Reviewer's report

Title: Schizophrenia clinical guidelines and clozapine prescribing: a review

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Reviewer: Maarten Bak

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Comments on:

Schizophrenia clinical guideline and clozapine prescribing: a review

It is an important contribution to the expanding work on clozapine. This paper summarizes eloquently some of the most important studies on comparing the effectiveness of clozapine en its superiority in the treatment of patients with pharmacological therapeutic resistant schizophrenia.

Major Compulsory Revisions

1
The main message is in my opinion the under-utilization of clozapine. I do agree that this is an important message. However, I doubt whether is this statement is correctly answered for. Th organisation of this paper makes me wonder if this paper is a systematic review or a personal statement how the state of the art prescription of clozapine should take place? I suggest rewriting this paper as systematic review addressing the question why if clozapine is prescribed along the guidelines present. If not it appears not to be the case, personal explanations and suggestions are welcome.

2
Either way, I suggest that a description of the search strategy is presented. In the background section it is mentioned that a search has been performed in PubMed, Psychinfo, EMBASE and Cochrane databases. This is not present in the paper.

3
Why was the search from 2005 – 2013?

4
It may be argued that clozapine is not a third line therapeutic agent but a second line. See the outstanding paper by Agid e.a. 2011 J Clin Psych. In this paper it is argued that switching from olanzapine to risperidone (if started with olanzapine in FE psychotic patients) of switching from risperidone to olanzapine does not offer a major additional effect. Instead switching to clozapine improves the outcomes significantly and clinical relevantly.
The literature reviewed in this paper focused upon the primary outcome of symptom improvement. Without dispute this is important, but incomplete within the paradigm of choosing a specific drug or not. The matrix should at least involve the side-effect profile of clozapine. Although it is shortly addressed, it is not discussed within perspective of the problem of under-utilization of clozapine.

Minor Revisions

1. The conclusion of this paper that despite outstanding clinical guidelines clozapine is still underutilized is of great importance. I do agree. However, the question is why psychiatrists are reluctant to prescribe clozapine and therefore do not optimally treat their patients? The solution of pushing forward the role of the pharmacist may be debated and is not a general procedure throughout the world.

2. Discussing medication by a psychiatrist is mostly a very delicate issue, explaining transparently the pro’s and con’s. In psychotic patients very often very anxious and/or paranoid this is a delicate problem for which a good doctor patient relationship is a primary condition not only symptoms present. So provide the doctor with strong arguments why he should prescribe clozapine

3. Please discuss the positive outcomes of clozapine in relation to the problematic side effects. The conclusion might be that psychiatrists do need to take precautions when they prescribe clozapine, but if appropriate measures are taken clozapine is safe and offers really opportunities to treat very severely ill patients with schizophrenia.

Discretionary Revisions

1. The title is misleading. I expected a paper about how to use and prescribe clozapine. Instead, the paper argues that clozapine should at least be use according outstanding guidelines.

Level of interest: An article of importance 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:
'I declare that I have no competing interests'