Author’s response to reviews

Title: Patient characteristics, burden and pharmacotherapy of treatment-resistant schizophrenia: results from a survey of 204 US psychiatrists

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Dear Dr. Darren Byrne,

Thank you for considering our manuscript, “Characteristics, burden and pharmacotherapy of treatment-resistant schizophrenia: results from a survey of 204 US psychiatrists,” for publication in BMC Psychiatry.

We are grateful to the reviewers for their comments and input that have helped us to further improve our submission.

Following peer review, we have submitted a revised version of the manuscript that takes into account the reviewers’ comments. In addition, please find our itemized responses to the comments below.

We hope that the current version of the manuscript will be acceptable for publication in BMC Psychiatry, and look forward to hearing from you.

Best regards,

Dr. Christoph U Correll
Reviewer reports:

Feras Ali Mustafa (Reviewer 1)
Thank you for the opportunity to review this manuscript. I commend the authors for their efforts to undertake this important survey. I find the common lack of awareness of the standard criteria of TRS among psychiatrists, as well as the underutilization of clozapine, to be striking. The dissemination of the results of this study may help rectify this deficit.

Response: Thank you very much.

Tomihisa Niitsu (Reviewer 2)
The topic seems to be interesting for researchers in this field. This paper is well-written.

Response: Thank you very much.

Jean-Pierre Lindenmayer (Reviewer 3)
The aim of this study is to characterize treatment-resistant schizophrenia (TRS) patients in terms of demographics, burden, treatment history, and factors influencing therapeutic choice using data from an on-line survey of 204 psychiatrists who self-selected and completed three patient records: two of TRS and one schizophrenia (‘non-TRS’) patients. This is an important survey as there are few literature reports specifically on the burden patients with TRS present for both providers and families.

1. The background should focus less on the underlying mechanisms of TRS but more on published reports on the social and economic burden of TRS.

Response: We agree and have expanded the section on the social and economic burden of TRS (Background section, page 3, lines 79–95). It now reads: “TRS has a severe clinical and economic impact on patients, carers, families, and society as a whole [14–16]. Whereas drug costs are relatively low in TRS, hospitalization and total health resource utilization costs are considerably higher than in non-treatment-resistant schizophrenia (‘non-TRS’) [14, 15]. Contributing to high hospitalization costs, the hospitalization rate is twice as high in TRS than non-TRS [14]. Considering the burden on patients, unemployment rates are higher in TRS than non-TRS, and cognitive functioning and global psychosocial functioning are more impaired [14]. The prevalence of smoking, alcohol abuse and substance abuse is generally higher in TRS than non-TRS, and much higher than in the general population [15]. Across studies, 79% of patients with TRS show aggressive behaviors, and more than half have suicidal ideation or have attempted suicide [15]. From a caregiving perspective, there is a substantial burden on the informal carers of patients with schizophrenia and other psychotic disorders in terms of time, money, and psychological distress [16–18]. In focus groups, carers of patients with TRS – the majority of whom were family members
– reported an average of 37 hours per week providing direct care, as well as being on call much of
the rest of the week, thereby affecting their own finances, career prospects, social relationships,
and sense of freedom [18].”

2. Given that most of the data derived from the present survey does not relate to the actual burden
psychiatrists are confronted with, the title of the paper should be changed to delete the "burden".
A more appropriate title would be "Psychiatrists' perceptions of definition and treatments used for
patients with TRS".

Response: We apologize for this misunderstanding: the reviewer refers to the burden of TRS
patients to the psychiatrist, whereas we refer to the burden of symptoms to the TRS patient (see
also comment 6 below). We have now changed the title to clarify that ‘burden’ and the other terms
apply to patients with TRS and not to the surveyed psychiatrists.

Revised title: “Patient characteristics, burden and pharmacotherapy in treatment-resistant
schizophrenia: results from a survey of 204 US psychiatrists.”

Background:

3. In their definition of TRS they refer to "inadequate response in target schizophrenia symptoms”.
However, most definitions in fact refer to inadequate response in positive symptoms.

Response: We have revised the definition (Background section, page 3, lines 70–73) to read:
“Treatment-resistant schizophrenia (TRS) is broadly defined in clinical guidelines as an inadequate
response in target schizophrenia symptoms (often positive symptoms) following treatment with
two or more antipsychotic treatments of adequate dose and duration.” A new reference was

Methods:

They describe well the inclusion criteria for the psychiatrists surveyed. Two questions should be
addressed as well:

4. Why did they not emphasize in their sampling psychiatrists working in the public sector where
most of the patients with TRS are seen?

Response: We appreciate this comment by the reviewer, and, in hindsight, emphasizing in our
sampling those psychiatrists who work in the public sector would have been potentially beneficial.
However, we did not want to preselect respondents to the survey.

We have added this issue as a limitation of the study (Discussion section, page 15, lines 409–411):
“Recruitment did not specifically target psychiatrists working in the public sector, where most
patients with schizophrenia (and, by extension, TRS) are seen [48].”
5. How did they decide on the target number of 200?

Response: Including 200 psychiatrists, to yield data on 600 patients, was recommended by HRW Healthcare Research (who conducted the survey) based on 1) their understanding of the medical environment (e.g., the number of treating physicians working with sufficiently severe patients); 2) their experience recruiting such psychiatrists previously for research (including their recruitment partners’ feedback on the size of their panels, etc.); and 3) our desire to conduct statistical analysis with the data yielded. With regard to point 3, in addition to the three different patient groups planned at the outset (i.e., TRS, clinician defined; TRS based on presented criteria; and non-TRS), the planned sample size was anticipated to have sufficient power to further stratify the subgroups (for example, by number of hospitalizations, or employment status), while maintaining a minimum of n=30 per subgroup.

6. In the three sections of the survey, this reviewer did not find any question addressing the burden psychiatrists were encountering in the treatment of TRS patients.

Response: As for comment 2, the reviewer refers to the burden of TRS patients to the psychiatrist, whereas we refer to the burden of symptoms to the TRS patient. The manuscript includes relevant data on the burden of symptoms to the TRS patient, showing that TRS has a higher burden of illness, being associated with more unemployment, hospitalization, suicidality, and comorbidities than non-TRS.

We have changed the manuscript throughout to clarify that the burden applies to patients not psychiatrists. For example, the Background section (page 4, lines 106–100) now reads: “Using data from a survey of psychiatrists in the US, the aim of this study was to clinically characterize a TRS population, compared with a non-TRS population, in terms of patient demographic characteristics, burden of symptoms, treatment history, and factors influencing therapeutic choice.” The Conclusions section (page 15, lines 424–425) now reads: “According to the treating psychiatrists who took part in this study, symptoms have a greater clinical burden on patients with TRS than non-TRS.”

Additional questions regarding the data capturing in the survey:

7. How did the psychiatrists surveyed measure the positive/negative symptoms in their patient cases chosen?

Response: “Psychiatrists completed the patient records section based on a review of their own chart notes” – added to Methods section (page 5, lines 136–137).

Specifically, symptom prevalence was measured by Q14a. ‘What symptoms of schizophrenia does this patient currently experience (either chronically or as breakthrough symptoms)?’, and symptom severity was measured based on Q14b. ‘How would you rate this patient’s positive symptomology currently in terms of severity?’ A 6-point Likert scale was used for severity, as described in Table 2: “Severity rated 1 (minimal), 2 (mild), 3 (moderate), 4 (moderate–severe), 5 (severe), or 6 (extreme), for those patients experiencing symptoms.” Please refer to the Appendix for the precise question and answer options.
8. How were concomitant non-antipsychotic medications assessed; these are frequently used in patients with TRS.

Response: Concomitant non-antipsychotic medications were assessed by the following survey question (presented in full in the Appendix): Q12. ‘Which of these adjunct therapies, if any, have you ever prescribed for this patient whilst they have been under your care? [Select all that apply]

- Mood stabilizer
- Antidepressant
- Anxiolytic medication
- Other [please specify]’

We present the results of this question in the Results section (page 9, lines 253–258): “Furthermore, patients with TRS versus non-TRS were more likely to have been prescribed the following adjunctive psychotropic medications while in the care of the psychiatrist: a mood stabilizer, 43.6% (178/408) versus 23.0% (47/204), p<0.001; an antidepressant, 38.0% (155/408) versus 26.5% (54/204), p=0.005; and an anxiolytic, 30.1% (123/408) versus 19.1% (39/204), p=0.004.”

9. How was the dosage of antipsychotics used assessed?

Response: The dosing discussion in the manuscript relates to psychiatrists’ strategies to manage TRS, based on the following survey question (presented in full in the Appendix): Q24. ‘If you are faced with a patient with schizophrenia who has had two prior failures of antipsychotic medication, in what order would you use each of the following options in order to manage their condition? Please select the options to indicate your preference. If you would not use any of these options, please choose the “would not consider this option” column.

- Increase dose of current antipsychotic medication (if tolerated)
- Add a second antipsychotic medication
- Add a third antipsychotic medication
- Add a mood stabilizer
- Add an antidepressant
- Add an anxiolytic medication
- Suggest a long-acting-injectable formulation
- Suggest clozapine
- Suggest switching to a (new) atypical antipsychotic (excluding clozapine)
- Suggest switching to a (new) typical antipsychotic’
We present the results of this question in the Results section (page 10, lines 274–282): “The psychiatrists were asked to rank the order in which they would use ten specific treatment options to manage a patient with schizophrenia who had failed on two prior antipsychotics. The options were ranked as follows (mean rankings shown in parentheses): increase the dose of current antipsychotic (if tolerated) (1.6); add a second antipsychotic (3.6); suggest an LAI formulation (4.1); add a mood stabilizer (4.6); suggest clozapine (4.9); suggest switching to a (new) atypical antipsychotic (excluding clozapine) (5.0); add an antidepressant (5.6); add a third antipsychotic (5.9); suggest switching to a (new) typical antipsychotic (6.3); add an anxiolytic medication (6.3).”

Results:

The response rate of eligible psychiatrists was 7.3%, which is quite low, but not unusual for such surveys. Understandably, they have no information on those non-responding psychiatrists, but who would have been eligible. In response to questions regarding the definition of TRS, only 16.7% of psychiatrists listed two failed anti-psychotic trials.

10. No information is available on whether psychiatrists felt that adherence to antipsychotic medication was a required part of the TRS definition. This may not have been asked in the survey?

Response: Psychiatrists entered a spontaneous definition of TRS into an open-ended text box. The criteria stated by ≥5% of psychiatrists are presented in Figure 1. Interestingly, ‘Patient complied with the treatment used’ was specified by only 2 psychiatrists (1.0%). We have now added this to the Results section (page 7, lines 186–188): “Just 7.8% of psychiatrists specified that medications must have been correctly dosed, and <5% specified that medications must have been used for 6 weeks or an ‘adequate’ period of time, or that patients must have been adherent to the treatment.”

On the other hand, psychiatrists clearly listed the presence of delusions and hallucinations as more predominant in TRS patients as compared to non-TRS patients. Overall, none of the psychiatrists' responses were unusual nor surprising. Two only note-worthy findings: 1) psychiatrists did not perceive a different level of adherence to antipsychotic medications in TRS patients vs. non-TRS patients. 2) Psychiatrists ranked clozapine in the order of treatment options to manage a patient with schizophrenia who has failed on two prior antipsychotics only in 5th position!

Interestingly, when the psychiatrists were asked to select their top antipsychotics from a comprehensive list in terms of their overall satisfaction with them for TRS patients, among the top three was aripiprazole: clozapine (49%); aripiprazole (43.1%); olanzapine (41.7%).

Discussion:

11. They conclude that among US psychiatrists there is lack of clarity regarding the definition of TRS. While this may be true, they should specify that this lack of clarity was based on a very small and self-selected sample of psychiatrists.

Response: We have revised the Discussion section (page 11, line 303–305) to read: “This online survey revealed that there is a lack of clarity among US psychiatrists regarding the definition of TRS, based on a relatively small sample of selected psychiatrists.”
12. They also again refer to the higher burden found for TRS patients, although little actual data derived from the surveyed psychiatrists underlies this statement.

Response: As discussed in points 2 and 6, we have revised the text to clarify that we mean the burden of symptoms on the patient. Discussion section, page 12, lines 325–328, now reads: “When psychiatrist-selected TRS and non-TRS patient records were compared, observations were in line with previous data suggesting that symptoms have a higher burden on patients with TRS than non-TRS, being associated with more unemployment, hospitalization, suicidality, and comorbidities [14, 15].”

13. Their discussion often restates the results of their survey without adding more to their findings.

Response: We understand the reviewer’s concern and have added qualifiers as to why the results that we found are relevant, where such qualifiers were previously missing.

Discussion section, page 12, lines 331–334, now reads: “Of note, in the present study, persistent schizophrenia symptoms had a greater impact on self-care and disturbing/aggressive behavior in TRS than in non-TRS, underscoring the importance of identifying and addressing TRS early and effectively in order to improve overall outcomes.”

Discussion section, page 12, lines 335–339, now reads: “Considering treatment patterns in the psychiatrist-selected patient records, the most widely used antipsychotics in the total population (TRS plus non-TRS) were risperidone, olanzapine, and aripiprazole. This result is broadly reflective of treatment patterns observed in the US [28], strengthening the results by showing external validity, despite the selected sample of survey responders.”

They did find a relatively high percentage of TRS patients being treated with clozapine (15.9 %) in this survey, which is unusually high as they note and the authors correctly related this to a selection bias in their respondent sample.

Response: Thank you for your comment and for acknowledging that it had already been addressed.