Cannabinoids for the treatment of cannabis abuse disorder

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Citation Rodríguez A, Zavala C. Cannabinoids for the treatment of cannabis abuse disorder. *Medwave* 2018;18(6):e7286

Doi 10.5867/medwave.2018.06.7286

Submission date 28/7/2018
Acceptance date 30/7/2018
Publication date 11/10/2018

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

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

Key Words Cannabinoids, cannabis abuse disorder, Epistemonikos, GRADE.

Abstract

Introduction

Cannabis stands as the most used illegal drug in the world. Currently there are no pharmacologic alternatives to treat its addiction, so the use of Cannabinoids has been postulated as a therapeutic tool. They would act mainly through decrease in abstinence and craving symptoms but its effectiveness remains unclear.

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, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified seven systematic reviews including 15 studies, of which four were randomized trials. We concluded the use of cannabinoids might result in little or no increase in abstinence at the end of treatment, and it probably increases adverse effects.

Problem

Substance abuse disorder is an important epidemiological problem which is defined by the development of a maladaptive behavioral pattern in relation to the use of a substance and is usually accompanied by tolerance, one of the diagnostic elements of dependence. In this context, cannabis stands as one the most consumed illicit drugs, with addictive potential[1].

Even though there are no specific pharmacological alternatives to treat cannabis use disorders, diverse studies have postulated that the endocannabinoid system has a role in the modulation of many neurological pathways associated to drug addiction. In this context, the use of cannabinoids has been proposed as a therapeutic alternative for patients affected by cannabis use disorder. In a similar way nicotine replacement therapy is used as tobacco cessation strategy, it is postulated cannabinoids might help decrease abstinence and craving in cannabis abuse disorder.

Key messages

- Use of cannabinoids might result in little or no increase in abstinence at the end of treatment, but the certainty of the evidence is low.
- It is not clear if cannabinoids decrease abstinence and craving symptoms because the certainty of the evidence is very low.
- The use of cannabinoids probably increases adverse effects.
- In consequence, balance is not favorable, as it is a costly intervention without proven benefits and associated to adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found seven systematic reviews[2-8] including fifteen primary studies[9-23], of which four corresponded to randomized trials[9-12].
What types of patients were included*	Three trials[9,11,12] included adult patients with cannabis dependence according to DSM-IV-TR diagnostic criteria and one[10] included patients described as cannabis dependent recruited from the community without specifying diagnostic criteria. Three trials[9,11,12] excluded patients that had significant psychiatric comorbidities or other substance dependence (except for nicotine and caffeine) and one[10] did not specify exclusion criteria.
What types of interventions were included*	Two trials evaluated nabiximol (Sativex) as intervention for 6 days[9] and for 9 weeks[10]. One trial[11] used oral dronabinol as monotherapy and another[12] used dronabinol associated with lofexidine (2-alpha adrenergic agonist). In one trial[9] both arms also received cognitive behavioral therapy.
What types of outcomes were measured	The trials evaluated multiples outcomes, which were grouped by the different systematic reviews as follow: • Abstinence and craving symptoms, measured by psychiatric scales: CWS (Cannabis Withdrawal Scale), WDS (Withdrawal Discomfort Score) and MCQ (Marijuana Craving Questionnaire) • Cannabis use and abstinence at the end of treatment using urine test and self report. • Number of patients that completed treatment. • Adverse Effects, measured by SAFTEE score (Modified Systematic Assessment for Treatment and Emergent Events).

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

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.

Summary of Findings

The information about the effects of cannabinoids is based on four randomized controlled trials including 338 patients[9,10,11,12]. One trial reported abstinence at the end of treatment (156 patients)[11], four trials reported abstinence and craving symptoms (338 patients)[9,10,11,12] and one trial reported adverse effects (156 patients)[11]. Regarding abstinence and craving symptoms, no systematic review allowed the extraction of data in a way that could be included in a meta analysis, so the information of this outcome is presented as a narrative synthesis.

The summary of findings is as follows:

- The use of cannabinoids might result in little or no increase in abstinence at the end of treatment, but the certainty of the evidence is low.
- It is not clear if cannabinoids decrease abstinence and craving symptoms because the certainty of the evidence is very low.
- The use of cannabinoids probably increase adverse effects. The certainty of the evidence is moderate.

Cannabinoids for cannabis abuse disorder				
Patients	Cannabis dependent adults			
Intervention	Cannabinoids (nabiximol- dronabinol)			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (IC 95%)	Certainty of evidence (GRADE)
	WITHOUT cannabinoids	WITH cannabinoids		
	Difference: patients per 1000			
Abstinence (at the end of treatment)	156 per 1000	178 per 1000	RR 1.14 (0.56 a 2.3)	⨁⨁◯◯[1,2] Low
	Difference: 22 patients more (Margin of error: 69 less to 203 more)			
Abstinence and craving symptoms	Abstinence and craving symptoms decreased in both groups, but symptoms did not decrease more in the cannabinoid group. [8],[9],[10],[11].			⨁◯◯◯[1,2,3] Very low
Adverse effects	584 per 1000	672 per 1000	RR 1.15 (0.9 a 1.46)	⨁⨁⨁◯[1,2,4] Moderate
	Difference: 88 patients more (Margin of error: 58 less to 269 more)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio
GRADE: Evidence grades of the GRADE Working Group (see later).

*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 the relative effect (and its margin of error).

[1] We downgraded one level of certainty of evidence for imprecision, since information was gathered from 1 study with a small sample.
[2] We downgraded one level of certainty of evidence for inconsistency of results between studies.
[3] We downgraded one level of certainty of evidence for imprecision because the margin of error includes the possibility of effect and no effect.
[4] We upgraded the certainty of evidence in one level because there is information from other samples about increased adverse effects.

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

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.

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* 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 cannabis dependent patients looking for treatment, who do not have relevant psychiatric comorbidities and who are not addicted to other type of substances, except caffeine and nicotine.

About the outcomes included in this summary

The outcomes presented in the summary of findings table are those considered critical for decision-making by the authors of this summary. In general, they coincide with the outcomes reported by the systematic reviews identified.

Balance between benefits and risks, and certainty of the evidence

The potential benefits of cannabinoid therapy in terms of abstinence or decrease in cannabis use are practically non-existent and there is not enough certainty of evidence to consider a benefit in terms of abstinence and craving symptoms. In consequence, the balance between risks and benefits is not favorable.

Resource considerations

In general, commercial formulations of cannabis are expensive and in many countries their use or distribution is not authorized. So, the costs associated with product regulation, good use and commercialization are probably substantive.

Considering the cost is high, there are no proven benefits and there are potential adverse effects, the balance between benefits and costs is not favorable.

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.

The use of oral formulations of cannabinoids as a therapeutic tool for cannabis abuse disorder is relatively unknown by both patients and clinicians, so preconceived ideas in this context may not have a role in decision-making.

Differences between this summary and other sources

In relation to the systematic reviews analysed in this summaries, most are in agreement with the conclusions presented in this summary.

No clinical guidelines evaluating the use of cannabinoids for cannabis abuse disorder were found.

Could this evidence change in the future?

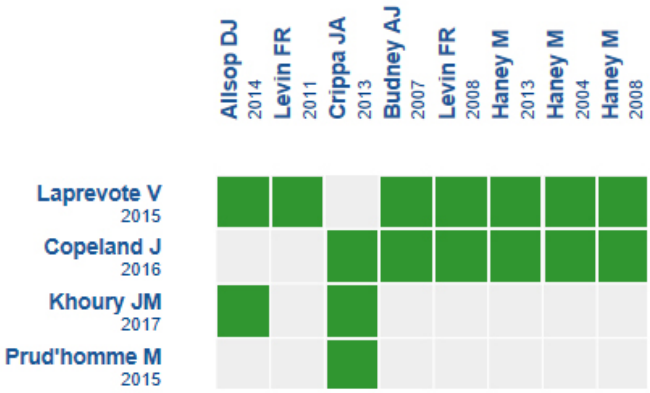
The probability of future evidence changing the conclusions of this summary is high, due to existing uncertainty in the evaluated outcomes.

We ran a search in the International Clinical Trials Registry Platform of the World Health Organization, on which no ongoing trials that may add relevant information were found.

New systematic reviews may offer better conclusions, since the ones identified in this summary have important limitations. We only identified one pertinent systematic review in progress in the PROSPERO database[24].

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 cannabis use disorder

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.

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