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Is electroconvulsive therapy effective as augmentation in clozapine-resistant schizophrenia?

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Abstract

Clozapine is considered to be the most effective antipsychotic drug for patients with treatment resistant schizophrenia, but up to a third of the patients do not respond to this treatment. Various strategies have been tried to augment the effect of clozapine in non-responders, one of these strategies being electroconvulsive therapy. However, its efficacy and safety are not yet clear. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified six systematic reviews including 55 studies, among them six randomized controlled trials addressing clozapine-resistant schizophrenia. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded electroconvulsive therapy probably augments response to clozapine in patients with treatment resistant schizophrenia, but it is not possible to determine if it leads to cognitive adverse effects because the certainty of the evidence is very low.

Problem

Up to 20-30% of patients with schizophrenia receive the diagnosis of treatment resistant schizophrenia, an entity that is defined as the absence of treatment response to two different antipsychotic drugs. In some of these cases, clozapine manages to control patient's symptoms, but 30-40% of them do not respond to this antipsychotic.

Various strategies have been tried to augment the effect of clozapine in non-responders, one of these strategies being electroconvulsive therapy, or the electric stimulation of the patient's brain under anesthesia. Its mechanism is not completely understood, but four pathways have been proposed: increased monoamine release, stimulation of the pituitary secretion of TSH, ACTH, endorphins and prolactin, increased neurogenesis, and post-session anticonvulsive effect.

This article seeks to address if electroconvulsive therapy is effective and safe as clozapine-augmentation in patients with treatment resistant schizophrenia.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 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

- Electroconvulsive therapy probably augments the effect of clozapine treatment in patients with treatment resistant schizophrenia
- It is not clear whether electroconvulsive therapy decreases the need of hospitalization in patients with treatment resistant schizophrenia because the certainty of the evidence is very low.
- It is not clear whether electroconvulsive therapy leads to cognitive adverse effects or if it increases the risk of seizures because the certainty of the evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found six systematic reviews [1],[2],[3],[4],[5],[6]that include 55 primary studies [7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[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], 24 of which are randomized control trials [7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30]. In six of the latter [7],[8],[9],[12],[16],[17], the patients were treated with clozapine, ergo our review will focus mainly in those studies. Nonetheless, the information about some of the outcomes was only reported in observational studies, and will be included in our analysis.
What types of patients were included	Four of the six randomized trials made the diagnosis of schizophrenia with CCMD-3 criteria [8],[9],[12],[17] and only one with DSM-IV criteria [16]. One study did not report the diagnostic method [7]. Two studies [9],[16] defined resistance as the lack of treatment response to two or more antipsychotics, while three studies defined it as the lack of response to three or more [8],[12],[17]. One study did not report the way in which they defined treatment resistance [7]. The observational studies [38],[55],[62] did not describe the diagnostic criteria used to define schizophrenia or how they defined treatment resistance.
What types of interventions were included	One trial [17] did not report the dose of clozapine used, three trials used >600mg/day of chlorpromazine equivalents [8],[9],[16], one used >250mg/day [7] and one used >1000mg/day [12]. The trials used 6 to 20 sessions of electroconvulsive therapy, but one study [7] did not report the number of sessions. The observational studies did not report the number of electroconvulsive therapy sessions used. Four trials performed electroconvulsive therapy sessions 2-3 times per week [8],[9],[16],[17] and two trials did not report the frequency [7],[12]. The observational studies [38],[55],[62] did not describe the dose or the frequency of electroconvulsive therapy. All trials compared the intervention against placebo or standard treatment.
What types of outcomes were measured	The systematic reviews evaluated the symptoms improvement according to any definition provided in the studies. The primary studies defined symptomatic improvement as a change in the Positive and Negative Syndrome Scale ≥20% [17], ≥25% [9] or ≥40% [16], or as a change in the Brief Psychiatric Rating Scale (BPRS) of ≥20% [7] or ≥25% [8],[12]. Only one systematic review evaluated the cognitive performance after electroconvulsive therapy [6].

Summary of findings

The information about the effects of electroconvulsive therapy is based on six randomized trials that include 368 patients, and in three observational studies for the outcomes in which no information was found in the trials. All of the trials measured treatment response. The information regarding performance in cognitive tests was reported in one systematic review [6], which included four primary studies for the measurement of the outcome. The presence of prolonged seizures was evaluated in only one observational study [55] and the influence over hospitalization days was reported in two observational studies [38],[62].

- Electroconvulsive therapy probably augments the effect of clozapine treatment in patients with treatment resistant schizophrenia. The certainty of the evidence is moderate.
- It is not clear whether electroconvulsive therapy decreases the need of hospitalization in patients with treatment resistant schizophrenia because the certainty of the evidence is very low.
- It is not clear whether electroconvulsive therapy produces cognitive adverse effects because the certainty of the evidence is very low.
- It is not clear whether electroconvulsive therapy increases the risk of seizures because the certainty of the evidence is very low.

Clozapine augmentation with electroconvulsive therapy				
Patients	Patients with treatment resistant schizophrenia			
Intervention	Electroconvulsive therapy (ECT) + clozapine			
Comparison	clozapine			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT ECT	WITH ECT		
	Difference: patients per 1000			
Treatment response **	576 per 1000	743 per 1000	RR 1.29 (1.08 to 1.55)	⊕⊕⊕◯[1,2] Moderate
	Difference: 167 patients more per 1000 (Margin of error: 46 to 317 more)			
Hospitalization	One study [62] showed the reduction of hospitalization days (from 176 to 73.8) in adolescent patients treated with ECT due to other pathologies. Other study [38] showed a lower rate of hospitalization relapse in 1 year in patients treated with ECT.		--	⊕◯◯◯[2,3,4] Very low
Cognitive performance ***	Difference: SMD -0.28 (Margin of error: -0.77 to 0.2)		--	⊕◯◯◯[2,3] Very low
Prolonged seizures	One study reported three episodes of prolonged seizures (over 90 seconds) in 8 reported cases [55]. No study reported convulsive status post ECT.		--	⊕◯◯◯[2,3] Very low

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

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

**Defined specifically for each study and exposed in the initial table.
*** The standardized mean difference is used when the outcome has been measured in different scales and is therefore difficult to interpret clinically. A general rule is that values under 0.2 are of lesser clinical relevance, values between 0.2 and 0.5 are of moderate relevance and values over 0.5 are considered of high clinical relevance.

1 Certainty was decreased in one level because the primary studies had serious risk of bias.
2 The evidence proceeds from observational studies.
3 Certainty of the evidence was decreased due to the indirect character of the information, as it was obtained from studies that include other kind of patients that received electroconvulsive therapy.
4 Given the imprecision of the results, the certainty of evidence was lowered for this outcome.

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 can be applied to patients with treatment resistant schizophrenia, defined as the lack of treatment response to at least 2 different antipsychotics, and users of clozapine in at least the dose of 600mg of chlorpromazine equivalents.

About the outcomes included in this summary

- In this summary we included all outcomes considered to be critical to the clinical decision making, according to the authors opinion. Because of this reason, outcomes to which scarce information exist are included (seizures and hospitalization).

Balance between benefits and risks, and certainty of the evidence

- Electroconvulsive therapy increases treatment response, but there is very low certainty evidence regarding various critical clinical outcomes.
- The certainty of the evidence regarding adverse effects is very low, because it was evaluated in a few observational studies. There is evidence about the cognitive performance in patients that undergo electroconvulsive therapy due to other conditions, especially depression, which concludes that the effects over memory are weak and limited to the first three days of treatment, with posterior recuperation of normal functionality [63].

What would patients and their doctors think about this intervention

- The evidence that proceeds from qualitative studies [64],[65] shows mixed results regarding the evaluation that users and families make regarding electroconvulsive therapy. Most studies show consistent results regarding the persistence of cognitive complaints (memory loss), which reinforces the importance of having evidence that proceeds directly from this kind of patients.
- Many clinicians tend to reserve electroconvulsive therapy for patients with treatment resistant schizophrenia, given the recommendations and clinical guidelines and the tendency of patients and their families to reject the treatment.

Resource considerations

- If the observed effects were certain, it would be a safe and effective intervention. The cost/benefit balance would be favorable.
- Cost-utility studies [66] suggest electroconvulsive therapy could be a recommendable alternative for patients with schizophrenia that do not respond well to clozapine.

Differences between this summary and other sources

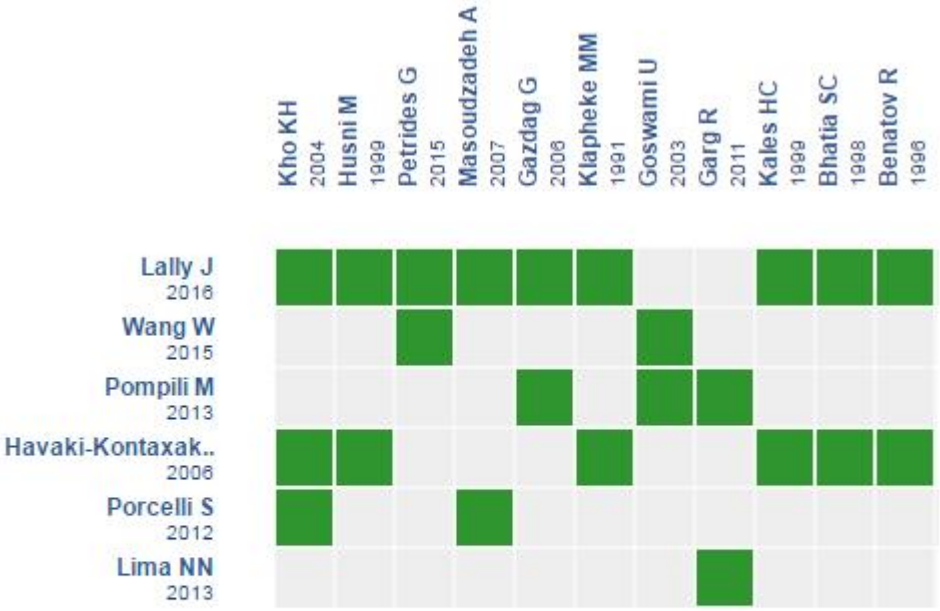
- The conclusions of this summary are partially concordant with the systematic reviews identified, but they put less emphasis in the limitations of the available evidence, and some relevant outcomes for decision-making.
- This summary is concordant with the American Psychiatric Association guidelines [67] that suggest electroconvulsive therapy use in patients with schizophrenia or schizoaffective disorder that do not respond to antipsychotic treatment.

Could this evidence change in the future?

- There is a high probability that the information provided by this summary changes with future evidence, because of the existing uncertainty.
- We did not identify randomized trials addressing this problem that are not included in the systematic reviews.
- We identified at least one ongoing trial [68] which could provide relevant information in the near future.

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:** Electroconvulsive therapy for treatment 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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