MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

Medwave 2018 Ene-Feb;18(1):e7144 doi: 10.5867/medwave.2018.01.7144

Do cannabinoids play a role in the control of glaucoma?

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Citation: Peña J, Jiménez C, Schmidt J. Do cannabinoids play a role in the control of glaucoma?. *Medwave* 2018 Ene-Feb;18(1):e7144 doi: 10.5867/medwave.2018.01.7144
Submission date: 23/11/2017
Acceptance date: 29/12/2017
Publication date: 10/1/2018
Origin: This article is a product of the Evidence Synthesis Project of Epistemonikos Fundation, in collaboration with Medwave for its publication.
Type of review: Non-blinded peer review by members of the methodological team of Epistemonikos Evidence Synthesis Project.

Abstract

INTRODUCTION
The use of cannabinoids in diverse clinical conditions is today a subject of debate. Its use has been proposed for the control of glaucoma. However, there is controversy about its real effectiveness and safety.

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 five systematic reviews including three studies overall, all of them randomized controlled trials. We concluded that although cannabinoids could decrease intraocular pressure, the effect would be transient and associated with frequent adverse effects.

Problem

Glaucoma is a multifactorial optic neuropathy, often related to an increase in intraocular pressure (IOP). The permanently elevated intraocular pressure produces a slow and progressive damage in the optic nerve, generating different sequelae in the visual field and eventually it can lead to irreversible blindness. Although the elevation of intraocular pressure is present in most patients, there is a group of patients who develop glaucoma with normal pressure.

Today there are different medical therapies for the treatment of glaucoma, such as topical betablockers and prostaglandin analogues. The use of cannabinoids has been proposed, since its administration is associated with a decrease in intraocular pressure, through an effect on the production and exit of aqueous humor mediated by the activation of CB1 receptors. Also, neuroprotective properties on the optic nerve have been proposed. However, its actual clinical role is still controversial.

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

- Although the use of cannabinoids for glaucoma could decrease intraocular pressure, it would be transient and associated with frequent adverse effects.
- The benefit/risk balance is probably not favorable.

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 three primary studies overall [6],[7],[8], all of which correspond to randomized controlled trials.
What types of patients were included*	All trials included adult patients with glaucoma [6],[7],[8], with average age over 50 years. Only one trial specified the type of glaucoma (primary open-angle glaucoma) [8]. Two trials [7],[8], included patients with intraocular hypertension.
What types of interventions were included*	One trial [8] used sublingual cannabinoid spray (Sativex®) at doses of 5, 20 and 40 mg. Another trial [6] used smoked marijuana with 2% tetrahydrocannabinol (THC), while the last trial [7] used marijuana in 0.01%, 0.05%, and 0.1% eye drops.All trials compared against placebo or standard treatment.
What types of outcomes were measured	The different systematic reviews identified [1],[2],[3],[4],[5] grouped the outcomes as follows: Decrease in intraocular pressure, measured immediately after cannabinoid administration. Adverse effects. Two trials [7],[8] analyzed the duration of the intraocular pressure decrease, while in the other trial this variable was not reported [6].

* 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 glaucoma is based on three randomized trials [6],[7],[8], which include 32 patients in total. All of the trials [6],[7],[8], reported intraocular pressure and adverse effects, and two of them [7],[8] specified the duration of the decrease in intraocular pressure. None of the trials reported decreased visual acuity or visual field deterioration. The summary of findings is the following:

- The use of cannabinoids for glaucoma could be associated with a transient decrease in intraocular pressure, but the certainty of the evidence is low.
- The use of cannabinoids for glaucoma leads to frequent adverse effects. The certainty of the evidence is high.

 doi: 10.5867/medwave.2018.01.7144

Cannabinoids for glaucoma		
Patients	Glaucoma	
Intervention	Cannabinoids	
Comparison	Placebo	
Outcomes	**Effect**	**Certainty of evidence (GRADE)**
Decrease intraocular pressure	Two trials [6],[7], reported a significant decrease in intraocular pressure. The other trial [8] reported a decrease in intraocular pressure with a dose of 5 mg of THC, however, a transient increase in intraocular pressure was reported with cannabidiol 20 mg and 40 mg. All trials [6],[7],[8] reported the decrease in intraocular pressure was transient.	⊕⊕◯◯[1,2] Low
Adverse effects	All trials [6],[7],[8] reported frequent adverse effects, such as sensory alterations, orthostatic hypotension and tachycardia.	⊕⊕⊕⊕ High

GRADE: Evidence grades of the GRADE Working Group (see later).

[1] One level of certainty of evidence was decreased due to a moderate risk of bias, since the majority of the included studies did not present enough information to assess the risk of bias.
[2] One level of certainty of evidence was reduced by imprecision, since the total number of patients evaluated was low.

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 comes from patients with primary open-angle glaucoma and patients with intraocular hypertension. However, in the absence of direct evidence it is reasonable to extrapolate to other forms of glaucoma with elevated intraocular pressure.
- It is not applicable to patients with normal tension glaucoma. On the other hand, it is questionable to apply it to patients with congenital glaucoma, since although the majority of patients present elevated intraocular pressure, the pathophysiology of the increase is different.

About the outcomes included in this summary

- The outcomes selected for the summary of findings table are those considered critical for decision-making in this clinical situation, according to the opinion of the authors of this article. In general, they coincide with those presented in the systematic reviews identified.
- It is important to emphasize that patient's preferences are more concerned about the visual implications of the disease and the prevention of blindness. However, there is evidence that the decrease in intraocular pressure maintained over time delays the progression of this disease, including the deterioration of the visual field [9].
- On the other hand, the decrease in intraocular pressure is a relevant element in clinical practice for follow-up and thus determine the success of the treatment or the need of new interventions.
- Although information on adverse effects is scarce in the evaluated trials, these are frequent in other conditions [4], so something similar should be expected in glaucoma.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to make an adequate balance between benefits and risks due to the existing uncertainty about the benefits. However, it is unlikely that the observed effect, being transient, will translate into a clinically relevant benefit. On the other hand, the intervention has frequent adverse effects, so the benefit/risk balance is probably not favorable.

Resource considerations

- Commercial formulations of cannabinoids generally have a high cost. Since there is no certainty about a possible benefit, it is not possible to make an adequate cost/benefit balance.

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 evidence presented in this summary.
- In addition, nowadays there are proven therapies for the control of glaucoma, with good results both in the short and long term.
- Some patients who place a greater value on an uncertain benefit may decide to use it, especially considering the preconceived ideas they may have about it.

Differences between this summary and other sources

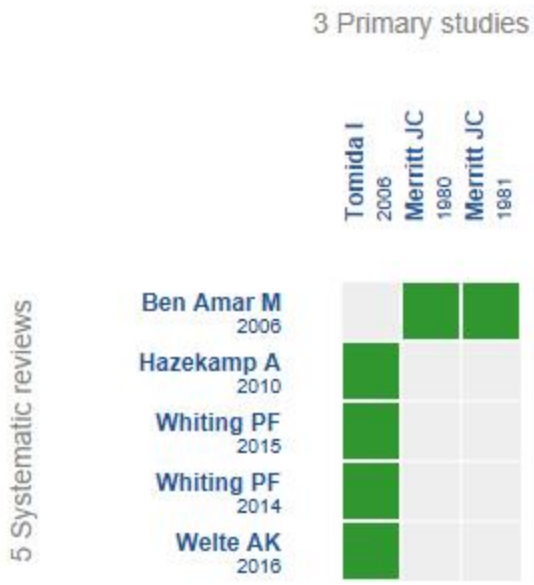
- The key messages of this summary are concordant with the conclusions of the systematic reviews identified.
- This summary also coincides with the statement of the Canadian Ophthalmological Society [10] and the American Ophthalmological Society [11], who do not recommend the use of cannabinoids for the treatment of glaucoma, since although it produces a decrease in intraocular pressure, it is transient and is associated with frequent adverse effects.

Could this evidence change in the future?

- The likelihood that future evidence changes the conclusions of this summary with respect to the benefits of cannabinoids in glaucoma is high due to the existing uncertainty. It is unlikely that the conclusions about adverse effects change.
- We did not identify any ongoing trial evaluating this question in the International Clinical Trials Registry Platform of the World Health Organization.

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 glaucoma

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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