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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are cannabinoids effective for HIV wasting syndrome?

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Abstract

INTRODUCTION
Wasting syndrome is a common problem in HIV. It leads to substantive morbidity and mortality. The use of cannabinoids has been suggested as a treatment for weight, but it is not clear whether they are really safe and effective.
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 eight systematic reviews including ten studies overall, of which six were randomized trials. We concluded it is not clear whether cannabinoids increase appetite or weight in HIV wasting syndrome because the certainty of the evidence is very low, and they probably lead to frequent adverse effects.

Problem

The high frequency of HIV-related wasting syndrome, defined as the involuntary loss of at least 10% of standard body weight associated with chronic diarrhoea or chronic fatigue and fever for at least 30 days, was observed at the onset of the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic [1]. This definition is no longer used, and the diagnosis is based mainly on the presence of significant, progressive or very fast weight-loss, which has led to various new definitions [2].

After the beginning of anti-retroviral therapy an important decrease of wasting syndrome cases was observed, but it still remains a common problem, estimated to affect up to 14-38% of patients [3].

Its relevance lies in its association to a greater risk of mortality [3] which makes important to look for treatment alternatives aimed to optimise the nutritional state [2].
It has been suggested the use of natural or synthetic cannabinoids would have a positive effect on appetite, weight gain and mood of adults with HIV/AIDS [4]. They

would increase appetite through activation of CB1 endocannabinoid receptors at a central level. However, the real clinical effect of this treatment is still unclear [5].

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 the use of cannabinoids in HIV wasting syndrome leads to weight gain or increased appetite, because the certainty of the evidence is very low.
- The use of cannabinoids is probably associated to frequent adverse effects in wasting syndrome.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found eight systematic reviews [4],[6],[7],[8],[9],[10],[11],[12] which include ten primary studies [13],[14],[15],[16],[17],[18],[19],[20],[21],[22] of which six are randomized controlled trials [13],[14],[15],[16],[17],[18]. This table and the summary in general are based on the latter.
What types of patients were included*	All of the trials were conducted in adults who were predominantly male. Average age ranged between 36 and 43 in the different trials. Intervention duration ranged between 2 weeks and 12 months. One of the trials was conducted in hospitalized patients [18], and the rest in outpatients. In five trials [13],[15],[16],[17],[18] certification of HIV infection was required in order to participate, and one of them included AIDS-related criteria [14]. In five trials [14],[15],[16],[17],[18] an ongoing antiretroviral treatment was required. The trials did not mention CD4 count and only one makes reference to viral count [16]. Four trials [13],[14],[15],[17] included some criteria related to weight-loss within a certain interval of time. Regarding previous cannabinoid use, two trials [17],[18] included patients that were cannabis consumers, while the other four required a given interval without cannabinoid use prior to participation [13],[14],[15],[16].
What types of interventions were included*	All of the trials evaluated the effect of dronabinol in various doses, administered orally between one and four times a day. In three trials [16],[17],[18] dronabinol was compared to inhaled marijuana in the form of cigarette with different doses of THC (between 1,8% and 3,9% THC content) and placebo. In one trial dronabinol was compared to megestrol [15], a steroid, without comparing with a placebo. Five trials compared against placebo [13],[14],[16],[17],[18].
What types of outcomes were measured	Appetite increase was evaluated in all of the trials with different visual analogous scales, along with adverse effects. Five trials [13],[14],[15],[16], [18] evaluated weight gain expressed as total weight gain [kg] in a given interval. In addition, functionality scales, subjective experience and mood changes were also evaluated. Only one trial evaluated laboratory nutritional indicators [16].

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

Summary of Findings

The information on the effects of cannabinoid use in HIV wasting syndrome is based on six randomized trials [13],[14],[15],[16],[17],[18] which included 298 patients.
All of the trials reported change in appetite (298 patients) and adverse effects (298 patients). Five trials [13],[14],[15],[16],[18] measured change in weight (268 patients).
However, none of the reviews identified was able to pool data from the trials into a meta-analysis, so the results are presented in a narrative form, based on the conclusions of the individual reviews.
The summary of findings is the following:

- It is not clear whether the use of cannabinoids in HIV wasting syndrome leads to weight gain because the certainty of the evidence is very low.
- It is not clear whether the use of cannabinoids in HIV wasting syndrome leads to an increase in appetite because the certainty of the evidence is very low.
- The use of cannabinoids in HIV wasting syndrome is probably associated to frequent adverse effects.

Cannabinoids for HIV wasting syndrome		
Patients HIV wasting syndrome **Intervention** Cannabinoids **Comparison** Placebo		
Outcome	**Absolute effect***	**Certainty of evidence (GRADE)**
Weight gain	According to three systematic reviews [8], [10], [12] weight gain varied between 100 and 1000 g.	⊕◯◯◯[1,2] Very low
Appetite	According to three reviews appetite increased with cannabinoid use [6], [8], [12].	⊕◯◯◯[1,3] Very low
Adverse effects	According to three reviews adverse effects were frequent or very frequent with cannabinoid use [6], [9], [12]. These were nausea, dizziness, headache, confusion, drowsiness, mood changes, cognitive alterations, among others. On the other hand, adverse effects in other groups of patients are frequent [12]	⊕⊕⊕◯[4] Moderate

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

[1] The certainty of evidence was downgraded in two levels due to risk of bias in the primary studies reported by the systematic reviews.
[2] The certainty of the evidence was downgraded in two levels due to inconsistency because in some trials patients experienced weight stabilization, whereas in others weight-loss.
[3] The certainty of the evidence was downgraded in one level due to reporting bias since most trials did not report this outcome. Moreover, publications that report it, do not provide quantitative results.
[4] The certainty of the evidence was downgraded in one level due to indirectness, since it derives from patients with different diseases.

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

- This evidence applies to adult patients with HIV wasting syndrome, more specifically to patients receiving antiretroviral treatment, regardless of the stage, CD4 count or viral count.

About the outcomes included in this summary

- The outcomes of weight gain and increase in appetite were included because they are the most relevant for decision-making according to the opinion of the authors, and were both measured in most evaluations.
- Adverse effects were included due to its importance in the evaluation of the clinical application of this treatment.

Balance between benefits and risks, and certainty of the evidence

- The use of cannabinoids did not show any positive effects, and is associated to adverse effects. Therefore, the risk-benefit balance is not favorable for the use of cannabinoids in HIV wasting syndrome.

Resource considerations

- Cannabinoids for therapeutic use in their various forms generally have a high cost. Considering they did not show any certaing benefit, the balance is against its use.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary most patients and clinicians should be inclined against the use of this intervention.
- Some patients and even clinicians might be in favour of their use despite the evidence, based on unfounded recommendations or extended recreational consumption, as seen in some of the trials.

Differences between this summary and other sources

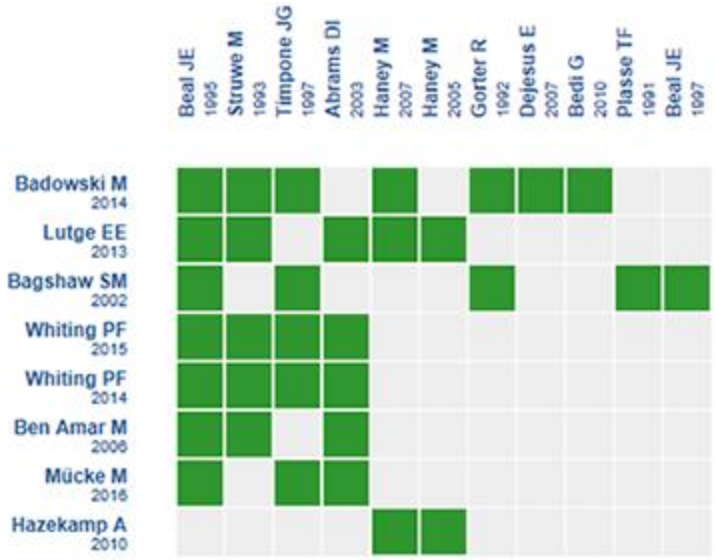
- The conclusions of this summary coincide with those of the included systematic reviews: they all agree on the lack of high-quality trials which would be needed in order to reach a conclusion regarding the effectiveness of the treatment on weight gain and appetite.
- The conclusion of this summary regarding cannabinoid use as a stimulator of appetite does not coincide with the US Food and Drug Administration, which authorised the use of dronabinol in 1992 for treating anorexia associated to weight loss in patients with HIV [23].
- The main guidelines about HIV treatment do not mention the treatment of wasting syndrome [24] and specialised guidelines have recommended the use of dronabinol based on FDA approval, although warning about possible adverse effects [25].

Could this evidence change in the future?

- The likelihood of future trials changing the conclusions of this summary regarding the effects of cannabinoids in treating HIV wasting is high, considering the existing uncertainty.
- The included systematic reviews present significant limitations, so a new systematic review with access to unpublished data of these trials could change the way available information is interpreted.
- Currently there are no ongoing trials registered on the World Health Organization's International Controlled Trials Registry Platform that involve cannabinoids and HIV wasting syndrome.

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 HIV/AIDS wasting syndrome

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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