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Does adding a second antipsychotic to clozapine improve clinical response in resistant schizophrenia?

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Abstract

Clozapine constitutes the treatment of choice in patients with schizophrenia with persisting symptoms despite antipsychotics at adequate dose and treatment duration. However, an important proportion does not respond to optimal doses of clozapine, so the addition of a second antipsychotic might increase clinical response.
Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified 17 systematic reviews comprising 62 studies addressing the question of this article, including 26 randomized trials. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded adding a second antipsychotic to clozapine in patients with refractory schizophrenia probably leads to little or no difference in clinical response, and increases adverse effects.

Problem

Among 20% to 30% of patients with schizophrenia are considered to have a treatment resistant illness, namely persistent psychotic symptoms despite adequate treatment with antipsychotic drugs [1]. For these patients, clozapine is the treatment of choice [2],[3],[4]. However, an important proportion might not achieve remission despite clozapine at optimal doses [5]. So, it has been postulated adding a second antipsychotic would improve clinical response, but there is no consensus about this issue. On the other hand, this measure is associated to important adverse effects and costs.

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Adding a second antipsychotic to clozapine in patients with refractory schizophrenia probably results in little or no difference in clinical response.
- Antipsychotic medications are usually expensive drugs that are required for long periods in the treatment of schizophrenia, and they are associated to a high rate of adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 17 systematic reviews [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21] that include 62 primary studies (reported in 63 references) [22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72][73],[74],[75],[76],[77],[78],[79],[80],[81],[82],[83],[84], of which 26 are randomized controlled trials [22],[23],[24],[25],[31],[34],[35],[36],[37],[39],[40],[41],[43],[44],[48],[52],[58],[62],[63],[64],[66],[67],[70],[75],[78],[79],[84]. This table and the summary in general are based on the latter.
What types of patients were included	All of the trials included adults with a diagnosis of schizophrenia (six trials using DSM IV or CIE 10 criteria [31],[39],[44],[62],[63],[64]), with persistence of psychotic symptoms despite adequate treatment with clozapine. Nineteen trials also included conditions related to schizophrenia [22],[23],[24],[25],[31],[35],[39],[40],[41],[44],[48],[58],[62],[63],[64],[66],[70],[79],[84]. The trials included in- and outpatients, with no major medical or psychiatric comorbidity. In relation to severity of illness at the beginning of the study, 11 trials reported PANSS >= to 60 [23],[24],[36],[41],[43],[44],[48],[52],[58],[64],[70], 11 trials BPRS >= to 25 [22],[25],[31],[34],[35],[40],[63],[66],[78],[79],[84] and two trials CGI >=4 [62],[75]. The rest of the trials did not report severity.
What types of interventions were included	All the trials compared a combination of clozapine with another antipsychotic against clozapine alone or clozapine plus placebo. Eleven trials added risperidone [23],[24],[39],[40],[43],[44],[48],[58],[62],[63],[64], five sulpiride [22],[25],[31],[70],[79], four aripiprazole [34],[37],[66],[67], two pimozide [35],[41], one pipotiazine [84], one haloperidol [52], one ziprasidone [78], one sertindole [36] and one amisulpiride [75].
What types of outcomes were measured	The trials measured multiple outcomes, however the different systematic reviews grouped them as follows: • Clinical response, considered as a decrease of 20% or more in the PANSS or BPRS score. • Failure in response to treatment, relapse, persistency of positive and negative psychotic symptoms, treatment dropouts. • Adverse effects related to central nervous system: extrapyramidal symptoms, dizziness, tardive dyskinesia, drowsiness • Adverse effects related to cardiovascular system: tachycardia, arrhythmia, bundle branch block • Adverse effects related to endocrine system: galactorrhea, weight gain, high LDL plasma level. • Gastrointestinal adverse effects: abdominal distension, anorexia, constipation, salivation, nausea. • Hematological adverse effects: Leukocytosis. • Other adverse effects: anxiety, headache, insomnia, mood symptoms.

Summary of findings

The information about the effects of adding a second antipsychotic to clozapine is based on 12 randomized trials [22], [25], [31], [39], [40], [44], [48], [58], [62], [63], [64], [79], which include 771 patients. The remaining trials did not report the outcomes of interest or did not provide data suitable for meta-analysis. The summary of findings is the following:

- Adding a second antipsychotic to clozapine in patients with refractory schizophrenia probably results in little or no difference in clinical response. The certainty of the evidence is moderate.
- Adding a second antipsychotic to clozapine in patients with refractory schizophrenia increases adverse effects. The certainty of the evidence is high.

Adding a second antipsychotic to clozapine in refractory schizophrenia				
Patients	Adults with schizophrenia resistant to an adequate clozapine treatment			
Intervention	Adding a second antipsychotic to clozapine			
Comparison	Clozapine alone or clozapine plus placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT a second antipsychotic	**WITH a second antipsychotic**		
	Difference: patients per 1000			
Response to treatment	646 per 1000	672 per 1000	RR 1.04 (0.92 to 1.17)	⨁⨁⨁◯[1,2] Moderate
	Difference: 26 patients more per 1000 (Margin of error: 52 less to 110 more)			
Adverse effects	Neurological adverse effects, cardiovascular, endocrine, gastrointestinal, among others.		--	⨁⨁⨁⨁ High

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT a second antipsychotic** is based on the risk in the control group of the trials. The risk **WITH a second antipsychotic** (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded because of inconsistency among the studies.
[2] Despite a high risk of bias found in six out of twelve trials meta-analyzed, the trials proving most information had high quality.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence is applicable to in- or outpatient adults with diagnosis of schizophrenia that persist with psychotic symptoms despite an adequate treatment with clozapine monotherapy.
- It does not apply to patients with other major medical or psychiatric comorbidities such as major depressive disorder, substance abuse or active suicidality.
- It does not apply to patients receiving clozapine augmentation with other medications different from antipsychotic drugs.

About the outcomes included in this summary

- The outcomes included are those considered critical for decision-making according to the opinion of the authors of this summary. They coincide with those presented in the majority of identified reviews, and the main clinical guidelines.

Balance between benefits and risks, and certainty of the evidence

- There is moderate certainty evidence showing addition of a second antipsychotic to clozapine does not improve clinical response in refractory schizophrenia. Considering adverse effects associated to their use are frequent and potentially severe, the balance between benefits and harms does not favor their use.
- The following adverse effects were reported by the trials: hypersalivation, hyperprolactinemia, metabolic syndrome, tardive dyskinesia, sedation, weight gain, cognitive deterioration, insulin resistance, akathisia, agranulocytosis, oculogyric crisis, seizures, extrapyramidal symptoms, neuroleptic malignant syndrome, QT interval prolongation.

What would patients and their doctors think about this intervention

- Even though the existing evidence should dissuade most patients and clinicians of using this intervention, considering there are no clearly effective measures for the treatment of clozapine resistant schizophrenia, we believe some clinicians will be inclined to use it in spite of what is presented in this summary, especially considering the existing recommendations in the main guidelines.

Resource considerations

- In general, antipsychotic drugs are expensive and require long-term use, so apart from not being effective they increase cost and adverse effects.

Differences between this summary and other sources

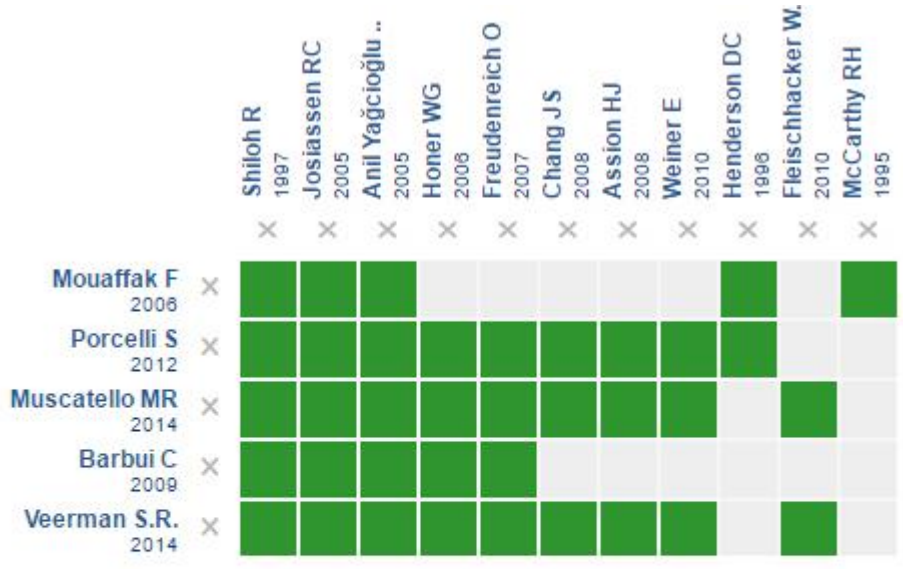
- The conclusions of this summary coincide with most systematic reviews included, although some indicate there is evidence to support augmentation of clozapine with some antipsychotics [8], [10], [14], [16]. Both NICE clinical guideline for schizophrenia [85] and APA guideline [86] consider the addition of a second antipsychotic to clozapine in refractory schizophrenia as a valid therapeutic alternative.

Could this evidence change in the future?

- It is unlikely that the conclusions of this summary regarding to the effectiveness of adding a second antipsychotic to clozapine in refractory schizophrenia change with future studies, because of the certainty of the evidence.
- We identified at least two ongoing trials [87], [88] addressing this topic in the International Clinical Trials Registry Platform of the World Health Organization, which could provide relevant information.
- New high quality systematic reviews could provide useful information, considering those we found have important limitations.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Adding a second antipsychotic to clozapine for resistant schizophrenia

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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