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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are cannabinoids effective in multiple sclerosis?

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Abstract

Multiple beneficial effects have been proposed lately for cannabinoids in different clinical situations. Among them, it has been postulated they would control symptoms of multiple sclerosis. However, there is no consensus about their real clinical role. To answer this question, we searched in Epistemonikos database, which is maintained by screening multiple databases. We identified 25 systematic reviews including 35 studies overall, of which 26 were randomized trials. We extracted data, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded cannabinoids in multiple sclerosis do not reduce spasticity or pain, and are probably associated to frequent adverse effects.

Problem

Multiple sclerosis is a demyelinating chronic disease of the central nervous system that might presents in a relapsing-remitting and/or progressive pattern. The clinical manifestations are multiple and include loss of strength and/or sensitivity in the limbs, visual loss, pain secondary to spasticity, ataxia, and bladder dysfunction. The treatment for relapses is usually based on corticosteroids. In the long term, different therapeutic alternatives are available, such as interferon beta, immunomodulatory agents, immunoglobulin, chemotherapeutic agents and sphingosine analogues. However, up to 30-40% of patients remain symptomatic.

Multiple beneficial effects have been proposed lately for cannabinoids in different clinical situations. Among them, it has been postulated tetrahydrocannabinol and cannabinidiol would control spasticity, pain and bladder dysfunction in multiple sclerosis, especially in patients with refractory symptoms. The proposed mechanisms are mediated through modulation of CB1 and CB2 receptors in the endocannabidiol system. However, the real clinical impact of cannabinoids in this condition is not clear.

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
- Cannabinoids do not reduce spasticity or pain in multiple sclerosis.
- Cannabinoids are associated to adverse effects, which are probably frequent in multiple sclerosis.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 25 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25], including 35 primary studies reported in 57 references [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],[85], among them 26 randomized controlled trials [26],[28],[33],[36],[38],[39],[40],[47],[48],[49],[52],[54],[57],[59],[60],[61],[62],[63],[70],[71],[73],[74],[76],[77],[79],[80]This table and the summary in general are based on the latter.
What types of patients were included	All of the trials included patients with multiple sclerosis, but just a few specified the subtype: six trials included patients with relapsing-remitting multiple sclerosis [39],[40],[52],[60],[73],[76],[80]; seven trials included patients with primary progressive multiple sclerosis [40],[49],[52],[65],[71],[76],[80]; and eight trials included patients with secondary progressive multiple sclerosis [28],[33],[40],[49], [52],[71],[76],[80]. The age of the included patients was reported only in some trials, with a variable range, greater than 18 years old in all the cases. The severity of the included patients was reported in only seven trials, using the EDSS score (expanded disability status scale), presenting a score greater than five in all of the trials [28],[36],[40],[49],[71],[76],[80]. In just eight trials the duration of disease was described, with a range of 4.5 to 17 years in the different trials [28],[33],[36],[49],[52],[71],[76],[80].
What types of interventions were included	One trial administered smoked cannabis [28], nine trials used cannabis capsules [39],[40],[49],[61],[73],[74],[76],[79],[80]; two trials used dronabinol [40],[71]; and ten trials used sublingual nabiximol spray [26],[33],[36],[38],[47],[48],[52],[59],[62],[70]. Other trials used less conventional presentations. All of the trials compared against placebo.
What types of outcomes were measured	The different systematic reviews grouped the outcomes in the following way: • Pain: evaluated according to visual analogue scale or numeric scale. • Bladder dysfunction: evaluated according to numeric scale or irritative symptoms. • Spasticity: evaluated according to Ashworth Scale or numeric scale. • Adverse effects: such as sedation, dizziness, headache, euphoria, among others. • Quality of life: according to subjective evaluation by patients. • Coordination: according to subjective evaluation by patients. • Mobility: according to subjective evaluation by patients. • Others: sleep quality, tremor, posture and balance, dependence.

Summary of findings

The information about the effects of cannabinoids in multiple sclerosis is based on seven randomized trials [33],[35],[36],[43],[52],[63],[69], that included 1,985 patients. The other trials did not report any outcome of interest, or did not present the information in a way it could be incorporated in a meta-analysis. Four trials [33],[36],[63],[80] reported spasticity (1,247 patients), three trials [33],[52],[70] reported pain (327 patients) and four trials [33],[36],[52],[63] reported adverse effects (1,025 patients). The summary of findings is the following:

- Cannabinoids do not reduce spasticity in multiple sclerosis. The certainty of the evidence is high.
- Cannabinoids do not reduce pain in multiple sclerosis. The certainty of the evidence is high.
- Cannabinoids are associated to adverse effects, which are probably frequent in multiple sclerosis. The certainty of the evidence is moderate.

Cannabinoids in multiple sclerosis

Patients Multiple sclerosis
Intervention Cannabinoids
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT cannabinoids	**WITH cannabinoids**		
	Difference: patients per 1000			
Spasticity	The spasticity scale was on average 0.07 standard deviation units ** lower in the group without cannabinoids.		---	⊕⊕⊕⊕[1] High
	SMD -0.07 (Margin of error: -0.19 to 0.04)			
Pain	392 per 1000	435 per 1000	RR 1.11 (0.94 to 1.32)	⊕⊕⊕⊕[2] High
	Difference: 43 patients more per 1000 (Margin of error: 24 less to 125 more)			
Adverse effects	Information about adverse effects in the identified trials was poor (RR 1.18; 95% CI 1.10 to 1.27). However, there is abundant information about adverse effects of cannabinoids for other conditions [23].		--	⊕⊕⊕◯[3] Moderate

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 cannabinoids** is based on the risk in the control group of the trials. The risk **WITH cannabinoids** (and its margin of error) is calculated from relative effect (and its margin of error)

**Standardized mean difference is calculated when the outcome is measured using different scales, and its clinical interpretation is difficult. A rule of thumb is a value of 0.2 SD represents a small, 0.5 a moderate, and 0.8 a large difference.

[1] Although one of the trials contributing most to the meta-analysis had high risk of bias the certainty was not downgraded because bias would reinforce the conclusion.
[2] The certainty of the evidence was not downgraded by inconsistency (I^2 = 57%) because it is determined by a trial with major limitations.
[3] The certainty of the evidence was downgraded 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 in this summary applies to patients diagnosed with multiple sclerosis with symptoms such as: pain, spasticity or bladder dysfunction.

About the outcomes included in this summary

- The outcomes presented in the summary of findings table, represent those considered critical for decision-making according to the opinion of the authors of this article. The symptoms frequently affect patients diagnosed with multiple sclerosis, and theoretically could be modified by cannabinoids.

Balance between benefits and risks, and certainty of the evidence

- There is high certainty about the absence of benefits, and adverse effects are frequent. Although most adverse effects are mild and transient, severe adverse effects have also been reported.
- The benefit/risk ratio is clearly not favorable.

What would patients and their doctors think about this intervention

- Based on the existing evidence, most patients and clinicians should avoid the use of this intervention.
- Some patients or even doctors could decide to use it because of preconceptions or ambiguous recommendations in current guidelines.

Resource considerations

- Since there is no benefit it does not correspond to estimate a cost/benefit balance.
- On the other hand, commercial formulations of cannabinoids vary in presentation and dosage but generally have a high cost.

Differences between this summary and other sources

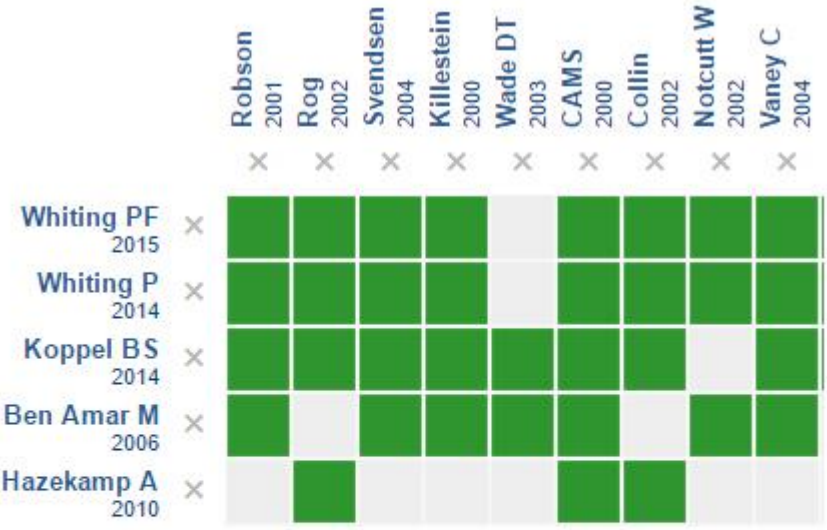
- The conclusions of the systematic reviews included in this article differ between each other. Although most conclude cannabinoids are not effective in multiple sclerosis or that existing evidence is not sufficient, some reviews, such as the one conducted to support the clinical guideline of the American Academy of Neurology, state they may be effective [11].
- The conclusions of the present summary partially coincide with the position of the main regulatory agencies; the U.S Food and Drug Administration (FDA) has not authorized the use of products containing or derivated from botanical marijuana because neither the safety or effectiveness have been proved for any indication [86]. Cannabinoids are not mentioned in the list of disease-modifying treatments approved by the European Medicines Agency (EMA). However, this agency authorized in 2014 the use of nabiximol in spray for the management of moderate to severe spasticity in adults diagnosed with multiple sclerosis who have not responded to conventional treatment, and who show clear clinical improvement in the initial period with this therapy [87].
- The main clinical guidelines also differ between each other: the guideline of the Association of British Neurologists about prescription of disease-modifyng treatment in multiple sclerosis does not include the use of cannabinoids [88]. The American Academy of Neurology [11] based on the systematic review mentioned above, recommends the use of oral cannabis extracts to reduce spasticity and pain (exluding neuropathic pain). It states nabiximol in spray may achieve improvement in spasticity, pain and urinary frequency, but recognizes existing evidence is insufficient to provide a recommendation for other symptoms derived from multiple sclerosis (anxiety, sleep disorders and cognition-related symptoms). The National Multiple Sclerosis Society recognizes the uncertainy and the need for more research, however it supports that patients and their doctors might eventually try this alternative [89].

Could this evidence change in the future?

- The probaility that future evidence changes the conclusions of this summary regarding the effects of cannabinoids in multiple sclerosis is low due to the certainty of the current evidence.
- There are no ongoing trials on this topic according to the records of the International Registry Platform for Controlled Trials of the World Health Organization.
- The identified systematic reviews include a low proportion of the trials identified in this article and generally incorporate few data in the evidence synthesis. Eventually, a new systematic review with more comprehensive methods in terms of identification and data analysis, or with access to unpublished data, could provide relevant information in this matter.

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 multiple sclerosis

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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