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Living Friendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are cannabinoids effective for fibromyalgia?

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Abstract

INTRODUCTION
Cannabinoids have been proposed as a therapeutic alternative for fibromyalgia. However, their clinical effectiveness is a matter of debate.

METHODS
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 extracted data from the systematic reviews, reanalyzed data of primary studies and generated a summary of findings table using the GRADE approach.

RESULTS AND CONCLUSIONS
We identified fifteen systematic reviews including two randomized trials overall. We concluded it is not clear whether cannabinoids have any benefit in fibromyalgia because the certainty of the evidence is very low. On the other hand, they are associated to frequent adverse effects.

Problem

Cannabinoids are a broad family of natural or synthetic compounds that can act as ligands in the cannabinoid receptors of the organism. It is postulated both CB1 and CB2 receptors have an influence on the nociceptive system [1].

The cause of fibromyalgia remains uncertain, and therapeutic response to pharmacological treatment is insufficient in a large number of patients. It is supposed cannabinoids would have a role in fibromyalgia since there is deficiency in the level of endocannabinoids in this condition [2]. It is also hypothesized that cannabinoids would reduce sensitivity of nociceptive pathways, altering cognitive and autonomous processing in states of chronic pain [3]. In addition, the distribution of cannabinoid receptors in the limbic-frontal system suggests cannabinoids may influence affective qualities of pain, which are believed to play an important role in fibromyalgia [4]. However, it is not clear what are the clinical effects of this intervention.

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 denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) 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 when it is possible, 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 improve symptoms in fibromyalgia because the certainty of the evidence is very low.
- Cannabinoids are associated to frequent adverse effects in fibromyalgia.

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About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 15 systematic reviews [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19], including three primary studies answering the question of interest [20],[21],[22]. Two studies correspond to randomized trials [20],[21]. This table and the summary in general are based on the latter, since the observational study did not increase the certainty of the existing evidence or provide relevant additional information.
What types of patients were included*	Both trials included patients diagnosed with fibromyalgia according to the ACR 1990 criteria. Both trials included adults over 18 years. One trial restricted age to 70 years [20]. One trial included patients with continuous pain despite another oral medication [20] and the other trial included patients with self-reported chronic insomnia [21]. Patients with a history of substance abuse, psychotic disorders, unstable angina and previous use of cannabinoids for pain management were excluded in both trials.
What types of interventions were included*	Both trials used oral nabilone as intervention. Regarding the dose, one trial used 0,5 mg to 1 mg per day [20] and the other used 0,5 mg per day [21]. Regarding the comparison, one trial [21] compared against oral amitriptyline 10 mg daily and the other trial [20] compared against placebo.
What types of outcomes were measured	Of the multiple outcomes measured by the randomized trials, the systematic reviews grouped them as follows: • Average daily pain, evaluated in VAS (Visual Analogue Scale) and McGill Pain Questionnaire • Anxiety assessed on the FIQ subscale (Fibromyalgia impact Questionnaire) • Sleep: Insomnia severity Index and Leeds Sleep Evaluation Questionnaire • Quality of life evaluated in the FIQ scale (Fibromyalgia impact Questionnaire) • Adverse effects (such as dizziness, dry mouth, ataxia, confusion) and withdrawal from the study due to adverse effects. • Serious adverse effects. One trial lasted 4 weeks [20] and the second trial 6 weeks (2 weeks in each period separated by two weeks of wash-out) [21].

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

Summary of Findings

The information on the effects of cannabinoids for fibromyalgia is based on two randomized trials including 72 patients overall [20],[21]. Both trials reported the effect on pain and adverse effects. Only one trial measure sleep [21].

None of the reviews was able to extract the data in a way that could be incorporated into a meta-analysis, so the information presented below corresponds to a narrative synthesis of the information obtained from them.

The summary of findings is the following:

- It is not clear whether cannabinoids reduce pain, because the certainty of the evidence is very low.
- It is not clear whether cannabinoids improve sleep because the certainty of the evidence is very low.
- Cannabinoids are associated to frequent adverse effects in fibromyalgia. The certainty of the evidence is high.

Cannabinoids for fibromyalgia		
Patients	Fibromyalgia	
Intervention	Cannabinoids (nabilone)	
Comparison	Placebo and amitriptyline	
Outcomes	**Effect**	**Certainty of evidence (GRADE)**
Pain*	One trial reported improvement in pain [20] and the other did not [21].	⊕◯◯◯[1,2] Very low
Sleep**	One trial reported improvement on sleep quality of nabilone over amitriptyline [21].	⊕◯◯◯[1,2] Very low
Adverse effects	Patients who used nabilone experienced more adverse effects than participants who took placebo or amitriptyline [20], [21]. Being the most frequent dizziness, dry mouth and vertigo. More participants dropped out of the studies due to adverse effects in the nabilone group than in the control group.	⊕⊕⊕⊕ High

GRADE: certainty of the evidence of GRADE Working Group (see later).

*According to scores VAS (Analogous visual scale (0-100)) and McGill Pain Questionnaire
**According to scores ISI (Insomnia severity index (0-25)) and LSEQ (Leeds Sleep Evaluation Questionnaire)

[1] We downgraded the certainty of the evidence in two levels for imprecision due to the small sample of population in both trials. We did not downgrade adverse effects for this criterion, since the frequency was high, and there is evidence from other populations reinforcing this conclusion.
[2] We downgraded the certainty of the evidence in one level for risk of bias, since both trials have important limitations.

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.

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Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary is applicable to any patient with fibromyalgia, who has not previously used cannabinoids and has persisting pain despite medical treatment.
- The conclusions of this summary are applicable to nabilone, not to cannabis or other cannabinoids. However, in the absence of direct evidence it is reasonable to extrapolate it.

About the outcomes included in this summary

- The outcomes presented in the summary of findings table are those critical for decision-making according to the opinion of the authors of this summary.
- In general, the outcomes selected coincide with those presented in the main systematic reviews evaluated.

Balance between benefits and risks, and certainty of the evidence

- It is not clear the intervention has benefits in the population assessed and it is associated to adverse effects.
- It is not possible to estimate an adequate benefit/risk balance since there is uncertainty about the former.
- On the other hand, the follow-up period for the trials is relatively short, which is not informative in this chronic condition.

Resource considerations

- Commercial formulations of cannabinoids are generally expensive.
- It is not possible to estimate an adequate cost/benefit balance since there is uncertainty about the former.
- Use and marketing of cannabinoids is not authorized in many countries.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary most patients and clinicians should lean against the use of this intervention, since there is uncertainty about the benefits, it is associated with frequent adverse effects and carries substantive costs.
- However, there is currently a positive general opinion regarding cannabinoids for therapeutic purposes, both in the public and in many health professionals, so some patients and clinicians could decide to use them despite the evidence presented in this article.

Differences between this summary and other sources

- The conclusions of this summary agree with all of the systematic reviews identified, especially with the more rigorous reviews [10].
- We did not identify recommendations in the main clinical guidelines about the use of cannabinoids for fibromyalgia. The conclusions of this summary do not agree with the Canadian Guidelines of Fibromyalgia [23] which recommend cannabinoid extract in people with fibromyalgia in the context of sleep disorders.

Could this evidence change in the future?

- The probability of future evidence changing the conclusions of this summary is high, due to the uncertainty of the existing evidence.
- We searched in the International Clinical Trials Registry Platform of the World Health Organization, but we did not identify any ongoing trial evaluating the effect of cannabinoids for fibromyalgia.

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.

An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Cannabinoids for fibromyalgia

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.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE 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).

Potential conflicts of interest
The authors do not have relevant interests to declare.

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