Reviewer's report

Title: Schizophrenia clinical guidelines and clozapine prescribing: a review

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Reviewer: J Gören

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Compulsory revisions:

This paper is of interest and could be an important addition to the medical literature with revision and expansion. I do believe with some work it could be an exceptional addition to the literature. However, in its current state it is a superficial review that is poorly organized and does not add much to the literature. Also there are statements that are confusing, untrue or inappropriately referenced. For example, one does not need to be hospitalized to start clozapine, the definition of treatment resistance should come from treatment guidelines not a paper from 2000 from a lower tier journal, etc.

There are discrepancies within the paper. For example, the paper discusses treatment resistant schizophrenia as failure of two antipsychotic trials but then in ongoing challenges section of the paper provides a different definition. One which is from a 2000 paper, that is not in a journal one would consider as providing the major definitions of a disease. Treatment guidelines would be a better source for what is currently accepted as a definition for treatment resistance.

Writing can be confusing at times. For example, I am unclear on what “51% of patients had previously discontinued medications due to ineffective therapeutic response, although only 11% used clozapine” adds. Are you suggesting all 51% should have tried clozapine? What are clozapine recommendations? Is that prescribing clozapine or offering clozapine regardless of whether the patient agrees to treatment?

I would consider reformatting as a systematic review and expanding information. So Introduction, aims and scope, methods, trial outcomes (or results) and discussion.

The paper currently is not well organized. More thought should go into the purpose of the paper, the headings of the sections and what should be included in each section. For example:

• Clozapine vs chlorpromazine is in the historical background section not the clozapine vs other antipsychotics section
• Early onset model is discussed in the clozapine vs other antipsychotic section
• Reasons for reluctance to prescribe is included in clozapine prescribing trends
The current historical background contains some interesting information but a lot of it is unnecessary. In this day and age of large amounts of new medical literature becoming available daily, the vast majority of data in a paper should add to the readers’ knowledge base. For example, the discussion of D2 receptor occupancy, the belief that clozapine didn’t work due to lack of EPS and so on does not add to the readers’ knowledge base. The discussion of the wide adoption of SGAs in clinical practice helps frame the clozapine issue but could be limited to 1 or 2 sentences. If the paper is to focus on clozapine, it is unclear why there is such a long discussion of FGA vs SGAs, development of other SGAs etc. All that would be pertinent to this paper is clozapine information or clozapine vs other antipsychotics.

The introduction could be used to describe, briefly, the history of clozapine and the current monitoring parameters. It might also be helpful to include a discussion of mortality associated with clozapine after initiation of monitoring. There could also be mention of the registry as an addition obstacle.

Given that this is a psychiatry journal, the discussion of FGAs and their side effects is not necessary as the readership will already be quite familiar with these issues. Perhaps a sentence about first vs second generation could be included to frame future use of FGA and SGA in the paper.

The discussion of early onset, while interesting, does not add much to the paper. The area is highly controversial and definition of an adequate trial should stick to the currently accepted standard with only a line mentioning the early onset theory.

Consider the major categories of studies and organize the efficacy of clozapine section by those. For example, Clozapine vs FGAs, clozapine vs SGAs, clozapine vs polypharmacy, clozapine vs high dose antipsychotics etc. A table of studies would be useful and could cut down on the amount of text needed if the table included major information such as n, duration, rating scale, primary outcome measure, results etc.

Clinical guidelines section could be much briefer if a table was used to compare recommendations.

The pharmacist’s role section is vague. Multiple concrete suggestions should be given, including facilitating registration, monitoring etc. Also, it is unclear where the belief clozapine must be started inpatient comes from as it is often initiated or titrated in the outpatient setting.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

No conflict of interest to report