

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

Medwave 2018 Ene-Feb;18(1):e7151 doi: 10.5867/medwave.2018.01.7151

Do cannabinoids constitute a therapeutic alternative for insomnia?

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Citation: Contreras T, Bravo-Soto GA, Rada G. Do cannabinoids constitute a therapeutic alternative for insomnia?. *Medwave* 2018 Ene-Feb;18(1):e7151 doi: 10.5867/medwave.2018.01.7151

Submission date: 29/12/2017

Acceptance date: 31/12/2017

Publication date: 13/2/2018

Origin: This article is a product of the Evidence Synthesis Project of Epistemonikos Foundation, 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

It has been suggested that cannabinoids would constitute a therapeutic alternative for patients with insomnia.

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 eight systematic reviews including three studies overall, of which two were randomized trials. We concluded it is not clear whether cannabinoids have an effect on insomnia severity or on sleep quality; that they might have no effect on sleep conciliation, sleep awakening or behavior during wakefulness, and are probably associated with frequent adverse effects.

Problem

Insomnia is the most frequent sleep disorder in general population and represents a common reason for consultation. This disorder has a great impact on the waking state, the work capacity and the quality of life of people who suffer from it.

It has been proposed cannabinoids would have an effect on the stimulation of sleep and thus could be an effective treatment for patients with insomnia and other sleep disorders. However, its clinical efficacy and safety are a matter of debate.

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 have an effect on insomnia severity or on sleep quality because the certainty of the evidence is very low.
- Cannabinoids may have no effect on sleep conciliation, sleep awakening or behavior during wakefulness, and are probably associated with frequent adverse effects.

About the body of evidence for this question

| | |
|---|---|
| <p>What is the evidence. See evidence matrix in Epistemonikos later</p> | <p>We found eight systematic reviews [1],[2],[3],[4],[5],[6],[7],[8] that included three primary studies reported in six references [9],[10],[11],[12],[13],[14], of which two correspond to randomized trials, reported in five references [9],[11],[12],[13],[14]. This table and the summary in general are based on the randomized trials, since the observational study did not increase the certainty of the existing evidence, nor did provide relevant additional information.</p> |
| <p>What types of patients were included*</p> | <p>The first trial [9] included 15 patients with insomnia (diagnostic criterion was not specified). The second trial [11] included 32 patients diagnosed with chronic insomnia, defined as a sleep disturbance according to self-report at least every other night alternately for a minimum of 6 months. Those who fulfilled these criteria were selected within a population of patients with fibromyalgia. In this last trial, a negative urine test for cannabinoids was also required. The average age was 49.5 years and 16% were men.</p> |
| <p>What types of interventions were included*</p> | <p>The first trial [9] compared cannabidiol at doses of 40, 80 and 160 mg versus nitrazepam 5 mg and versus placebo. The second trial [11] compared the effect of nabilone between 0.5 to 1 mg versus amitriptyline between 10 to 20 mg. All these drugs were administered orally once a day, before going to sleep.</p> |
| <p>What types of outcomes were measured</p> | <p>The first trial [9] measured the duration of sleep and the induction of sleep. The second trial [11] measured the results according to the ISI (Insomnia Severity Index) and LSEQ (Leeds Sleep Evaluation Questionnaire) scales. LSEQ evaluates the reconciliation of sleep, quality of sleep, awakening from sleep and behavior during wakefulness. In addition, the occurrence of adverse effects associated with the use of cannabinoids was evaluated. The follow-up of the first trial [11] was 6 weeks (2 weeks each period separated by 2 weeks), the second trial [9] did not specify the duration of follow-up, only that it was "acute".</p> |

* 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 on insomnia is based on two randomized trials [9],[11] that included 47 patients.

The first trial [9] measured the duration of sleep and the induction of sleep, the second trial [11] measured the results according to the ISI (Insomnia Severity Index) and LSEQ (Leeds Sleep Evaluation Questionnaire) scales. LSEQ evaluates the reconciliation of sleep, quality of sleep, awakening from sleep and behavior during wakefulness.

The summary of findings is as follows:

- It is not clear whether cannabinoids have an effect on insomnia severity because the certainty of the evidence is very low.
- Cannabinoids might have no effect on sleep conciliation, but the certainty of the evidence is low.
- It is not clear whether cannabinoids have an effect on sleep quality because the certainty of the evidence is very low.
- Cannabinoids might have no effect on waking sleep and waking behavior, but the certainty of the evidence is low.
- Cannabinoids are probably associated with frequent adverse effects in patients with insomnia. The certainty of the evidence is moderate.

| Cannabinoids for sleep disorders | | | |
|---|--|-------------------|-----------------------------------|
| Patients | Sleep disorders | | |
| Intervention | Cannabinoids: nabilone and cannabidiol | | |
| Comparison | Other active treatments (nitrazepam or amitriptyline) and placebo | | |
| Outcome | Absolute effect | | Certainty of evidence (GRADE) |
| | WITHOUT cannabinoids | WITH cannabinoids | |
| ISI scale (Insomnia Severity Index) | 18.3 | 15.1 | ⊕○○○ ^{1,2} Very Low |
| | MD: 3.25 better (Margin of error: 1.24 to 5.26 better) The use of cannabinoids was associated with insomnia improvement when compared to amitriptyline [11]. | | |
| Sleep reconciliation | No significant difference was found between cannabinoids and amitriptyline for this outcome [11]. | | ⊕⊕○○ ^{1,3} Low |
| | No effect was found on the use of cannabinoids when compared with nitrazepam or placebo [9]. | | |
| Sleep quality | Restful sleep | | ⊕○○○ ^{1,2,4} Very Low |
| | MD: 0.48 worse (Margin of error: 0.01 to 0.95 worse) The use of cannabinoids increased restful sleep more than amitriptyline [11]. | | |
| | Duration of sleep | | |
| | A significant increase in sleep duration was found with the use of cannabinoids compared with nitrazepam [9]. | | |
| Awakening of sleep and behavior during wakefulness | No significant difference was found between cannabinoids and amitriptyline for these outcomes [11]. | | ⊕⊕○○ ^{1,3} Low |
| Adverse effects | The most frequent adverse effects were dizziness, nausea, dry mouth and somnolence [11]. In addition, adverse effects are common in other populations [7]. | | ⊕⊕⊕○ ⁵ Moderate |
| Margin of error: 95% confidence interval (CI). MD: Mean difference. GRADE: Evidence grades of the GRADE Working Group (see later). ¹ Two levels of certainty of evidence were downgraded due to imprecision because the sample of the population studied was very small. ² One level of certainty was reduced due to risk of bias in the primary studies. ³ We decided not to diminish the certainty of the evidence due to risk of bias, since the presence of bias would reinforce the conclusion of no effect ⁴ One level of certainty of the evidence was downgraded due to inconsistency since there is discrepancy in the conclusions of the different trials. ⁵ One level of certainty of the evidence was reduced because it was indirect, 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 people with chronic insomnia.
 - It is not specified in the systematic reviews if the population of the primary studies was evaluated in ambulatory or hospitalized context, but it seems reasonable to extrapolate the results of this summary to both scenarios.
 - The population studied in one of the trials [11] corresponds to patients diagnosed with fibromyalgia in concomitance with insomnia, but the results of this summary could be applicable to patients without fibromyalgia.
-

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 article.
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Balance between benefits and risks, and certainty of the evidence

- It is an intervention that could have no benefits and that has adverse effects, so the risk / benefit balance is not favorable.
-

Resource considerations

- Commercial formulations of cannabinoids are generally expensive.
 - The cost/benefit balance is not favorable, because it is a costly intervention that has no clear benefit and has adverse effects.
 - In addition, in many countries the use and commercialization of these drugs is not authorized, so the cost associated with the process of legalization, production, commercialization and inspection is probably substantive.
-

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 cannabinoids in insomnia.
 - There is currently a positive perception about the therapeutic effects of cannabinoids, both in the public and in many health professionals, which places additional difficulties in making decisions informed by evidence in this context.
-

Differences between this summary and other sources

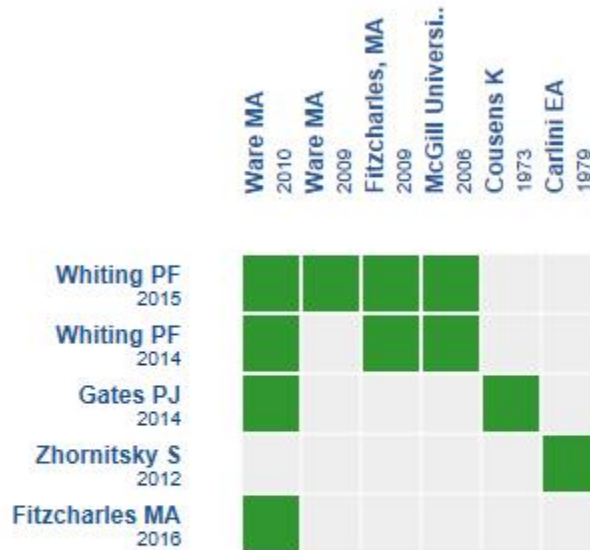
- There is disagreement with some of the systematic reviews identified. The main reason is because of different weight given to the certainty of the evidence and the incorporation of this factor in the conclusions they present. In addition, two of the reviews [6],[7] interpreted the results of one of the primary studies differently [11]. This error was detected in the guideline The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research [15], in which the correct result is shown when mentioning the two systematic reviews in question.
 - The conclusions of this summary disagree with one of the main guidelines [15], which indicates there is moderate evidence for the effectiveness of cannabinoids for short-term outcomes in patients with insomnia associated with other conditions. However, they did not consider the imprecision of the results, the risk of bias of the trials or the inconsistency in some outcomes.
-

Could this evidence change in the future?

- The probability that future evidence changes the conclusions of this summary on the benefits of cannabinoids for insomnia is high due to the associated uncertainty.
 - According to the International Clinical Trials Registry Platform of the World Health Organization, there is an ongoing trial [16] which could change the conclusions presented in this summary.
 - New systematic reviews could provide clearer conclusions, given the ones identified may not contain all of the evidence and have important limitations. We did not identify ongoing systematic reviews in the PROSPERO database (International prospective register of systematic reviews).
-

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 insomnia](#)

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.

References

1. de Souza Nascimento S, Desantana JM, Nampo FK, Ribeiro EA, da Silva DL, Araújo-Júnior JX, da Silva Almeida JR, Bonjardim LR, de Souza Araújo AA, Quintans-Júnior LJ. Efficacy and safety of medicinal plants or related natural products for fibromyalgia: a systematic review. *Evid Based Complement Alternat Med*. 2013;2013:149468. | [CrossRef](#) | [PubMed](#) | [PMC](#) |
2. Fitzcharles MA, Ste-Marie PA, Häuser W, Clauw DJ, Jamal S, Karsh J, Landry T, Leclercq S, Mcdougall JJ, Shir Y, Shojania K, Walsh Z. Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials. *Arthritis Care Res (Hoboken)*. 2016 May;68(5):681-8. | [CrossRef](#) | [PubMed](#) |
3. Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. *Sleep Med Rev*. 2014 Dec;18(6):477-87. | [CrossRef](#) | [PubMed](#) |
4. Parmar JR, Forrest BD, Freeman RA. Medical marijuana patient counseling points for health care professionals based on trends in the medical uses, efficacy, and adverse effects of cannabis-based pharmaceutical drugs. *Res Social Adm Pharm*. 2016 Jul-Aug;12(4):638-54. | [CrossRef](#) | [PubMed](#) |
5. Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. *Cochrane Database Syst Rev*. 2016 Jul 18;7:CD011694. | [CrossRef](#) | [PubMed](#) |
6. Whiting PF, Wolff R, Westwood M, Duffy S, Misso K, Keurentjes C, Lang S, Harker J, Deshpande S, Ryder S, Di Nisio M, Hernández AV, Schmidtkofer S, Kleijnen J. Systematic review of cannabis for medical use. *Kleijnen Systematic Reviews Ltd*. 2014.
7. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidtkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA*. 2015 Jun 23-30;313(24):2456-73. Review. Erratum in: *JAMA*. 2016 Apr 12;315(14):1522. *JAMA*. 2015 Dec 1;314(21):2308. *JAMA*. 2015 Aug 4;314(5):520. *JAMA*. 2015 Aug 25;314(8):837. | [CrossRef](#) | [PubMed](#) |
8. Zornitsky S, Potvin S. Cannabidiol in humans—the quest for therapeutic targets. *Pharmaceuticals (Basel)*. 2012 May 21;5(5):529-52. | [CrossRef](#) | [PubMed](#) | [PMC](#) |
9. Carlini EA, Masur J, Magalhaes CCPB. Possible hypnotic effect of cannabidiol on human. preliminary study. *Ciência e Cultura*. 1979;31:315-322.
10. Cousins K, DiMascio A. (-) Delta 9 THC as an hypnotic. An experimental study of three dose levels. *Psychopharmacologia*. 1973 Dec 20;33(4):355-64. | [PubMed](#) |
11. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg*. 2010 Feb 1;110(2):604-10. | [CrossRef](#) | [PubMed](#) |
12. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Canadian Rheumatology Association Meeting*. 2009.
13. Fitzcharles, MA, Shir, Y, Joseph, L, Ware, MA. The effects of nabilone on insomnia in fibromyalgia: results of a randomized controlled trial. *American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting*. 2009.
14. McGill University Health Center. Nabilone Versus Amitriptyline in Improving Quality of Sleep in Patients With Fibromyalgia. *clinicaltrials.gov*. 2006.
15. National Academies of Sciences, Engineering, and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press. 2017. | [CrossRef](#) |
16. University Health Network Toronto, Valeant Pharmaceuticals International Inc. Use of the cannabinoid nabilone for the promotion of sleep in chronic, non-malignant pain patients. In: *ClinicalTrials.gov [Internet]*. Bethesda (MD): National Library of Medicine (US). 2006- [cited 2014 Apr 7]. | [Link](#)

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