Reviewer's report

Title: Randomised trials in treatment resistant schizophrenia: a broad overview

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Reviewer: Stefan Leucht

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In this manuscript entitled “Randomised trials in treatment resistant schizophrenia: a systematic review of the evidence” the authors covered all randomised trials investigating treatment options in treatment-resistant schizophrenia. Altogether, 268 trials were identified, most of them evaluated pharmacotherapy with clozapine (N=82). This article did not aim to determine the efficacy or tolerability of the various therapeutic options but to provide an overview in terms of the research activities in treatment-resistant conditions. The main outcome was the number of trials and participants examining a treatment approach in treatment-resistant schizophrenia. The most commonly evaluated treatments were, apart from pharmacotherapy, cognitive behavioural therapy, electroconvulsive therapy, or transcranial magnetic stimulation. Especially for treatments that are used in daily clinical practice very commonly the evidence is based on only a few and mostly underpowered studies.

The topic is highly relevant although no direct clinical implications can be derived from the results. Moreover, this submitted investigation can be regarded as a starting point for further analyses derived from the identified studies data that focused more on efficacy, acceptability, and tolerability of the different treatments. The methodology appears appropriate and the description and discussion of the findings is balanced.

INTRODUCTION:

The introduction focusses on the issue of non-response to antipsychotic medication in treatment-resistant schizophrenia, especially with clozapine which can be considered as first-line treatment in treatment-resistant schizophrenia. However, the scope of this investigation was broader. All randomised trials examining treatment options were covered including psychotherapeutic/psychosocial interventions and other biological approaches such as ECT or transcranial magnetic stimulation. This should be reflected in the introduction.

METHODS:

The sentence “The data extraction was done independently by DS” remains unclear in this context. Was this a double-check of the extracted data? Please specify.

The methods section would benefit from a clear definition of the criteria that were applied to consider a study as investigating treatment-resistant schizophrenia.
Especially for pharmacological studies, patients with intolerance to previous medication are often included.

DISCUSSION:

Interestingly, the authors identified more studies investigating clozapine augmentation strategies compared to some famous meta-analyses dealing with this topic, for example: Taylor DM, Smith L, Gee SH, Nielsen J. Augmentation of clozapine with a second antipsychotic - a meta-analysis. Acta Psychiatr Scand 2012 25(1):15-24. According to the online supplementary material, this discrepancy is not only caused by the newer search date and the inclusion of Chinese studies. Perhaps it would be of interest for the readers to mention/discuss this issue within the text.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

In the past 3 years:
Consulting/advisory board honoraria from Alkermes, Bristol-Myers Squibb, Eli Lilly, Janssen, Johnson & Johnson, Lundbeck, MedAvante, Roche
Lecture honoraria from Abbvie, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Essex Pharma, Janssen, Johnson & Johnson, Lundbeck Institute, Pfizer, Sanofi-Aventis
Eli Lilly has provided medication for a trial with me as the primary investigator