Reviewer’s report

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

Version: 3
Date: 16 June 2014

Reviewer: Henk Temmingh

Reviewer’s report:

Review of: “Randomized trials in treatment resistant schizophrenia: a systematic review of the evidence”

Thank you for the opportunity to review this manuscript. This paper addresses an important aspect in the treatment of people with schizophrenia who do not respond to initial treatment efforts.

Following are some aspects of the manuscript that need attention:

Title:

Discretionary revisions:

1. The title is somewhat misleading in that it creates the impression that this is a systematic review summarising the state of the evidence of interventions for treatment resistant schizophrenia (TRS). Although many boxes are ticked in the PRISMA statement, some may argue that one critical aspect of systematic reviews is not fully present, i.e. the assessment of risk of bias or systematic error. This is despite the author including an assessment of “double counting” of studies as inflating the number of studies.) See discussion below; see Cochrane handbook definition of systematic review).

2. I would suggest perhaps changing the title to include words “A comprehensive survey…. of RCT’s…”

Abstract:

Minor essential revisions:

3. When reporting the median, add the interquartile range as well. (25th to 75th percentiles).

4. The author uses the words “systematic review” and “survey” interchangeably. I would suggest sticking to one term throughout. This occurs discussion and limitations section of the paper as well.

Introduction:

Discretionary revision:

5. Reference needed at end of “…, and are enormously resource intensive- often for decades.”

Minor essential revision:

6. Please revise the sentence: “Whilst clozapine is the…, clinicians do often try
other approaches before its prescription (47.7 months delay in use of clozapine [9]….” brackets and punctuation need revision.

Major compulsory revision:
7. The choice of the primary outcome is stated only later under methods and the rationale for this choice needs to be developed in the introduction. The primary outcome is the number of studies and number of participants enrolled in RCT’s. In the discussion and conclusion sections frequent mention is made of sample size as often being inadequate in many studies - this seems somewhat abrupt and the reader is not informed earlier on about the importance and rationale of sample size assessments.

8. A rationale and argument needs to be developed in the introduction section and the authors should give reasons why they consider study numbers, size and total participant numbers to be important early on in the introduction section as to balance the discussion with the introduction, and to create a linear argument that runs through the introduction methods, results and conclusion section. The focus of the critical appraisal seems on random error and the likelihood of imprecision. Brief discussion of GRADE article: “Guyatt et. al. J Clin Epidemiol. 2011 Dec;64(12):1283-93”, seems warranted.

Aim:
Discretionary revision:
9. Suggest to specify “(pharmacological or non-pharmacological)” after “evidence for interventions”.

Methods:
Major essential revisions:
10. Please add the dates that are covered by the search (i.e. 1960 to 2012? Etc).

11. As mentioned before the authors need to clarify their risk of bias assessment. Are they arguing that double counting in more publication that arise from the same RCT are a form of “other bias” leading to systematic error? It would seem that double counting would lead merely to random error. Random error is not strictly related to bias and does not necessarily lead to invalid results, merely to imprecision. Perhaps mention the importance of sample size in the context of the total event rate (which is likely to be quite low in TRS trials).

Discretionary revision:
12. The authors mention that few Cochrane reviews provide data on the subgroup of TRS. Which Cochrane reviews are they referring to? Perhaps reference and point out in tables.

Tables 1-4:
Minor essential revision:
13. The Column header “Cochrane review *” is confusing. In the copy I received this column is empty and the star*, which seems to serve to indicate if a Cochrane review was done (table 1) seems to be used for none of the listed trials. Referencing of trials also seems missing.
Discussion:

Minor essential revision:

14. The sentences in the first paragraph: “Our broad overview did not look…., described or reported group of people whose illness is resistant to treatment.”, seem to refer to limitations and the same comments are repeated in the limitation section. Perhaps consider revising, reporting on only on the most prominent findings, and contrast with other available similar research and leave these two sentences for the limitation section.

Limitations:

See earlier suggestions on critical appraisal focusing on random error, precision versus systematic error (the later which is more characteristic of traditional systematic reviews).

Conclusion:

Major essential revisions:

15. This paragraph “Too often funders….proxy scales that are rarely used in clinical practice” seems out of place in the conclusion and should rather be worked into the discussion section.

16. The first mention is made here of “proxy scales” needs to be more clearly defined and examples given from some of the trials. A brief clarification of why these are considered “proxy” is warranted.

17. An example of a sample size calculation is given There seems to be an error with the type I and II error rates in brackets “(#=0.05, #=80%)”. Should this rather be #=0.20, indicating 80% power to detect a 20% difference? Furthermore in this example of a power calculation it is not mentioned whether the author means a 20% difference in relative risk or absolute terms. This calculation seems to refer to a relative risk difference, and should be specified as such. Also the authors might want to mention that GRADE would downgrade based on optimal information size which is related to the event rate and likely to be quite low if sample size isn’t at least N=300.

Discretionary revision:

18. Referencing of statements made such as “We don’t need…” is also desirable.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I have received a speaker honorarium from Pharma Dynamics