MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2017; 17(Suppl1):e6821 doi: 10.5867/medwave.2017.6821

Are cannabinoids effective for epilepsy?

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Citation: Peña J, Rada G. Are cannabinoids effective for epilepsy?. *Medwave* 2017; 17(Suppl1):e6821 doi: 10.5867/medwave.2017.6821
Publication date: 13/1/2017

Abstract
Several beneficial effects have been proposed for cannabinoids in different clinical conditions, including epilepsy. However, their clinical role is controversial. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified five systematic reviews including four randomized trials addressing the question of this article. We extracted data and generated a summary of findings following the GRADE approach. We concluded it is not clear whether cannabinoids reduce the frequency of seizures in epilepsy because the certainty of the evidence is very low, and they probably increase adverse effects.

Problem

Epilepsy is a condition that disturbs the normal functioning of the brain and it is characterized by stereotyped and recurrent seizures. Although antiepileptic drugs usually achieve disease control, about 30% of patients have persistent seizures. Both tetrahydrocannabinol and cannabidiol have anticonvulsant properties by activating the CB1 and/or CB2 receptors of endocannabidiol system. However, their actual clinical role is not clear.

Methods

We used Epistemonikos database, which is maintained by screening multiple information sources, 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
- It is not clear whether cannabinoids reduce the frequency of seizures because the certainty of the evidence is very low.
- Cannabinoids are probably associated with transient but frequent adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found five systematic reviews [1],[2],[3],[4],[5] including six primary studies [6],[7],[8],[9],[10],[11], of which four [6],[7],[8],[9] correspond to randomized controlled trials.This table and the summary in general are based on the latter.
What types of patients were included	All trials [6],[7],[8],[9] included patients with epilepsy, however only one trial [9] specified the type of epilepsy (secondarily generalized). Two trials [8],[9] included refractory epilepsy. Only one trial [9] reported seizure frequency (one per week) and one trial [7] included patients with mental retardation. No trial reported the age of the participants, but two trials mentioned adult patients were included [8],[9].
What types of interventions were included	All trials [6],[7],[8],[9] compared oral cannabidiol in different doses and different periods against placebo. The regime used was 200 to 300 mg of cannabidiol daily for 18 weeks. In one trial [9], 100 mg cannabidiol daily for one week, and then 200 mg daily for another three weeks in one trial [7], 200 mg of cannabidiol for three months in one trial [8] and one trial used placebo for six months and then 300 mg of cannabidiol [6].
What types of outcomes were measured	The systematic reviews identified [1],[2],[3],[4],[5] grouped outcomes in the following way: Seizure frequency in a specific period (the duration of the intervention), and adverse effects associated with the use of cannabidiol. One of the reviews [1] states none of the trials reported seizure-free period for 12 months.

Summary of findings

The information about the effects of cannabinoids for control of epilepsy is based on four randomized trials including 48 patients [6],[7],[8],[9]. All of the trials reported both the frequency of seizures and adverse effects associated with its use, but none of the systematic reviews was able to conduct a meta-analysis with their data. The information on adverse effects was supplemented with a systematic review evaluating the adverse effects of cannabinoids in different populations, and includes 29 studies reporting this outcome [12]. The summary of findings is as follows:

- It is not clear whether cannabinoids reduce the frequency of seizures because the certainty of the evidence is very low.
- Cannabinoids are probably associated with transient but frequent adverse effects. The certainty of the evidence is moderate.

Cannabinoids for epilepsy		
Patients Epilepsy **Intervention** Cannabinoids **Comparison** Placebo		
Outcomes	Effects	Certainty of the evidence (GRADE)
Reduced frequency of seizures	No trial reported long-term effects (i.e. one year). In the short term, the trials differ in their results. Two trials [2], [4] reported there was no effect and the other two [8], [9] reported improvement.	⨁◯◯◯[1,2,3] Very low
Adverse effects	The information about adverse effects is poor in the trials identified. However, adverse effects on other populations [12] are frequent.	⨁⨁⨁◯[4] Moderate

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

[1] The certainty of the evidence was downgraded because the risk of bias in the trials was very serious.
[2] The certainty of the evidence was reduced by imprecision.
[3] The certainty of the evidence was reduced by inconsistent results across studies.
[4] The certainty of the evidence was reduced because it is indirect, because 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 in this summary applies to all patients with epilepsy, especially those refractory to treatment with antiepileptics.
- The trials analyzed include oral cannabidiol in different doses. They do not address the effect of smoked or vaporized cannabis, neither the effect of tetrahydrocannabinol. One of the reviews [4] advises against the use of smoked tetrahydrocannabinol, because of its possible proconvulsant effect.

About the outcomes included in this summary

- The outcomes selected for this summary are those critical for decision-making according to the opinion of the authors. They coincide with those presented in the systematic reviews identified.
- Although the trials analyzed report minimal adverse effects associated with the use of cannabidiol, higher quality evidence from other conditions [12] reported more frequent adverse effects. There are no good reasons for not expecting a similar rate of adverse effects in this population.

Balance between benefits and risks, and certainty of the evidence

- The evidence about benefits is of very low certainty, and adverse effects are frequent. The benefit/risk balance is probably unfavorable.

What would patients and their doctors think about this intervention

- Most patients and doctors should lean against the use of this intervention based on the existing evidence.
- However, some patients putting higher value in an uncertain benefit might consider its use, especially in the context of preconceptions they might have about the particular.

Resource considerations

- Commercial formulations of cannabinoids are generally expensive. As there is no certainty about a possible benefit, it is not possible to estimate a proper cost/benefit balance.

Differences between this summary and other sources

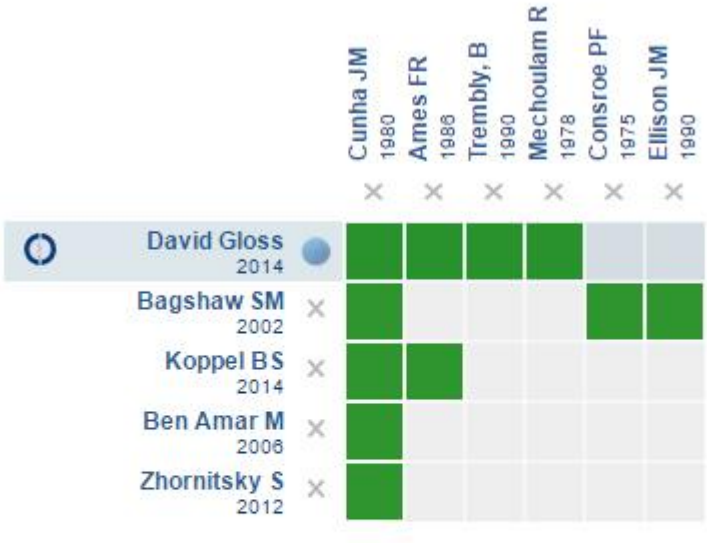
- The key messages of this summary are consistent with the findings of the systematic reviews identified.
- This summary also coincides with the Position on Medical Marijuana of the American Epilepsy Society [13], it does not recommend its use for the control of epilepsy, because safety and efficacy of this intervention are unknown. However, it strongly supports clinical research to determine its real value.

Could this evidence change in the future?

- The probability that future evidence change the conclusions of this summary about the benefits of cannabinoids in epilepsy is high, because there is high uncertainty. Regarding adverse effects, the probability is low.
- There are several ongoing trials, according to the International Clinical Trials Registry Platform of the World Health Organization, which could provide relevant information in the 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.

Siga el enlace para acceder a la **versión interactiva:** Cannabinoids for epilepsy

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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