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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are cannabinoids effective for treatment of pain in patients with active cancer?

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Abstract

Cannabinoids have been proposed for the treatment of patients with cancer pain, especially if standard treatment does not control symptoms. Using Epistemonikos database, which is maintained by searching 30 databases, we identified nine systematic reviews including seven trials that answer the question of interest, of which six are randomized trials. We performed a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded it is unclear whether cannabinoids decrease pain and improve quality of life in patients with refractory cancer pain because the certainty of the evidence is very low, and it probably increases adverse effects substantially.

Problem

Cannabis has been used for centuries both recreationally and therapeutically. However, its use has been restricted since the United Nations banned it in 1971. The interest in potential therapeutic uses led to the discovery of endocannabinoid receptors CB1 and CB2, which through a G-protein associated mechanism, would lead to reduced pain. Considering many cancer patients persist with pain despite maximal analgesic therapy, plant extracts with the active agent delta-9-tetrahydrocannabinol or its analogues have been proposed. However, it is unclear what their real clinical role is.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary 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, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- It is unclear whether cannabinoids reduce pain or improve the quality of life of patients with refractory cancer pain, because the certainty of the available evidence is very low.
- Cannabinoids probably lead to a substantial increase on adverse events in patients with active cancer and refractory pain.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified nine systematic reviews [1],[2],[3],[4],[5], [6],[7],[8],[9], including seven primary studies[10],[11], [12],[13],[14],[15],[16] of which six are randomized controlled trials [10],[11],[12],[13],[14],[15]. This table and the summary in general are based on the latter.
What types of patients were included	All of the trials included adults with active cancer and pain of diverse etiology (cancer, bone or neuropathic)[10],[11],[12],[13],[14],[15]. Four trials included inpatients [10],[11],[12],[13], and two outpatients [14],[15]. Only two trials [14],[15] included patients that were refractory to treatment, defined as moderate or intense pain despite treatment with 80 mg or more morphine equivalents.
What types of interventions were included	Three trials evaluated delta-9-tetrahydrocannabinol extracts [10],[11],[14], two trials [14],[15] addressed nabiximol, a preparation of tetrahydrocannabinol and cannabidiol, one trial tested a nitrogen analogue ofCannabis (NIB) [12] and one trial evaluated benzopyranoperidine [13]. All of the studies compared against placebo or treatment with codeine (in less than standard dose). One trial had several arms, including comparison against other cannabinoids [14].
What types of outcomes were measured	The main outcome pooled by the systematic reviews identified was pain reduction evaluated with Houde's scale, visual-analogue scale or numerical-rating scale. Other outcomes pooled were quality of life, and adverse effects such as gastrointestinal (nausea, vomiting), central nervous system (ataxia, memory impairment, disorientation, confusion), psychiatric (euphoria, depression, anxiety, psychosis), and death, among others.

Summary of findings

The information on the effects of cannabinoids is based on two randomized trials (290 participants) that evaluated patients with refractory pain [14],[15]. Both trials measured reduction of pain and one reported quality of life [14]. The information on adverse effects is based on a systematic review [7] evaluating adverse effects of cannabinoids in different populations, and includes 29 studies reporting this outcome.

- It is unclear whether cannabinoids reduce pain in patients with refractory cancer pain, because the certainty of the available evidence is very low.
- It is unclear whether cannabinoids improve quality of life in patients with refractory cancer pain, because the certainty of the available evidence is very low.
- Cannabinoids probably lead to a substantial increase on adverse events in patients with active cancer and refractory pain. The certainty of the evidence is moderate.

Cannabinoids for refractory cancer pain

Patients Active cancer and refractory pain
Intervention Cannabinoids
Comparison Placebo

Outcomes	Absolut effects*		Relative effect (IC 95%)	Certainty of the evidence (GRADE)
	WITHOUT cannabinoids	**WITH Cannabinoids**		
	Difference: patients per 1000			
Pain reduction**	245 per 1000	331 per 1000	RR 1.35 (0.63 to 2.9)	⊕OOO Very low[1,2,3]
	Difference: 86 patients more per 1000 (Margin of error: 91 less to 465 more)			
Quality of life***	**2.47 points better** in a scale from 0 to 100 (Margin of error: -3.87 to 8.81)		--	⊕OOO Very low[1,3]
Adverse effects	780 per 1000	915 per 1000	OR 3.03 (2.42 to 3.80)	⊕⊕⊕O Moderate[4]
	Difference: 135 patients more per 1000 (Margin of error: 116 to 151 more)			

RR: Risk ratio.
OR: Odds Ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* 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)
** The pain reduction was defined in the studies as a reduction of at least 30% of baseline visual analog or numeric-rating scales.
*** EORTC QLQ -C30 is a questionnaire to assess the quality of life of cancer patients. The scale goes from 0 (worse quality of life) to 100 (best quality of life).

1 The certainty of the evidence was reduced because the high risk of bias reported in the included studies.
2 The certainty of the evidence was decreased given the inconsistency between studies.
3 The certainty of the evidence was reduced by imprecision.
4 The certainty was reduced because it is indirect evidence. Most information comes from patients with diseases other than cancer.

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.

⊕⊕⊕O
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕OO
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕OOO
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 presenting with pain of difficult management in the context of active cancer.
- None of the included studies evaluated the effects of smoked or vaporized*Cannabis*. There are more than 60 cannabinoids in the *Cannabis* plant, and route of administration might modify the effects, so any extrapolation to other therapeutic forms or route of administration not evaluated in the studies might be premature.

About the outcomes included in this summary

- The outcomes selected in this summary are those critical for decision-making according to the opinion of the authors of this summary. They coincide with the outcomes presented in most systematic reviews and guidelines.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to make a proper benefit/risk assessment because the certainty of the evidence on the effectiveness is very low. However, considering any effect is probably small, and side effects are common, the risk/benefit balance probably does not favor this intervention.

What would patients and their doctors think about this intervention

- Given the nature of this evidence most patients and physicians should be inclined against the use of this intervention. However, the social connotation of natural medicines and *Cannabis* particularly, might make some people favor its use despite the information provided in this summary.

Resource considerations

- These drugs are generally of high cost. In the case of oral drugs, the direct cost is usually high. In the case of *Cannabis*, there are high costs associated with its production, regulation and distribution.

Feasibility and acceptability

- It is important to note the difficulties on access to these medicines in countries where the formulations derived from *Cannabis* are prohibited by law.
- The drug that was used in the studies selected for this summary is not commercially available yet.

Differences between this summary and other sources

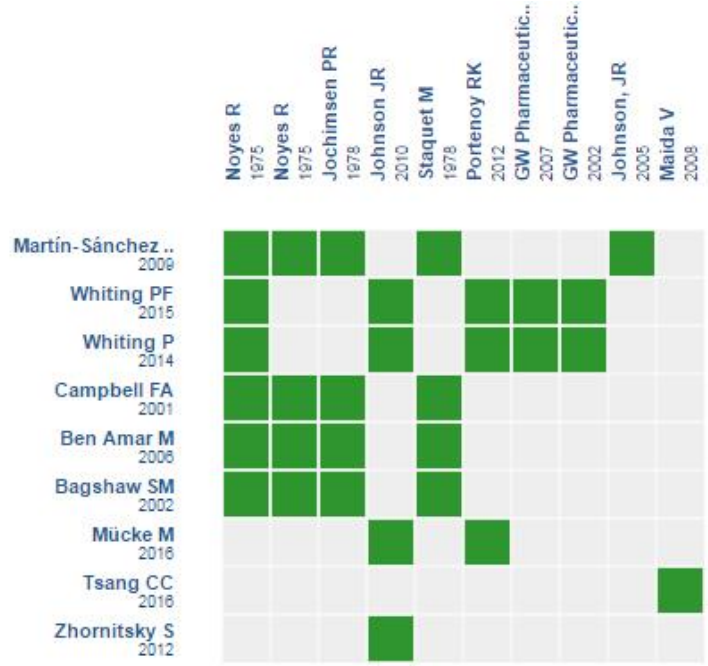
- The conclusions of this summary are consistent with the systematic reviews identified, although some reviews [6],[7] analyzing a broader spectrum of types of pain provide a more positive conclusion in favor of cannabinoids.
- The National Comprehensive Cancer Network guideline, European Society for Clinical Oncology guideline and the NICE guideline for clinical care at the end of life [17],[18],[19] do not mention cannabinoids as a therapeutic alternative. On the contrary, they recommend other analgesic agents, such as ketamine or new generation opioids like tapentadol. The American Society of Clinical Oncology guideline [20], which deals with surviving patients, recommends the use of cannabinoids for the treatment of chronic pain (regardless of type or origin) after making an appropriate cost/benefit consideration, an according to local laws.

Could this evidence change in the future?

- The likelihood of future evidence changing the conclusions of this summary about the benefits of cannabinoids in patients with cancer pain is very high, given the existing uncertainty.
- We identified at least two ongoing trials [21],[22] in the WHO International Clinical Trials Registry Platform addressing this topic, which could provide relevant information.
- New high quality systematic reviews might provide relevant information, considering most reviews identified have important limitations.

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.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Cannabinoids for treatment of pain in patients with active cancer

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.

The details about the methods used to produce these summaries 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).

These summaries follow a rigorous process of internal peer review.

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

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