Author’s response to reviews

Title: Understanding the emotions of patients with inadequate response to antidepressant treatments: Results of an international online survey in patients with major depressive disorder

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Author’s response to reviews:

1. Reviewer 1

1. Please provide some additional details on the random forest analysis, since it is not commonly employed, and on the type of software/package used to analyze data

Response: We have added an accessible explanation of the analysis to the methods section (page 6) and have specified the software used.

Descriptive statistics included means and frequency of responses (%). A driver analyses was conducted using random forest analysis [11]. A random forest is a method where many decision trees (500 in our analysis) are constructed. The analysis selects a random sample of cases as the training set for each tree, and at each potential branching of the tree, a random subset of variables is evaluated as potential splits. The output of a random forest analysis provides ratio-level data of the influence that each characteristic has on the presence of dependent variable. Higher scores mean that, on average, the nodes created when the tree splits on this variable are more homogenous than nodes created by splitting on variables with lower scores – in other words they are considered more important. Patient characteristics entered as independent variables into the analysis included time since first episode, past hospitalization, past psychotherapy, number of episodes experienced, length of current episode, number of ADT failures, current treatment of monotherapy vs. combination therapy, change on current treatment (PGI-C), level of impairment (PHQ item 10) and disruption of daily living (SDS mean score). The dependent variable was the presence of moderate-to-severe frustration with their treatment. The random forest analysis was performed using the “randomForest” statistical package in R. Validity testing was done using a logistic regression to determine the explanatory power of the entered predictors.
2. Another useful addition to improve clarity would be data related to regression analyses - e.g. one or more tables to be presented in additional materials

Response: We respectfully disagree and think that additional tables on the regression analyses will not improve clarity. We have added a full description of the Forest analysis in the previous response.

3. Under figure 1, line 42 please omit the article in "the depression"

Response: Removed as requested.

4. The authors may want to add information as to why patient-related characteristics were entered as predictors in the models (if I understood clearly), but some factors related to care were not. They may be relevant and may be investigated in this study or in future analyses (e.g. public vs private HCP; care provided by nurse vs. physician vs. specialist etc.)

Response: We have included this in our discussion of the limitations (page 19).

To the best of our knowledge, it is the first survey to evaluate the impact of frustration in patients with MDD. Strengths of this survey include its size and international approach. While this allowed us to note some interesting differences between countries, we did not explore the influence of culture or differing healthcare systems on the feelings of frustration. For example, we did not include type of healthcare (or type of healthcare provider) in the random forest analysis.

5. One important aspect that seem to have been overlooked is the study limitations. These should include the fact that data is self-report, which has both advantages (full disclosure by participants) and disadvantages (patient diagnosis was not confirmed by structured interviews; self-selection of participants and so on)

Response: We have added a new section (page 19).

To the best of our knowledge, it is the first survey to evaluate the impact of frustration in patients with MDD. Strengths of this survey include its size and international approach. While this allowed us to note some interesting differences between countries, we did not explore the influence of culture or differing healthcare systems on the feelings of frustration. For example, we did not include type of healthcare (or type of healthcare provider) in the random forest analysis.
analysis. The survey was conducted in Western countries, which limits its generalizability to other regions of the world. Other limitations include those inherent to patient self-report surveys, which are based on the patient’s own understanding of their condition, and are not compared with objective clinical information (e.g. about symptom severity, or response to treatment). Indeed, since our intent was to examine the patient perspective, we purposefully used subjective scales (instead of more standard clinical scales) to define an ‘inadequate response’ (PGI-C) and level of impairment (PHQ9 item 10). Patients were recruited from existing consumer panels, and we do not know how this may have biased the results. For example, it may be that patients who are frustrated with their healthcare are more likely to respond to health surveys. Conversely, they could be less motivated to reply to the invitation.

Reviewer 2

1. The introduction section should include work by Mark Zimmerman et al. (http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.163.1.148) who have previously published on what constitutes improvement from a patient's perspective.

Response: We have added a new sentence (page 3) using the suggested reference.

From the patient perspective, people with MDD want their treatment to help them return to their usual level of functioning, return to their ‘usual self’ and to regain optimism and self-confidence [5].

2. Additionally, the target population in this study seems to be patients with Treatment Resistant Depression (TRD) -- 82.8% respondents reported 2 or more treatment failures. Thus, authors may consider including unique challenges and burdens associated with TRD. Authors reference STAR*D and a major finding of STAR*D was that likelihood of responding to a third or fourth step treatment after failing the initial two steps were below 20% (one in five). Thus, lack of effective treatment could be a cause of frustration in TRD patients.

Response: We have incorporated this aspect into our discussion (page 17).

The primary reasons for frustration with medication were directly related to the unresolved symptoms and side-effects of ADTs. A major finding of STAR*D was that likelihood of responding to a third or fourth step treatment after failing the initial two steps was <20% [3]. Thus, the high levels of frustration with medication may reflect the fact that current treatment approaches/medications have not been effective, and that there is still an unmet need for treatments with an improved efficacy-tolerability profile.
3. It is unclear as to how these panelists were selected. Was this part of an ongoing study or were these participants selected just for this survey?

Response: Respondents were selected from a consumer panel as clearly outlined in Figure 1. We have emphasized this in our new strengths and limitations section (page 19).

Patients were recruited from existing consumer panels, and we do not know how this may have biased the results. For example, it may be that patients who are frustrated with their healthcare are more likely to respond to surveys. Conversely, they could be less motivated to reply to the invitation.

4. Of those reported here, how many were invited to participate in the survey (I assume 3243, but this has to be clearer)?

Response: Figure 1 gives the numbers of patients who met the various screening criteria. We have re-iterated in the limitations section that patients were recruited from existing panels, and that we do not know how this may have impacted our findings (see above).

5. Why was overall depression severity defined with the tenth item of PHQ-9? Such a use of PHQ-9 is non-standard. A sum of the remaining 8 items (as authors excluded the 9th item) would be a better indicator of current depressive symptom severity. The forest analyses should be repeated with the sum of 8 PHQ-9 items instead of just using the tenth PHQ-9 item.

Response: Since this survey was to examine the patient perspective, we felt it appropriate to gauge their perceptions regarding the overall level of impairment they experience due to their depression (which may be influenced by more than the 8 domains included in the PHQ-9). We realize that we should more accurately describe item 10 as ‘level of impairment’ vs ‘severity’ and have made this terminology change throughout the paper. We have also mentioned the reason for this decision in our new strengths and limitations section (page 19). We were not able to use item 9 of the PHQ-9 for ethical reasons. As suggested below, we have moved the PHQ-9 data to a supplementary appendix.

6. Authors have cited employment status and work productivity in introduction as well as discussion. Were employment status and work productivity impairments assessed? Being unemployed and persistent work productivity impairment early in course of antidepressant treatment have both been associated with poorer long-term clinical outcomes.
Response: We have added in the employment data to Table 1, and a comment on page 8. We did not, however, correlate this information with other outcomes.

7. Authors need to provide more information on how the open-ended responses were coded. Was this done manually or using a software? If manually, one or more rater and methods for inter-rater reliability.

Response: We have clarified (page 6) that responses were manually coded and that coded responses were validated by a second coder and quality checked by a research analyst.

8. Some of the findings could be summarized. Unclear as to the relevance of individual PHQ9 items in figure 2 when there were not used as measure of overall symptom severity. The number of figures should be reduced as it distracts from the main findings of the manuscript.

Response: We have moved the PHQ9 data to a supplementary appendix.

9. Generalizability of these findings needs to be addressed in the discussion section. This is consistent with the comment about greater details in methods section regarding participant selection. This study brings an important perspective from TRD patients but selection from narrow patient population (e.g. over 70% depressed patients fail to meet at least 1 in 10 commonly used exclusion criteria in antidepressant clinical trials - Carlos Blanco et al. and Mark Zimmerman et al.) may restrict the applicability of these findings to wider population.

Response: We have emphasized that the patient population was recruited from extensive consumer panels, and have noted in our limitations section (page 19) that ‘we do not know how this may have biased the results. For example, it may be that patients who are frustrated with their healthcare are more likely to respond to health surveys. Conversely, they could be less motivated to reply to the invitation.’

Reviewer 3.

1. Defining an "inadequate response" was done based on the PGI-C. When we assess inadequate response in clinical trial, we usually implement HAM-D. Considering the study's characteristic, it was inevitable to use a subjective scale. Thus, please i) describe PGI-C in a more detailed and ii) the reason it was chosen among many scales available.
Response: We have included more information about the PGI-C on page 5, and have alluded to the reasons why we used subjective scales such as the PGI-C in our discussion of the strengths and limitations of this study (page 19).

“Other limitations include those inherent to patient self-report surveys, which are based on the patient’s own understanding of their condition, and are not compared with objective clinical information (e.g. about symptom severity, or response to treatment). Indeed, since our intent was to examine the patient perspective, we purposefully used subjective scales to define an ‘inadequate response’ (PGI-C) and level of impairment (PHQ9 item 10).”

2. The discussion section lacks comments about limitation. Addressing possible limitation is necessary because it provides an insight for future researcher when they want to replicate the study or perform similar researches. The study was conducted only in the western world, so it may be difficulty generalize the results. The authors should mention them in the limitation section.

Response: We have added a new section (page 19). This also addresses the comments of the other reviewers.

To the best of our knowledge, it is the first survey to evaluate the impact of frustration in patients with MDD. Strengths of this survey include its size and international approach. While this allowed us to note some interesting differences between countries, we did not explore the influence of culture or differing healthcare systems on the feelings of frustration. For example, we did not include type of healthcare (or type of healthcare provider) in the random forest analysis. The survey was conducted in Western countries, which limits its generalizability to other regions of the world. Other limitations include those inherent to patient self-report surveys, which are based on the patient’s own understanding of their condition, and are not compared with objective clinical information (e.g. about symptom severity, or response to treatment). Indeed, since our intent was to examine the patient perspective, we purposefully used subjective scales (instead of more standard clinical scales) to define an ‘inadequate response’ (PGI-C) and level of impairment (PHQ9 item 10). Patients were recruited from existing consumer panels, and we do not know how this may have biased the results. For example, it may be that patients who are frustrated with their healthcare are more likely to respond to health surveys. Conversely, they could be less motivated to reply to the invitation.

3. The limitation of random forest analysis should also be addressed.
Response: The discussion about the random forest model already notes (page 18) that it is important to remember that our explanation power, or lift in this case, is low suggesting there are many things influencing feelings of frustration that are not included in the model.

4. In contrast to limitation, the authors did not emphasize the strength of this study. Were there similar studies in the past? If so, how are the present studies different from the previous ones. If no similar studies were done before, then the discussion should address this impact of the "new data."

Response: Please see our response to the comments above.

5. The authors cite same reference multiple times, which is not a proper way because readers may be confused with the core contents of the journal that you have cited.

Response: The maximum times any reference has been cited is 3 times (the STAR*D study).