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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is cannabidiol an effective treatment for schizophrenia?

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Abstract

Cannabidiol has recently been proposed as an antipsychotic for schizophrenia. However, its clinical use and safety is controversial. To answer this question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We identified six systematic reviews incorporating four primary studies overall, including two randomized trials. We extracted data from the systematic reviews, reanalyzed data from primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded cannabidiol probably does not improve symptoms in schizophrenia and leads to frequent side effects.

Problem

Research has shown the endocannabinoid system plays an important role in the pathophysiology of schizophrenia. Several studies have concluded the use of cannabis is a risk factor for development and early onset of the illness. Moreover, tetrahydrocannabinol has been associated to psychotic symptoms typical of schizophrenia like hallucinations, delusions, depersonalization, and others [1],[3],[15],[16].

Nonetheless, cannabidiol might exert an antipsychotic effect opposing tetrahydrocannabinol in the brain and having an inverse relation with the positive symptoms of schizophrenia. Its mechanism of action is not clear, but it is suggested it would involve the cannabinoid receptors CB1/CB2 which inhibit anandamide reuptake, increasing endocannabinoid levels.

However, its efficacy and safety for the treatment of schizophrenia are not certain.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. 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

- Cannabidiol probably does not decrease symptoms in patients with schizophrenia.
- Cannabinoids probably lead to frequent adverse effects in patients with schizophrenia.

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], including four primary studies reported in seven references [7],[8],[9],[10],[11],[12],[13], including two randomized trials [7],[12]. This table and the summary in general are based on the latter.
What types of patients were included*	All the trials included patients with the diagnosis of schizophrenia, but only one specified the type, including patients with acute paranoid schizophrenia or schizophreniform disorder.
What types of interventions were included*	One trial used 600 mg of cannabidiol orally [12] and one trial used 300 mg or 600 mg of cannabidiol orally [7]. It could not be retrieved information related to the baseline treatment of patients. Both trials compared against placebo.
What types of outcomes were measured	The different systematic reviews used the following psychiatric scales as outcome measure of the improvement of psychotic symptoms: • BPRS (Brief Psychiatric Rating Scale) • PANSS (Positive and Negative Syndrome Scale) In addition, one trial evaluated the cognitive deficit through the SCWT scale (Stroop Color Word Test) Other outcomes evaluated were the presence of side effects associated to the traditional treatment of schizophrenia like extrapyramidal symptoms, levels of prolactine and weight gain. One trial lasted four weeks [12]. No information about the duration of the second trial could be retrieved.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of findings

The information about the effects of cannabidiol in schizophrenia is based on two randomized trials that include 57 patients [7],[12].
Both trials measured the improvement of symptoms through the PANSS and BPRS scale. One trial measured the cognitive deficit through the SCWT. None of the reviews identified were able to extract data in a way that could be incorporated in a meta-analysis, so the information presented below corresponds to a narrative synthesis of the information obtained from the reviews.
The summary of findings is the following:

- Cannabidiol probably does not decrease symptoms in schizophrenia measured by the PANSS scale. The certainty of the evidence is moderate.
- Cannabidiol probably does not decrease symptoms in schizophrenia measured by the BPRS scale The certainty of the evidence is moderate.
- Cannabidiol probably does not improve cognitive deficit of schizophrenia measured in SCWT. The certainty of the evidence is moderate.
- Cannabinoids probably lead to frequent adverse effects in patients with schizophrenia. The certainty of the evidence is moderate.

Cannabidiol for the treatment of schizophrenia		
Patients	Schizophrenia	
Intervention	Cannabidiol	
Comparison	Placebo	
Outcomes	**Absolute effect***	**Certainty of the evidence (GRADE)**
Symptoms measured by PANSS*	No systematic review found an effect on this outcome [1], [2], [4]	⨁⨁⨁◯[1] Moderate
Symptoms measured by BPRS**	No systematic review found an effect on this outcome [1], [4]	⨁⨁⨁◯[1] Moderate
Cognitive deficit measured in SCWT***	No systematic review found an effect on this outcome [1], [3], [6]	⨁⨁⨁◯[1,2] Moderate
Adverse effects	The information about adverse effects is limited in the evidence identified. However, adverse effects in other populations are frequent [5]	⨁⨁⨁◯[3] Moderate

GRADE: evidence grades of the GRADE Working Group (see later in this article)

* PANSS: *Positive and Negative Syndrome Scale*
** BPRS: *Brief Psychiatric Rating Scale*
*** SCWT: *Stroop Color Word Test*

[1] We downgraded the certainty of the evidence in one level for imprecision due to the small sample of population studied.
[2] We decided not to downgrade the certainty of the evidence due to risk of bias, because the presence of bias would reinforce the conclusion of no effect.
[3] We downgraded the certainty of the evidence in one level for indirectness since it comes from patients with other conditions.

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

- The evidence presented is applicable to any patient with the diagnosis of schizophrenia but it could be extrapolated to any patient with psychotic symptoms.
- The conclusions in this summary apply to cannabidiol only, not to cannabis or other cannabinoids. There is consensus that the use of other cannabinoids could worsen the illness [14],[15],[16].
- The limited evidence cannot establish if there is a subgroup of patients that could have a different effect with this intervention.

About the outcomes included in this summary

- The outcomes presented in the summary of findings are those considered critical for decision-making by the authors of this article and in general agree with the main systematic reviews.

Balance between benefits and risks, and certainty of the evidence

- The intervention probably has no benefit on the studied population and it could lead to adverse effects, so the risk/benefit balance is not favorable.

Resource considerations

- It is an intervention that probably has no benefit, so it does not correspond to estimate a balance between benefits and costs.
- Notwithstanding, commercial formulations of cannabinoids are generally expensive.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary most patients and clinicians should incline against the use of this intervention in schizophrenia.
- However, considering the positive perception of medical cannabinoids in public opinion, some patients and clinicians could choose to use them despite the evidence presented in this summary.

Differences between this summary and other sources

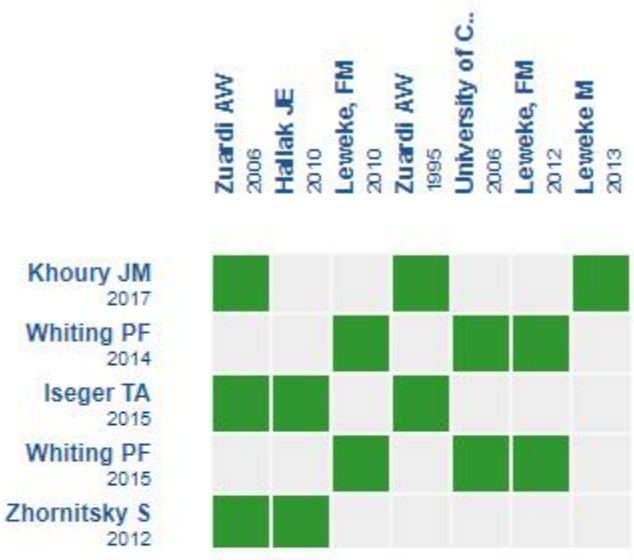
- The conclusion of this summary agree with most identified systematic reviews, specially with the more rigorous ones [4],[5].
- The American Psychiatric Society (APA) clinical guideline for the treatment of schizophrenia does not mention the therapeutic use of cannabinoids. Instead it warns about the potential harm of its consumption [17].

Could this evidence change in the future?

- The likelihood that future evidence changes the conclusion of this summary is low, due to the certainty of the evidence.
- A search in the International Clinical Trials Registry Platform of the World Health Organization retrieved at least three ongoing trials [18],[19],[20], that could provide relevant information.
- New systematic reviews could shed more light on this issue since the ones identified have serious limitations. We did not identify any ongoing systematic reviews in the PROSPERO database.

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:** Cannabidiol versus placebo for the treatment of 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 matrices 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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