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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are cannabinoids an alternative for cachexia-anorexia syndrome in patients with advanced cancer?

Authors: Claudia Cabeza[1,3], Oscar Corsi[2,3], Pedro Pérez-Cruz[2,3,4]

Affiliation:
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[3] Proyecto Epistemonikos, Santiago, Chile
[4] Programa de Medicina Paliativa y Cuidados Continuos, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

E-mail: pperezc@med.puc.cl

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Abstract

INTRODUCTION
Cachexia and anorexia are among the most frequent symptoms in patients with cancer. Cannabinoids have been used in patients with advanced cancer; however, their role is still controversial.

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 ten systematic reviews including three studies overall, of which two were randomized trials. We concluded it is not clear whether cannabinoids have any positive effect on increasing weight because the certainty of the evidence is very low. They might not have any effect on appetite, and are probably associated to frequent adverse effects.

Problem

The anorexia-cachexia syndrome corresponds to an hypercatabolic state characterized by an absence of desire to eat and an involuntary weight loss associated with a loss of muscle mass. This phenomenon is observed in up to 80% of patients with cancer and in variable percentages in patients with other non-oncological diseases [1].

In oncological patients, anorexia is explained by a variety of causes (e.g. dysphagia, dry mouth, nausea, depression), which determine a decrease in intake and in the availability of nutrients, and as a consequence, weight loss. In patients with isolated anorexia, the increase of the intake and the availability of nutrients can revert weight loss. Although anorexia by itself does not explain the deterioration observed in cancer patients, it is a factor that contributes

to weight loss and is considered a relevant parameter in the quality of life [2]. Cachexia corresponds to a multifactorial syndrome characterized by loss of skeletal muscle mass, with or without loss of fat mass, which leads to progressive functional deterioration [3]. It is among the most common symptoms in cancer patients, with a prevalence of 50% at the time of diagnosis and 80% at the end-of-life stage. It is associated with a decrease in quality of life and survival (it can be the direct cause of 20% of deaths related to this disease) and to other symptoms such as anorexia (in up to 90% of cancer patients), fatigue, asthenia, weakness, early satiety, among others [4]. It is known the pathophysiology of cachexia is multifactorial; for example, tumor growth is associated with profound metabolic and neurochemical alterations, such as the production of a series of proinflammatory cytokines, including TNF-alpha, IL-1 and IL-6, which favour an hypercatabolic state and hamper the use of available nutrients.

Several interventions focused on these particular mechanisms have been proposed, within which we find progestogens, corticoids and cannabinoids [5], the latter would seek to improve appetite through the activation of the CB 1 (central nervous system) and CB 2 (immune cells) receptors of the endocannabidiol system [6], and to decrease weight loss through immunomodulating effect of cytokines [7]. However, it is not clear if this theory actually translates into a clinical effect.

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 leads to weight gain, and might not even increase appetite in patients with advanced cancer.
- The use of cannabinoids is probably associated to frequent adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 10 systematic reviews [8],[9],[10],[11],[12],[13],[14],[15],[16],[17] that included three primary studies relevant to the question [18],[19],[20]; two of these correspond to randomized trials [18],[19]. This table and the summary in general are based on the latter.
What types of patients were included*	Both trials included adults (older than 18 years), of both sexes with solid or stage IV hematologic cancer. One trial established inclusion criteria for weight loss in the last 2 to 6 months and also selected by ECOG less than 2 [18].
What types of interventions were included*	Both trials evaluated oral delta-9-tetrahydrocannabinol (THC). One trial [18] used oral THC (5 mg / day) and cannabidiol (2 mg / day) for six weeks versus placebo. The other trial [19] used only oral THC in three daily doses (0.1 mg / kg / day) for two weeks versus placebo.
What types of outcomes were measured	The trials measured multiple outcomes, but the systematic reviews pooled them as follows: Appetite, measured by analog visual scale Weight gain, measured as average weight gain Adverse effects

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

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Summary of Findings

The information about the effects of cannabinoids for anorexia-cachexia syndrome in patients with advanced cancer is based on two randomized trials involving 218 patients.
One trial [18] reported weight gain (164 patients). Both trials [18],[19] reported increased appetite (218 patients).

The summary of findings is as follows:

- It is not clear whether the use of cannabinoids leads to weight gain in patients with advanced cancer, because the certainty of the evidence is very low.
- The use of cannabinoids might not increase appetite in patients with advanced cancer. The certainty of the evidence is low.
- The use of cannabinoids is probably associated to frequent adverse effects. The certainty of the evidence is moderate.

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Cannabinoids in anorexia-cachexia syndrome associated with cancer		
Patients	Stage IV cancer with anorexia-cachexia syndrome	
Intervention	Cannabinoids (oral THC, cannabidiol)	
Comparison	Placebo or no treatment	
Outcomes	Effect	Certainty of evidence (GRADE)
Weight gain	One trial reported that oral THC produced greater weight gain than placebo	⊕◯◯◯[1,2] Very low
Increase appetite	Both trials reported no effect	⊕⊕◯◯[2,3,4] Low
Adverse effects	Adverse effects (dizziness, drowsiness and confusion) limit use in 25% of cases [19]. On the other hand, adverse effects in other populations are frequent [21].	⊕⊕⊕◯[5] Moderate

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 relative effect (and its margin of error).

[1] One level of certainty of evidence was decreased for serious risk of bias.
[2] Two levels of certainty of evidence were decreased by small sample size of the trials.
[3] One level of certainty was reduced by inconsistency because the different trials led to different conclusions.
[4] It was decided not to downgrade the certainty of the evidence due to risk of bias, since the absence of bias would reinforce the conclusion of no effect.
[5] one level of certainty was reduced because it is indirect evidence, because 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 adult patients with advanced solid or hematologic cancer (stage IV) who suffer from anorexia and cachexia.
- The included studies use different doses of oral THC [18],[19] therefore, its extrapolation to other forms of cannabis or cannabinoids is questionable.

About the outcomes included in this summary

- The outcomes included in the table are those considered critical for decision-making by the authors of this summary. They generally agree with those presented in the systematic reviews identified and with the main guidelines.

Balance between benefits and risks, and certainty of the evidence

- None of the trials presented appropriate data for meta-analysis, so it was not possible to quantiry the magnitude of the effects of cannabinoids and the only conclusion is there is a high degree of uncertainty about the alleged benefits.
- On the other hand, adverse effects were evaluated consistently among the included studies, and are consistent with what has been observed in patients with other conditions that use this intervention [21].
- It is not possible to make an adequate balance between benefits and risks, due to the uncertainty about the former. However, it is reasonable to estimate the likelihood that the balance is favorable is low.

Resource considerations

- Commercial formulations of cannabinoids generally have a high cost, without mentioning the costs associated with the distribution and regulation of these drugs.
- It is worth mentioning that the trials administered a known and standardized dose of THC and oral cannabidiol, which is not directly applicable to the cannabis-independent preparation.
- Although it is not possible to make an adequate balance between benefits and costs, due to the uncertainty about the former, it is unlikely that it will be favorable.

What would patients and their doctors think about this intervention

- In relation to the evidence presented in this summary most physicians and their patients should lean against the use of this intervention.
- However, it is likely that some patients may decide to use it, due to the usually positive perception of the efficacy of these drugs or in the absence of other therapeutic options, especially in cases of difficult management or lack of response to other interventions.

Differences between this summary and other sources

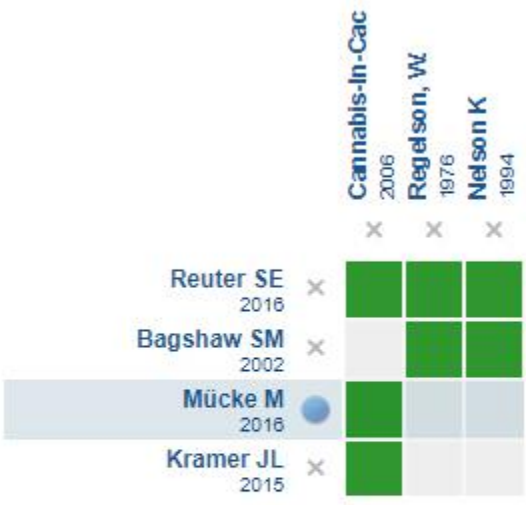
- The conclusion of this summary is concordant with the results of the included systematic reviews and recommendations of international organizations [22], which indicate there is insufficient evidence to support the use of cannabinoids over other therapies such as progestogens or corticosteroids.

Could this evidence change in the future?

- The probability that future evidence changes the conclusions of this summary with regard to the benefits of cannabinoids in cachexia-anorexia associated with cancer is high, due to the existing uncertainty.
- No ongoing trials were found in the International Clinical Trials Registry Platform of the World Health Organization.
- The systematic reviews identified have important limitations regarding the data delivered. Eventually, a new systematic review following high methodological standards and with access to unpublished data from the studies could change the interpretation of the available information.
- On the other hand, it is likely that in the future, therapeutic strategies for the management of cachexia-anorexia in patients with advanced cancer will change, since there are several ongoing trials registered in the International Clinical Trials Registry Platform of the World Health Organization that evaluate the utility of new immunomodulators (OHR / AVR118), cytokine blockers and ghrelin.

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 versus placebo for cachexia-anorexia 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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Author address:
[1] Centro Evidencia UC
Pontificia Universidad Católica de Chile
Centro de Innovación UC Anacleto Angelini
Avda.Vicuña Mackenna 4860
Macul
Santiago
Chile