.”

2. Comment: Further details of the calculations need included in the paper, as will the proposed analyses, specifically the analyses the calculations are based upon.

Response: We included further details of our planned analyses in the manuscript. We clarified the planned analysis of the following:

(A) medication interruption as an outcome measure with the following text:

On page 10, paragraph 3:
“For the outcome of medication interruption, we plan to first conduct univariate analyses on each patient level, environmental, provider level and other factors. If individual
factors are associated with the outcome, we plan to include them in a multivariable analysis to examine the independent effects of these factors on medication interruption.”

(B) withdrawal symptom as an outcome measure to examine the association with medication interruption with the following text:

On page 11 paragraph 2:
“For the outcome of withdrawal symptoms, we plan to compare proportions of patients who developed withdrawal symptoms if they had medication interruption to those who did not have medication interruption. For the sample size of 200 AI episodes, we estimated that 20% of them would have an interruption of CNS medications. Assuming that the proportion who would have withdrawal symptoms without interruption of CNS medications (due to other causes such as the acute illness itself) to be 15%, this will provide 83% power (with an alpha of 0.05) to detect an absolute difference of 25% in the proportion with interruption of CNS medications who develops withdrawal symptoms (with a proportion of 40%).”

(C) Other symptoms including pain, depression, disturbed behavior as outcome measures to examine the association with medication interruption:

On page 10, paragraph 2:
“We plan to estimate separate multivariable logistic regression models for the occurrence of outcomes of symptoms including pain, depression and disturbed behavior at the moderate or severe level as dependent variable for interruption in CNS medications. Covariates will include patient and illness characteristics outlined in Figure 1.”

3. Comment: Opiate withdrawal is measured with COWS, and Anti-depressants with DESS for SSRI. There appears to be no mention of withdrawal measures for antipsychotics other than the separate issue of relapse. How will this affect how antipsychotics cessation is dealt with in analysis?

Response: The effect of antipsychotic medication cessation is measured with symptom relapse using the Cohen Mansfield Agitation Index (CMAI). The reason we used this scale to measure the effect of antipsychotic medication cessation is because antipsychotic withdrawal has been associated with rapid relapse or rebound psychosis.¹ There is no clear established measure for measuring antipsychotic medication “withdrawal symptoms” per se. Relapse of psychosis or agitation, however, can be more reliably measured and is likely to be clinically relevant.

We have clarified the use of CMAI as a measure of antipsychotic cessation with the following text:

On page 9, paragraph 1:
“We used this scale [CMAI] as a measurement of the effect of antipsychotic cessation, because antipsychotic withdrawal has been associated with relapse symptoms which can be reliably measured using this scale.”

4. Comment: Can the following points be clarified in the text: is the full battery of measures administered at diagnosis of an acute illness, and then 14 days afterwards? Is baseline information collected at recruitment, and 14 days afterwards, or at multiple time points throughout the study? The statistical analysis mentions comparing functional decline when healthy and when unhealthy, is this change between these two 14 day periods i.e. the change in decline, or the change in score for each item? What statistical test is to be used to compare these two changes?

**Response:** The full battery of measurements of symptoms including pain, Clinical Opiate Withdrawal Scale (COWS), Discontinuation Emergent Signs and Symptoms (DESS) scale, and CMAI were measured during the time of acute illness. Because symptoms of withdrawal can occur acutely and resolve in a short period of time, the scales were repeated three times a week during AI episodes to determine if withdrawal symptoms occurred. Baseline assessment was performed at the time of enrollment. We also collected functional status data at the time of enrollment, subsequently at 3 month intervals, and at the time of illness onset and 14 days after illness.

The following text was added to clarify the schedule in addition to referral to Figure 2 which outlines the assessment scheduled.

On page 9, paragraph 3:
“The full battery of measurements of symptoms including pain, Clinical Opiate Withdrawal Scale (COWS), Discontinuation Emergent Signs and Symptoms (DESS) scale, and CMAI were measured during the time of acute illness. Because symptoms of withdrawal can occur acutely and resolve in a short period of time, the scales were repeated three times a week during AI episodes to determine if withdrawal symptoms occurred. Baseline assessment was performed at the time of enrollment. Functional status data were collected at the time of enrollment, subsequently at 3 month intervals and at the time of illness onset and 14 days after illness. Figure 2 outlines the timeline of our data collection during the study period.”

Discretionary Revision:

5. Comment: This protocol outlines two areas of interest, the effect of acute illness and the effect of medication cessation. The way these two factors relate and overlap may need more clearly stated. My initial feeling is that it may be more useful to separate the assessment of the physical effects of acute illness on one hand, and correlates of drug cessation on the other.
**Response:** Agree that these factors may overlap. To determine their independent effects, we have included in our models acute illness severity and type to account for the effect of acute illness in modifying the effect of medication interruption. This approach of course depends on the observation that only some (not all) acute illnesses are associated with medication interruption, and on our ability to compare 2 similar acute illnesses: one with, and one without, medication interruption.

6. Comment: While I agree that different factors may affect decisions at different stage of the treatment process, I would suggest that illness severity is more important at the start of treatment than at discharge, because at discharge, the illness is less severe, or cured, by nature of having been treated. Can the authors justify including medication withdrawal symptoms as a symptom of acute illness? Would it be more likely that acute illness (of a particular type, or a particular severity (e.g. one that causes a hospital transfer) may be a cause of medication cessation?

**Response:** Agree, we plan to examine the effects of different factors on medication interruption, including acute illness severity and whether one is transferred to the hospital. It is possible that providers could have decided to interrupt CNS medication because of clinical judgment based on the characteristics and severity of the acute illness. It is the potential benefit/harm of this judgment that it is our objective to determine.

7. Comment: While I understand withdrawal is an important outcome in itself, I would worry that including it as an outcome would lead to “double counting”. Pain may be both an outcome measure and an item on the withdrawal outcome.

**Response:** Our planned analysis for symptom included estimating logistic regression models for pain, depression, disturbed behavior, and withdrawal symptoms. To avoid “double counting” we can also calculate modified COWS and DESS scores (our withdrawal scales), leaving out the pain and irritability items, and see if our results change. The following text reflects this plan:

On page 10, paragraph 2:
“We plan to estimate separate multivariable logistic regression models for the occurrence of outcomes of symptoms including pain, depression and disturbed behavior at the moderate or severe level as dependent variable for interruption in CNS medications. Covariates will include patient and illness characteristics outlined in Figure 1.”

8. Comment: The title states this is a prospective study of symptoms, function and medication use during acute illness. As the eligibility criteria includes only those currently using medication and who are not sick, this is a study of onset of illness, symptoms, function, and also medication cessation & withdrawal symptoms among nursing home (NH) residents being treated with Opioids, antidepressants...
or anti-psychotics, and only those who have used the drugs to a level developing tolerance. The protocol title may benefit from clarity of purpose.

**Response:** We have changed the title to: “A Prospective Study of Symptoms, Function, and Medication Interruption During Acute Illness” to more accurately reflect the study.

Reviewer: Timo Strandberg

1. Comment: “My major query relates to how this population, especially the VA cohort being relatively "young", is comparable to nursing home residents in general. This should be commented.”

   **Response:** The VA cohort is relatively young compared to the JHL cohort and to nursing home populations in general. Also there are other differences in gender, race and chronic disease burden. The following text has been added to describe these differences and the implications for generalizability of the cohort:

   On page 14 paragraph 3:
   “Considering the two cohorts included in the sample, there were significant differences in the characteristics of the VA cohort compared with the JHL cohort. The VA cohort was younger, more likely to be male, black and less likely to have dementia. The different characteristics of the VA cohort may limit generalizability to community nursing homes, but the inclusion of the VA cohort also help complement the gender, racial makeup of the study sample.”

**References:**