MEDwave

Living Friendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2016;16(Suppl5):e6793 doi: 10.5867/medwave.2016.6793

Do cannabinoids have a role to play in Tourette's syndrome?

Authors: Karen García**[1,2]**, Gabriel Rada**[2,3,4,5,6]**

Affiliation:
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Proyecto Epistemonikos, Santiago, Chile
[3] Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[4] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[5] GRADE working group
[6] The Cochrane Collaboration

E-mail: radagabriel@epistemonikos.org

Citation: García K, Rada G. Do cannabinoids have a role to play in Tourette's syndrome?. *Medwave* 2016;16(Suppl5):e6793 doi: 10.5867/medwave.2016.6793
Publication date: 9/12/2016

Abstract

It has been suggested that the use of cannabinoids might play a role in the treatment of Tourette's syndrome, but there is no consensus. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified seven systematic reviews including two randomized trials addressing the question of this article. We extracted data, combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded it is not clear whether cannabinoids reduce tics in Tourette's syndrome, and they are probably associated to frequent adverse effects.

Problem

Tourette's syndrome is a neuropsychiatric disorder characterized by the presence of involuntary movements (motor tics) and vocalizations (vocal tics). In this condition, there is a lack of inhibition of neuronal cortico-striatal-thalamic-cortical circuits. Many drugs have been tried in order to reduce tics, with responses not entirely satisfactory. In the search for new therapies, the use of cannabinoids has been put forward, but there is no clear consensus about their clinical role.

Methods

We used Epistemonikos database, which is maintained by screening multiple 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 not clear whether cannabinoids reduce tics in Tourette's syndrome, and they are 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 seven systematic reviews [1],[2],[3],[4],[5],[6],[7] including two randomized controlled trials reported in four references [8],[9],[10],[11].
What types of patients were included	Both trials enrolled men and women diagnosed with Tourette's syndrome based on DSM III criteria.
What types of interventions were included	Both trials evaluated the use of tetrahydrocannabinol capsules administered orally. In one trial, the dose was 5 mg, 7.5 mg or 10 mg once [9], and in the other trial, the dose was not specified [8]. Both trials compared against placebo.
What types of outcomes were measured	The systematic reviews assessed the following outcomes: • Improvement in severity of tics measured by different scales (TSSL, STSSS, YGTSS, TSGS, TS-CGI*). • Adverse effects followed up to 42 days after the end of trial. • Other outcomes measured were obsessive-compulsive disorder, foreboding anxiety, cognitive function alteration, attention deficit hyperactive disorder.

* TSSL = Tourette's syndrome symptoms list; STSSS = Shapiro Tourette syndrome severity scale; YGTSS = Yale Global Tic Severity Scale; TSGS = Tourette's syndrome global scale; TSC-GI = Tourette's syndrome clinical global impression scale

Both trials evaluated the use of tetrahydrocannabinol capsules administered orally. In one trial, the dose was 5 mg, 7.5 mg or 10 mg once [9], and in the other trials, the dose was not specified [8]. Both trials compared against placebo.

Summary of findings

The Information on the effects of cannabinoids for Tourette's syndrome is based on two randomized trials including 28 patients in total [8], [9]. Both trials measured the severity of tics, using different scales. The summary of findings is as follows:
Key messages

- It is not clear whether cannabinoids reduce tics in Tourette's syndrome because the certainty of the evidence is very low.
- Cannabinoids are probably associated to frequent adverse effects. The certainty of the evidence is moderate.

Cannabinoids in Tourette's syndrome

Patients Adults with Tourette's syndrome
Intervention Cannabinoids
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT cannabinoids	**WITH cannabinoids**		
	Difference: patients per 1000			
Severity of tics	The severity of tics was measured on different scales, some exhibited differences while others did not.		-	⊕◯◯◯[1,2] Very low
Adverse effects	217 per 1000	478 per 1000	RR 2.20 (0.91 to 5.34)	⊕⊕⊕◯[1,2] Moderate
	Difference: 261 patients more per 1000 (Margin of error: 20 less to 943 more)			

RR= Risk 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).

[1] The certainty of the evidence was downgraded in two levels due to risk of bias because both studies have major limitations. For adverse effects, the certainty was not decreased for these criteria, since bias would reinforce the conclusion.
[2] The certainty of the evidence was decreased by one level due to imprecision since the effect was not significant in most scales measured.
[3] The certainty of the evidence was decreased for imprecision, as the confidence interval is wide and includes no-effect. Adverse effects were generally mild or moderate and transient (anxiety, restlessness, dry mouth, tremor, dizziness, headache, decreased concentration, ataxia, anhedonia, hot flashes, and nausea).

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.

 doi: 10.5867/medwave.2016.6793

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to adults with Tourette's syndrome diagnosed according to DSM III criteria.
- While there are no trials in children, in the absence of evidence, it is reasonable to extrapolate the findings of this summary.

About the outcomes included in this summary

- The outcomes severity of tics and adverse effects were considered critical for decision making by the authors of this summary, and this is in line with those used by systematic reviews and guidelines.

Balance between benefits and risks, and certainty of the evidence

- The evidence on the benefits has very low certainty, and adverse effects are common. So, the benefit/risk ratio is not favorable.

What would patients and their doctors think about this intervention

- Based on the existing evidence most patients and doctors should lean against the use of this intervention.
- Some patients putting more value on an uncertain benefit might decide to use it, especially taking into account preconceived ideas or non-conclusive recommendations in some guidelines.

Resource considerations

- Commercial formulations of cannabinoids are generally expensive. Since there is no certainty about benefits, it is not possible to estimate a cost/benefit balance.

Differences between this summary and other sources

- The systematic reviews differ slightly between them. Some argue it is a promising therapy [2],[5],[6], while others emphasize the lack of evidence [1],[3],[7].
- The conclusions of this summary partially disagree with some of the major guidelines, which make a weak recommendation in adults (not in children, because there are no studies), or take no clear position on the issue [12],[13].

Could this evidence change in the future?

- The probability that future evidence changes the conclusion of this summary regarding the benefits of cannabinoids in Tourette's syndrome is high, because of the existing uncertainty. Regarding adverse effects, the probability is low.
- There are no ongoing trials on this topic according to the International Clinical Trials Registry Platform of the World Health Organization.

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 Tourette's 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.

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.

References

1. Curtis A, Clarke CE, Rickards HE. Cannabinoids for Tourette's Syndrome. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006565 | CrossRef | PubMed |
2. Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential.J Ethnopharmacol. 2006 Apr 21;105(1-2):1-25 | PubMed |
3. Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and

safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014 Apr 29;82(17):1556-63 | CrossRef | PubMed |
4. Waldon K, Hill J, Termine C, Balottin U, Cavanna AE. Trials of pharmacological interventions for Tourette syndrome: a systematic review. Behav Neurol. 2013;26(4):265-73 | CrossRef | PubMed |
5. Whiting P, Wolff R, Westwood M, Duffy S, Misso K, Keurentjes C, et al. Systematic review of cannabis for medical use. Kleijnen Systematic Reviews Ltd. 2014 | Link |
6. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73 | CrossRef | PubMed |
7. Andrzejewski K, Barbano R, Mink J. Cannabinoids in the treatment of movement disorders: A systematic review of case series and clinical trials. Basal Ganglia. 2016;6(3):173-181 | CrossRef |
8. Müller-Vahl KR, Koblenz A, Jöbges M, Kolbe H, Emrich HM, Schneider U. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. Pharmacopsychiatry. 2001 Jan;34(1):19-24 | PubMed |
9. Müller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC):no influence on neuropsychological performance. Neuropsychopharmacology. 2003 Feb;28(2):384-8 | PubMed |
10. Müller-Vahl KR, Schneider U, Koblenz A, Jöbges M, Kolbe H, Daldrup T, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry. 2002 Mar;35(2):57-61 | PubMed |
11. Müller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. J Clin Psychiatry. 2003 Apr;64(4):459-65 | PubMed |
12. Roessner V, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. Eur Child Adolesc Psychiatry. 2011 Apr;20(4):173-96 | CrossRef | PubMed |
13. Pringsheim T, Doja A, Gorman D, McKinlay D, Day L, Billinghurst L, et al. Canadian guidelines for theevidence-based treatment of tic disorders: pharmacotherapy. Can J Psychiatry. 2012 Mar;57(3):133-43 | PubMed |

Author address:
[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile