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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are cannabinoids effective for Parkinson's disease?

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Abstract

It is postulated cannabinoids may have benefits in Parkinson's disease. However, its actual clinical effectiveness is still discussed. 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 including eight studies overall, of which four were randomized trials relevant for the question of interest. We extracted data from the systematic reviews, reanalyzed data of primary studies included in these reviews, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded cannabinoids probably do not decrease symptoms in Parkinson's disease or dyskinesia, and probably are associated to frequent adverse effects in patients with Parkinson's disease.

Problem

The concept of cannabinoids includes organic compounds that interact with cannabinoid receptors in the body. These are in general active metabolites of the cannabis plant, and would explain its pharmacological effects in humans.

Theories to justify the effect of these drugs in Parkinson's disease point to alterations in the cerebral endocannabinoid system, at substantia nigra, caudate and putamen. However, it remains unclear how effective or well tolerated cannabinoids are in Parkinson's disease.

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), a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Cannabinoids probably do not decrease symptoms or dyskinesia, and are probably associated to frequent adverse effects in patients with Parkinson's disease.

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 eight studies that answer the question of interest [7],[8],[9],[10],[11],[12],[13],[14] from which four [7],[8],[12],[13] were randomized trials. This table and the summary in general are based on the latter.
What types of patients were included*	Patients with Parkinson's disease with or without motor complications, especially dyskinesia, were included. It was not possible to obtain information about the proportion of patients with cognitive impairment or other non-motor manifestations.
What types of interventions were included*	One trial used extract of Cannabis sativa (tetrahydrocannabinol 2.5 mg with 1.25 mg cannabidiol) [7], one trial used cannabidiol 75 to 300 mg daily [8], one trial used cannabinoid receptor agonist-1 (SR141716) 20 mg daily [12] and other trial used oral nabilone 0.03 mg/kg daily [13]. All trials compared against placebo.
What types of outcomes were measured	From multiple outcome measured by the trials, the systematic reviews grouped them as follows: • Motor symptoms measured by UPDRS (Unified Parkinson's Disease Rating Scale) • Quality of life measured by PDQ-39 (The Parkinson's Disease Questionnaire) • Antiparkinsonian effect • Levodopa-induced dyskinesias • Interaction with levodopa • Adverse effects • Severe adverse effects Mean follow-up was four weeks, with a range of two to six weeks.

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

Summary of findings

The information about the effects of cannabinoids for Parkinson's disease is based on four randomized trials [7],[8],[12],[13] including 63 patients.
None of the systematic reviews presented meta-analysis, so the information presented below corresponds to a narrative synthesis of the information obtained.
The summary of findings is the following:

- Cannabinoids probably do not decrease symptoms of Parkinson's disease. The certainty of the evidence is moderate.
- Cannabinoids probably do not decrease dyskinesia in Parkinson's disease. The certainty of the evidence is moderate.
- Cannabinoids are probably associated to adverse effects in patients with Parkinson's disease. The certainty of the evidence is moderate.

Cannabinoids for Parkinson's disease		
Patients	Parkinson's disease	
Intervention	Cannabinoids	
Comparison	Placebo	
Outcome	**Effect**	**Certainty of the evidence (GRADE)**
Symptoms measured by *UPDRS* *	No effect [1],[2]	⊕⊕⊕◯ Moderate[1,2]
Dyskinesia	No effect [1],[2],[3],[4],[5]	⊕⊕⊕◯ Moderate[1,2]
Adverse effect	The information about adverse effects in the identified trials was poor. However, adverse effects on other similar populations [15] are frequent	⊕⊕⊕◯ Moderate[3]

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

* UPDRS: Unified Parkinson's Disease Rating Scale

[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.

Follow the link to access the interactive version of the Summary of Findings (iSoF) table

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 is broadly applicable to any patient with Parkinson's disease.
- Limitations of existing evidence, both from systematic reviews and primary studies, do not allow to establish whether there is any subset of patients where there may be a different effect.

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.
- If there are effects on other outcomes, they were not reported in the identified systematic reviews.

Balance between benefits and risks, and certainty of the evidence

- It is an intervention that probably has no benefits and that leads to adverse effects, so the risk/benefit balance is not favorable.
- If its use is considered, it should also be noted that despite the limited evidence about adverse effect, it is reasonable to assume they could be even greater in patients with cognitive or behavioral symptoms.

Resource considerations

- Commercial cannabinoid formulations are generally expensive.
- The cost-benefit is highly unfavorable because it is an expensive intervention that has no benefit and has adverse effects.
- In many countries, the use and marketing of these drugs is not authorized.
- The cost associated with regulating its production, good use and marketing is most likely substantive.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary, most patients and caregivers should lean against the use of cannabinoids in Parkinson's disease.
- Currently, there is a positive perception of the therapeutic effects of cannabinoids, both by citizens and many health professionals, which puts additional difficulties for evidence-informed decision-making in this context.

Differences between this summary and other sources

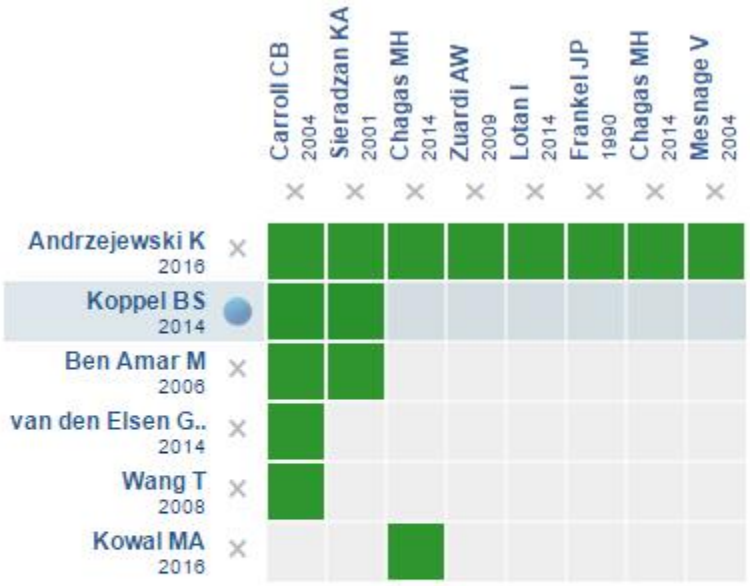
- In general, the conclusions of this summary are similar to the results presented by the different systematic reviews. The main clinical guidelines, such as the guidelines of the Movement Disorders Society [16], the Canadian Society [17], NICE [18] and the European Federation of the Neurological Societies [19] do not mention use of cannabinoids as a therapeutic option, nor do they mention it is an alternative in evaluation.

Could this evidence change in the future?

- The probability that future evidence changes the conclusion of this summary about the benefit of cannabinoids in Parkinson's disease is low, due to the certainty of the evidence.
- There are at least three ongoing studies [20],[21],[22], including one randomized trial [20], according to the International Clinical Trials Registry Platform of the World Health Organization, which could provide relevant information.

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:** Cannabinoids for Parkinson's disease

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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