Author's response to reviews

Title: Unintentional non-adherence to chronic prescription medications: How unintentional is it really?

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Author's response to reviews: see over
Response to Reviewers' Comments

Reviewer: Dianne Goeman

Reviewer's report:

1. Is the question posed by the authors well defined?
   The authors state two objectives:
   1. to study the prevalence and predictors of unintentional non-adherence
   2. to explore the inter-relationship between intentional and unintentional non-adherence vis-à-vis patients’ medication beliefs
   Objective two would be clearer if the authors removed the term ‘vis-à-vis’ and replaced this with ‘in relation to’.
   Response: We replaced "vis-à-vis" in our objective with "in relation to". (page 2, paragraph 1; page 5, paragraph 1).

2. Are the methods appropriate and well described?
   The authors reported that the adults with chronic disease that they surveyed were selected using the Harris Interactive Chronic Illness Panel (CIP). Although they state that it is designed to be nationally representative internet-based panel of adults with chronic diseases, it is not clear how the membership of this panel is selected. Clearly, the survey participants were not representative. As stated by the authors themselves compared to the US adult population the sample was under-represented by adults with an income less than $25,000, those with only high school education or less and were over-represented by Caucasians.
   Response: In the Methods section, we replaced the text "…which is designed to be a nationally-representative, Internet-based panel of adults with chronic diseases" with more detailed description of panel recruitment, as requested by the reviewer. (page 5, paragraph 2) Also, in the Limitations section, we added the following text: "The CIP recruits panel members through multiple avenues in an attempt to provide a representative sample of the adult, chronically-ill population and to reach under-represented and hard-to-reach populations of interest. However, some demographic biases were observed in the sample." This is in addition to other limitations previously stated. (page 19, paragraph 2)
   Also the authors state that all respondents identified themselves as adherent (persistent) to prescription medications.
   Response: In this study, we were interested in exploring patients' unintentional gaps in therapy. As stated in the Methods section (page 7, paragraph 1, last sentence), we deliberately excluded non-persisters (i.e., those who had discontinued their medication) from the analytic sample because their complete discontinuation of therapy cannot, logically, be unintentional.

3. Are the data sound?
a. The response rate for the survey was only 29% and as stated above, the sample was clearly biased toward well educated, high income Caucasians. A group who are more likely to be adherent.

**Response:**
We agree that our sample is not perfectly representative of the U.S. population with chronic disease. However, in the Limitations section (page 19, paragraph 2), we were transparent about observed biases relative to the U.S. adult population. Given that the study was conducted in a very large sample of patients with multiple chronic diseases, we believe it makes a worthwhile contribution to the literature on medication adherence. Importantly, to the best of our knowledge, this study is the first to explore the previously-untested relationship between unintentional and intentional non-adherence in relation to patients' medication beliefs.

b. There is no discussion in regard to cost of medication and how this may vary depending on the illness and insurance status.

**Response:**
We assessed patients' perceived medication affordability (see pages 8-9) and it was included as a key predictor variable in the bivariate as well as multivariate analyses.

c. I am surprised that the authors have chosen to investigate non-adherence linking asthma, hypertension, diabetes, hyperlipidemia, osteoporosis and depression. Reasons for non-adherence are known to vary across illnesses and in the case of asthma severity can be a significant factor to adherence to preventer medication.

**Response:**
The reviewer makes a good point that patients' reasons for non-adherence may vary across diseases. In fact, we just recently published a manuscript on this topic and found quite modest variations in patient-centered reasons for non-fulfillment and non-persistence across five chronic diseases, including asthma. In the current manuscript, we also studied variation in unintentional non-adherence across disease areas (see Tables 3 and 4). As noted in the Discussion (page 18, paragraph 3), one of the strengths of our study compared to previous research is that we studied multiple chronic diseases.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Given my concerns in regard to sample selection and the study of multiple conditions as one I am not convinced that the evidence provided supports the conclusion made by the authors.

**Response:**
We respectfully disagree with the reviewer. As we point out in our response to #3 above, we were transparent in our description of the biases in the obtained sample and appropriately noted that generalizations to all U.S. adults with chronic disease should be made with caution. Further, neither income nor education (the two key variables on
which our sample differed from the general U.S. adult population) was a principal focus of the manuscript. The principal focus of the analysis was the impact of medication beliefs on unintentional non-adherence. It is unclear to us how the observed education and income biases would negatively impact the meditational analyses. We are aware of no peer-reviewed literature which demonstrates persuasive effects of income and education on perceived need for medications or perceived medication concerns. Given that lower-income persons were under-represented in the sample, the observed effect of perceived medication affordability likely represents a lower-bound estimate. Rather than a limitation, our inclusion of multiple chronic diseases, instead of small niche disease groups included in past research, is a significant strength of this study. We are regrettably at a loss to understand how the inclusion of multiple chronic diseases could negatively impact the validity of our analyses and conclusions.

The authors conclude that unintentional non-adherence is not random and is predicted by medication beliefs, chronic disease and socio-demographics. They advise that health care providers should therefore screen for unintentional non-adherence by proactively addressing patients suboptimal medication beliefs before choosing to discontinue therapy. This conclusion does not appear to differ from previously published work and fails to add to the debate.

**Response:**
As indicated above, our study on unintentional non-adherence has two key strengths over the existing literature: a significantly larger sample and inclusion of patients with multiple disease areas rather than small niche disease groups. In addition, we explored the interrelationship between unintentional and intentional non-adherence vis-à-vis patient beliefs - a concept that has not been previously reported in the peer-reviewed literature. We would respectfully argue that this constitutes a significant contribution to the literature.

The authors also fail to address the significant issues of the cost and side effects of medication and that these can only be addressed by ensuring medication is affordable and safe.

**Response:**
We do, in fact, assess perceived medication affordability (which includes cost issues) and perceived medication concerns (which include side-effect concerns). These highly-reliable multi-item scales are described on pages 8-9 and their results are tabulated in Table 4. Perceived medication affordability and perceived medication concerns (along with perceived need for medications) are also included in the meditational analyses (Table 5).

6. Are limitations of the work clearly stated?
Some limitations are stated. I would like to see a clearer description of the Harris Interactive Chronic Illness Panel (CIP). Who set it up and for what purpose.

**Response:**
In response to the reviewer's suggestion, we provide a more detailed description of the Harris Interactive Chronic Illness Panel. (page 5, paragraph 2; page 19, paragraph 2).
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes, although I am surprised that many publications the authors refer to report on illnesses such as HIV, breast cancer and glaucoma. These are outside those listed for investigation in regard to non-adherence eg. Asthma, hypertension, diabetes, hyperlipidemia, osteoporosis or depression. Clearly, adherence issues to medication to treat illnesses which are life-shortening would differ.

Response:
The reviewer's comment supports the significant contribution our study makes to the debate in this research area. The existing evidence on unintentional non-adherence is limited because a majority of such studies were conducted in small samples in niche patient populations such as those with HIV, breast cancer, and glaucoma. The publications we cite in our introduction speak to the paucity of literature in major chronic disease areas such as diabetes, hypertension, hyperlipidemia, and depression. By studying patients with these prevalent chronic diseases, we add greatly to the body of research on this topic.

8. Do the title and abstract accurately convey what has been found?
The title ‘Unintentional non-adherence to chronic prescription medications: how unintentional is it really?’ conveys what the authors conclude from their research. I found the abstract difficult to follow. I think the authors should simplify it.

Response:
We performed copy edits to the Methods and Results section of the abstract to make it clearer and easier to follow (page 2, paragraphs 2 and 3).

9. Is the writing acceptable?
OK
Reviewer: Sarah Clifford

Reviewer's report:

Major Compulsory Revisions

Methods section: this section needs further information/clarification on the following points so that the reader can be clear about exactly who was studied and the measures used.

1. Study population, third paragraph: Could the authors explain what they mean by “index condition”? What did they do if participants had multiple conditions? How did they decide what was the “index condition”?
   Response: The index disease was the disease for which respondents completed the medication belief items. If self-reported persisters reported more than one of the six target conditions, one was randomly selected as the index disease (pages 6-7).

2. Study population, third paragraph: It isn’t clear why non-persisters were excluded, as patients can be non-persistent to one medication but persistent to others. The definition the authors used to define non-persisters (“if they had, in the last year, stopped taking a prescription medication for ONE of the six conditions without their providers telling them to do so”), means that they may have excluded people who were non-persistent to one medication for one of the conditions but were persistent to other medications for the main condition or persistent to medications for other conditions. This needs to be clarified. Would it be more accurate to say, “Only subjects who self-identified themselves as persistent to (i.e. currently on therapy with) ALL the prescription medications for their index disease form the analytic sample for the current study”?
   Response: In this study, respondents could only qualify for one medication-taking behavior (persistence, non-persistence, or non-fulfillment). If a respondent reported both non-persistence and persistence, their non-persistence behavior qualified them for the study. If a respondent reported both non-fulfillment and persistence, their non-fulfillment behavior qualified them for the study. If a respondent reported both non-fulfillment and non-persistence, their non-fulfillment behavior qualified them for the study.

3. Survey content, first paragraph: Were participants asked the adherence questions about each of their prescription medications for their index condition or were they just asked the questions once in relation to their prescription medications overall?
   Response: Participants were asked questions about their intentional and unintentional non-adherence as well as their medication beliefs in relation to all the prescription medications for their index disease.
4. Survey content, first paragraph: The authors should provide more information about where the three questions on unintentional non-adherence and the 11 questions on intentional non-adherence came from and whether they have been validated?

**Response:**
The three questions on unintentional non-adherence and the 11 questions on intentional non-adherence were adapted from validated measures published in the peer-reviewed literature. We now reference this literature in text (page 7, paragraph 2).

5. Analysis section: In the second paragraph, which adherence measure was used in the analysis needs to be clearer – e.g. it’s not clear whether the 3 items of unintentional non-adherence and 11 items of intentional non-adherence were used or the Adherence Estimator® to create the scale score of 0 – 100% adherence.

**Response:**
Thank you for helping us to describe the analysis more clearly. In the analysis referenced in the comment above, the three items on unintentional non-adherence were used to create a score of 0-100 for unintentional non-adherence, while the 11 items on intentional non-adherence were used to create a score of 0-100 for intentional non-adherence. We have clarified this in the manuscript as well (page 10, paragraph 1).

In the first paragraph it would be helpful to see more information on how exactly patients were classified as low, medium or high risk for non-adherence.

**Response:**
Details on how respondents were classified as low, medium, and high risk based on the Adherence Estimator® score are described in the publication cited as ref #30 in that paragraph. However, we added a brief description of the scoring algorithm to the text (page 9, paragraph 1).

Minor Essential Revisions
None.

Discretionary Revisions

1. Study population, first paragraph: a little more detail is needed about what the Harris Interactive Chronic Illness Panel is, e.g. what is meant by the term “panel” and does it consist solely of adults in the US or further afield?
Also, a brief mention is needed of the rationale for why the inclusion criteria were focused on the 6 specific chronic diseases and those aged 40 or over.

**Response:**
Per suggestion from reviewer #1 and 2, we have added text to the Methods section that provides more details on the Harris Interactive Chronic Illness Panel and how its members are recruited. (page 5, paragraph 2).

Only respondents aged 40 and older were included because patients in this age bracket bear a greater burden of chronic disease compared to adults age 18-39. The six chronic diseases that were chosen reflect a mix of symptomatic, asymptomatic, and mental-health conditions. They are some of the most highly prevalent conditions in the U.S. and are
associated with a significant clinical and economic burden for the U.S. health care system.³ This is now reflected in the text. (page 5, paragraph 3)

2. In the Discussion section, paragraph 4, some of the results are repeated. It would be more useful for the reader to see an explanation of these results rather than the numbers (which are already in the results section), e.g. that lower perceived need for medications was associated with greater likelihood of being careless with medications, etc.

   **Response:**
   We appreciate the reviewer's comment. However, we believe that the results referenced above form the crux of some of our key arguments in the manuscript and, thus, bear minor repetition. Also, the recap of these results naturally flows into the conclusion we draw at the end of the paragraph.

3. Discussion, paragraph 8: the authors state that “Most intentional non-adherence occurs in the first six months of therapy” but intentional non-adherence can occur at any time. Maybe it would be more accurate to say, “non-persistence most commonly occurs in the first six months of therapy”?

   **Response:**
   Good point. We made the change as suggested. (page 20, paragraph 2)
Reviewer: Alistair W Stewart

Reviewer's report:

This manuscript reads well. I found I occasionally got overloaded with detail as I read but this paper is not in my area of interest. The authors may like to reflect on whether all the analyses are needed.

Response:
We appreciate the kind words about the manuscript reading well. Per your suggestion, we did reflect on all of the analyses. However, we believe that all of the analyses and tables are necessary to make novel contributions to the peer-reviewed literature.

My specific comments are very few.

Minor Essential Revisions

The description of the study participants needs some clarification. Do they need to have exactly one chronic disease or at least one? If it is at least one then how is the index condition chosen?

Response:
The index disease was the disease for which respondents completed the medication belief items. If self-reported persisters reported more than one of the six target conditions, one was randomly selected as the index disease (pages 6-7).

Table 4 should report the reference category for the multi-category variables.

Response:
Thank you. The reference categories are now listed as a footnote to the table. (page 35).

Reference List

