

## ## Reviewer 1

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

### Comment-1

Specific Comments to Authors: It is a well thought and valid clarification.

#### Response to Comment-1:

We appreciate the reviewer's comments.

## ## Reviewer 2

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

### Comment-1

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 trial should be assessed (how resistance should be defined). The letter would perhaps have a greater impact if these two issues were addressed.

#### Response to Comment-1:

We appreciate the reviewer's comments. We have added these two points in the revised paper.

#### Original:

A diagnosis of CRS is made when blood levels of clozapine is  $\geq 350$  ng/mL;

**Revised:**

A diagnosis of CRS is made **when an optimal blood level of clozapine ( $\geq 350$  ng/mL) has been reached for at least 3 months, and the changes in positive and negative symptoms and functional impairment have been assessed by validated instruments.**<sup>[2]</sup>

**Comment-2**

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)?

**Response to Comment-2:**

We appreciate the reviewer's important suggestions. We have added this point. Please see below.

**Original:**

however, if obtaining blood samples is not feasible, a minimum dose of 500 mg/day is recommended.<sup>[2]</sup> In the review article by Subho Chakrabarti,<sup>[1]</sup> the adequate dose of clozapine (200 to 500 mg/day) in patients with CRS may be low.

**Revised:**

If obtaining blood samples is not feasible, **500 mg/day is the recommended minimal dosage to define CRS unless intolerability issues exist. In the review article by Subho Chakrabarti,<sup>[1]</sup> the adequate dose of clozapine (200 to 500 mg/day) for defining patients with CRS is too low. However, the therapeutic dosage of clozapine may vary with the clozapine clearance. For example, the Asians have lower clozapine metabolism and need lower clozapine doses than the Caucasians.**<sup>[3]</sup> **Future studies can consider the variables that influence clozapine clearance in the definition of CRS.**

**Comment-3**

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.

### Response to Comment-3:

We are grateful for the reviewer's reminder. We have added this point.

### Revised:

If obtaining blood samples is not feasible, 500 mg/day is the recommended minimal dosage to define CRS unless intolerability issues exist. In the review article by Subho Chakrabarti,<sup>[1]</sup> the adequate dose of clozapine (200 to 500 mg/day) for defining patients with CRS is too low. However, the therapeutic dosage of clozapine may vary with the clozapine clearance. For example, the Asians have lower clozapine metabolism and need lower clozapine doses than the Caucasians.<sup>[3]</sup> **Future studies can consider the variables that influence clozapine clearance in the definition of CRS.**

### Comment-4

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 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.

### Response to Comment-4:

We appreciate the reviewer's important suggestions. We have added this point. Please see below.

### Original

Patients in the clozapine group achieved a 40% reduction of the Positive and Negative Syndrome Scale scores. Therefore, participants in the study by Masoudzadeh and Khalillian[3] may be TRS but not CRS.

### Revised

Patients in the clozapine group achieved a 40% reduction of the Positive and Negative Syndrome Scale scores. **Although regression to the mean may contribute to some improvement, a 40% reduction in symptom severity still implied that**

participants in the study by Masoudzadeh and Khalillian<sup>[3]</sup> were TRS but not CRS.

## ## Reviewer 3

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

### Comment-1

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."

### Response to Comment-1:

We appreciate the reviewer's comments. We have revised these sentences. Please see below.

### Revised:

If obtaining blood samples is not feasible, 500 mg/day is the recommended minimal dosage to define CRS unless intolerability issues exist. In the review article by Subho Chakrabarti,<sup>[1]</sup> the adequate dose of clozapine (200 to 500 mg/day) for defining patients with CRS **is too low**.

and

Patients in the clozapine group achieved a 40% reduction of the Positive and Negative Syndrome Scale scores. Although regression to the mean may contribute to some improvement, a 40% reduction in symptom severity still implied that participants in the study by Masoudzadeh and Khalillian<sup>[3]</sup> **were TRS but not CRS**.

## ## Reviewer 4

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

### Comment-1

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 criteria for treatment resistant schizophrenia and fail to respond to an adequate trial of clozapine. The criteria for response differ a bit between different definitions."

#### Response to Comment-1:

We appreciate the reviewer's comments. We agree you point. Therefore, we did not comment on this in our letter.

### Comment-2

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.

#### Response to Comment-2:

We appreciate the reviewer's important suggestions. We have added this point. Please see below.

#### Revised:

**However, the therapeutic dosage of clozapine may vary with the clozapine clearance. For example, the Asians have lower clozapine metabolism and need lower clozapine doses than the Caucasians.<sup>[3]</sup> Future studies can consider the variables that influence clozapine clearance in the definition of CRS.**

### Comment-3

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.

#### **Response to Comment-3:**

We appreciate the reviewer's comments.