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PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 71360

Title: Difference between treatment-resistant schizophrenia and clozapine-resistant schizophrenia

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02445242
Position: Editorial Board
Academic degree: MAMS, MBBS, MD
Professional title: Professor
Reviewer's Country/Territory: India
Author's Country/Territory: Taiwan

Manuscript submission date: 2021-09-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-08 14:57

Reviewer performed review: 2021-09-11 18:31

Review time: 3 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [Y] Yes [ ] No

SPECIFIC COMMENTS TO AUTHORS

The authors have raised some interesting issues. However, they might have to look at some of the other studies pertaining to these issues. 1. To meet the criteria for for clozapine resistance schizophrenia (CRS), patients have to meet the citeria for treatment resistant schizophrenia and fail to respond to an adequate trial of clozapine. The criteria for response differ a bit between different definitions. 2. An adequate dose of clozapine is defined as the dose needed to achieve plasma levels > 350 ng/mL. A daily clozapine dose of 400 mg has been shown to achieve a threshold of 350 ng/mL in most trials. The recommended clozapine dose range is from 300-900 mg/day. Average dosages are about 300 mg/day for women and 400 mg/ day for men. The minimum dose of clozapine required for establishing CRS is defined as the midpoint of the dose range. A Cochrane review comparing clozapine at very low doses (up to 149 mg/day), low doses (150 mg/day to 300 mg/day) and standard doses (301 mg/day to 600 mg/day) found no evidence of effect on mental state between standard, low and very low dose regimes. Additionally, the dose of clozapine required for adequate response among Asians patients varies from 150mg/day among women to 300 mg/day for men who smoke. Therefore, the recommendation of a dose range 200-500 mg/day of clozapine based on all these considerations cannot be considered low. 3. The authors are right in pointing out that the patients included in the study by by Masoudzadeh and Khalillian were suffering from treatment resistant schizophrenia rather than CRS. This is pointed out in table-4 of the paper. It has also been pointed out in the text that studies with ECT augmentation of clozapine response have been mainly conducted among patients with treatment resistant schizophrenia rather than those with CRS.

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Reviewer's code: 00632509
Position: Peer Reviewer
Academic degree: PhD

Professional title: Senior Scientist

Reviewer's Country/Territory: Croatia

Author's Country/Territory: Taiwan

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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is very vague: if the doses of clozapine are too low, it should be clearly stated in: "in the review article by Subho Chakrabarti [1], the adequate dose of clozapine (200 to 500 mg/day) in patients with CRS may be low." Also the clear statement needs to be written here if the authors are sure that these patients did not have CRS but had only TRS, (not "may"): "Therefore, participants in the study by by Masoudzadeh and Khalillian[3] may be TRS but not CRS."

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Reviewer's code: 02164764
Position: Peer Reviewer
Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Canada

Author's Country/Territory: Taiwan

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SPECIFIC COMMENTS TO AUTHORS

In providing a commentary on Chakrabarti (WJP, 2021) this letter highlights the distinction between TRS and CRS. The main message here is for researchers, who the authors believe should pay greater attention to this distinction: "Disentangling the differences between treatment-resistant schizophrenia and clozapine-resistant schizophrenia could be an important point for future studies". Mainly, the authors assert that a diagnosis of CRS should not be made until there has been an adequate trial of clozapine, either at 500 mg. per day or with serum levels confirmed to be adequate. They do not comment on the duration of such a trial, nor on how the outcome of the trail should be assessed (how resistance should be defined). The letter would perhaps have a greater impact if these two issues were addressed. The point that 200 mg. is too low seems important and perhaps deserves greater emphasis and clarity. I wonder if it would also be reasonable to identify 500 mg. as a minimal target dose, and to perhaps allude to the fact that there is some variability in recommended minimal dosages. If patients cannot tolerate this dosage, then is their schizophrenia clozapine resistant if the maximal tolerable dosage is lower, or if this a different issue (lack of tolerability rather than resistance per se)? What should future studies do? Since recommendations in the letter seem targeted partially towards research in future studies, it behooves the authors to make specific recommendations if the letter is to have an impact. The penultimate paragraph raises a difficult issue, but is limited to non-specific comments about it. There are many reasons for improvement or worsening in symptoms and a single trial in a single person is clinically practical, but scientifically limited. For example, when subjects are recruited into studies or clinical medication trials are started they are often at a stage

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in their disease course where they are more ill than is usual for them. Due to regression to the mean, some improvement may occur even if the clozapine is ineffective. None of these are problems with the content of the letter – which is effective at raising a particular distinction – I just feel (see points above) that it could be more impactful if a few additional details are further discussed.

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Position: Editorial Board
Academic degree: BSc, MSc, PhD
Professional title: Full Professor, Professor
Reviewer's Country/Territory: India
Author's Country/Territory: Taiwan

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

It is a well thought and valid clarification.