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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are cannabinoids effective for the management of chemotherapy induced nausea and vomiting?

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Abstract

INTRODUCTION
Nausea and vomiting are common side effects in cancer patients treated with chemotherapy. Proper control of these symptoms might improve quality of life in these patients. Addition of cannabinoids to standard antiemetic treatment has been proposed in order to improve control of these symptoms.

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 16 systematic reviews that include 61 primary studies. Out of these, four were randomized trials that answered our question. At present, given that the certainty of the evidence is very low, it is unclear whether the addition of cannabinoids to standard antiemetic regimes benefits patients with chemotherapy induced nausea and vomiting. Cannabinoids probably increase adverse effects substantively.

Problem

Acute and delayed nausea and vomiting are commonly associated to chemotherapy treatments. These are common side effects usually known and feared by oncological patients [1],[2]. In recent years, several new drugs have been incorporated into treatment regimes in order to prevent and manage emesis. Despite this, some patients remain unresponsive to standard management [3]. The use of cannabinoids (delta-9 tetrahydrocannabinol (THC) or its derivatives) as antiemetic has been postulated mainly based on its effects upon CB1-endocannabinoid receptors located at the central nervous system and their action over the emetic center of the brain, similar to the 5-HT3 serotonin receptors [4],[5]. However, from a clinical

point of view, the role of cannabinoids upon chemotherapy-induced emesis is still controversial.

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 unclear whether the addition of cannabinoids to standard antiemetic regimes benefits patients with chemotherapy induced nausea and vomiting, because the certainty of the evidence is very low.
- The use of cannabinoids is probably associated to a substantive increase in adverse effects.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 16 systematic reviews [6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20], [21] that included 61 primary studies contained in 69 references [22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72], [73],[74],[75],[76],[77],[78],[79],[80],[81],[82],[83],[84],[85],[86],[87],[88],[89],[90] out of these, 58 were randomized trials [22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50], [51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72], [73],[74],[75],[76],[77],[78],[79]. Within this group, 21 trials reported the outcomes chosen by the authors, and only four associated additional antiemetic treatments. This summary analyzed four trials, reported across eight references [22],[23],[24],[25],[26],[27],[28],[29], that compared the effect of cannabinoids against placebo in patients under an antiemetic regime, reporting the control of nausea and vomiting during the intervention period, which is the clinically relevant question for the authors.
What types of patients were included*	All selected trials included male and female adults. The trials also included elderly patients, up to 81 years old. Patients included in these trials had solid [22],[25], and solid or hematological tumors [23],[24]. The trials included chemotherapy regimes with a high to moderate [22], only moderate [23],[25], and not classifiable risk of emesis [24] (the latter included several chemotherapies with a high risk of emesis, but also some with low to minimum risk). Three out of four trials reported previous use of cannabinoids at any time, one of these trials included only patients with no previous exposure [24], and 2 trials included patients with or without previous exposure [22],[25].
What types of interventions were included*	Studied cannabinoids were dronabinol (a synthetic THC derivative) with a maximum dose of 10 mg/day [22], 15 mg/day [23] or 40 mg/day [24] and nabiximol (a THC and cannabidiol extract) up to 8 sprays over a 4-hour period every 24 hours [25]. Regarding the associated antiemetic regime, two trials used corticosteroids combined with 5HT-3 antagonists [22],[23]; one trial used corticosteroids plus 5HT-3 antagonists or metoclopramide [25], and one study used prochlorperazine only [24].
What types of outcomes were measured	All trials evaluated the control of nausea and vomiting during the study period [22],[23],[24],[25] quantifying partial and complete responses. Three out of four of these trials [22],[24],[25] reported adverse effects. Also, some trials measured the tolerability of the intervention (measured as dropout from treatment due to adverse effects), the impact of nausea and vomiting upon quality of life, its frequency, duration and severity [22],[24],[25], percentage of patients and physicians satisfied with the intervention [25], ECOG score and quality of life [22]. Three out of four trials had a 5-day follow up [22],[23],[25] and one had a 6-day follow up [24].

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

Summary of Findings

The information obtained about the effects of cannabinoids on nausea and vomiting induced by chemotherapy is based on four randomized trials that involved a total of 176 patients [22],[23],[24],[25]. All four trials measured control of nausea and vomiting, while three measured the occurrence of adverse events [22],[24],[25].
The summary of findings is the following:

- It is unclear whether adding cannabinoids to standard antiemetic regimes improves the control of nausea and vomiting induced by chemotherapy, because certainty of the evidence is very low.
- The use of cannabinoids probably increases the occurrence of adverse effects in these patients. The certainty of the evidence is moderate.

Cannabinoids for the control of nausea and vomiting induced by chemotherapy				
Patients	Oncological patients receiving chemotherapy			
Intervention	Cannabinoids (oral THC, cannabidiol) plus standard antiemetic therapy			
Comparison	Placebo plus standard antiemetic therapy			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT cannabinoids	WITH cannabinoids		
	Difference: patients per 1000			
Control of nausea and vomiting	264 per 1000	507 per 1000	RR 1.92 (1.26 a 2.91)	⊕◯◯◯[1] Very Low
	Difference: 243 patients more per 1000 (Margin of error: 69 less to 504 more)			
Adverse effects	Three out of four trials reported adverse effects. The reported incidence in the cannabinoid group was 71-86%. The incidence in the control group was 50-88%. In both groups the most frequently observed adverse effects were somnolence, fatigue, dizziness and dry-mouth			⊕⊕⊕◯[2] Moderate

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
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] The certainty of the evidence was downgraded due to risk of bias, imprecision and indirectness (different interventions, some are not the first currently recommended therapeutic option)
[2] The level of certainty of the evidence was downgraded because of the risk of bias.

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 solid or hematologic tumors following chemotherapy treatment associated to any emetogenic risk, mainly moderate to high. Included patients received a variety of antiemetic regimes based on 5HT-3 antagonists, corticosteroids and/or prochlorperazine, in addition to cannabinoids.

About the outcomes included in this summary

- Complete response outcomes– meaning absence of nausea and vomiting – and the development of adverse effects were included because these are the critical outcomes that determine decision-making, according to the opinion of the authors of this summary.
- Currently there are several therapeutic alternatives to control chemotherapy induced nausea and vomiting, with proven safety and effectiveness, which are considered the current standard of care. Therefore, the authors postulate that critical outcomes should be measured under these conditions, comparing the addition of cannabinoids to standard antiemetic regimes and not against placebo, as proposed by Hesketh et al [91].
- Partial response outcomes were not included due to the high variability of the scales used across different studies in order to quantify the severity of nausea and vomiting.

Balance between benefits and risks, and certainty of the evidence

- It is unclear if the addition of cannabinoids to standard antiemetic regimes could improve the control of nausea and vomiting caused by chemotherapy. Also there is a likely increase in the occurrence of adverse effects. Therefore, the risk/benefit balance is not favorable.
- Unfortunately, many trials do not report the outcome of interest or only report partial control of symptoms, which limits the number of patients that can be included in our analysis and consequently lowers the certainty of the existing evidence in this matter.
- According to some of the reviews referenced in this article [9],[12],[13],[14],[15] several adverse effects seems quite frequent.

Resource considerations

- Therapeutic use of cannabinoids in all its presentations has an elevated cost in the market.
- Given their benefit is still unclear in this scenario, it is not posible to estimate a cost/benefit balance. However it is probably not favorable.

What would patients and their doctors think about this intervention

- Given the evidence presented in this summary, most patients and their doctors should be inclined against the use of cannabinoids in this setting. However, those who value the possibility of an uncertain benefit could decide to use this intervention in refractory patients due to the absence of therapeutic alternatives, as suggested by some clinical guidelines [92].

Differences between this summary and other sources

- The results in this summary are for the most part in agreement with the systematic reviews included in our article.
- In general, international guidelines recommend different antiemetic regimes based on 5HT-3 serotonin receptor antagonists and dexametasone according to the emesis risk associated to the chemotherapy protocol used. Other recommended interventions are neurokinin-1 (NK1) antagonists and anti-psychotic drugs (olanzapine) [92],[93], [94].
- The National Comprehensive Cancer Network (NCNN) [92] and the European Society of Medical Oncology (ESMO) - Multinational Association of Supportive Care in Cancer (MASCC) guidelines propose the use of cannabinoids for the management of refractory nausea and vomiting or as a rescue therapy [93]. In contrast, the American Society of Clinical Oncology (ASCO) guidelines [94] have no indications regarding the use of cannabinoids.

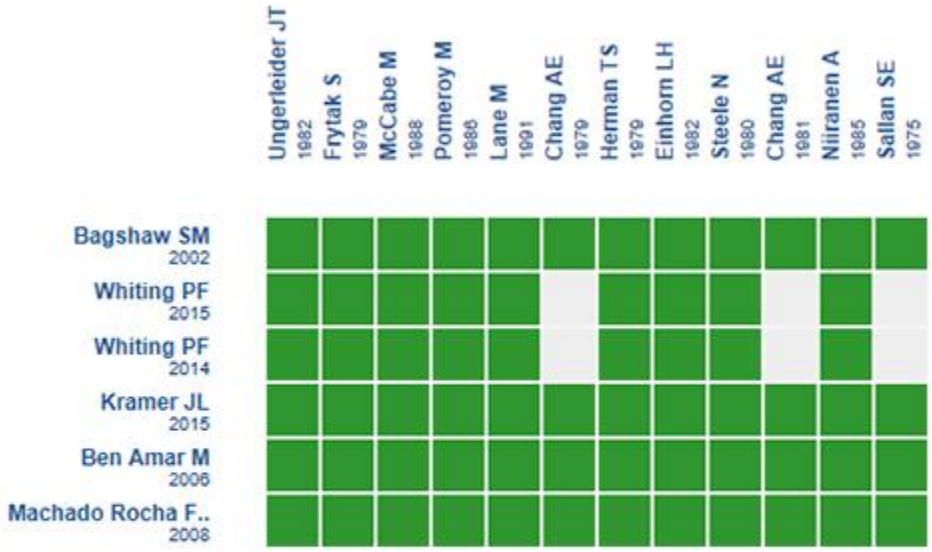
Could this evidence change in the future?

- The probability that future studies change the conclusions of this summary is high, especially regarding the potential benefits, since the certainty of the evidence is very low.
- There are three ongoing trials on this topic at the International Controlled Trials Registry Platform [95],[96],[97]. Also, there is an abstract in the American Society of Clinical Oncology (2012) meeting database, that answers this clinical question [98] however these data are not in any of the systematic reviews we found. An ongoing systematic review was identified in the PROSPERO registry [99].

- On the other hand, we did not find studies using NK1 receptor antagonists or olanzapine as a part of the basal antiemetic regime or as a comparison regime, both drugs are well recommended in clinical guidelines.
- The identified systematic reviews had important limitations regarding the presented data on the emetogenic potential and administration regime of cannabinoids. Eventually, a new systematic review could provide new data or analyses in order to answer this question.

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 chemotherapy induced nausea and vomiting

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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