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Are Cannabis, Cannabis-Derived Products, and Synthetic Cannabinoids a Therapeutic Tool for Rheumatoid Arthritis? A Friendly Summary of the Body of Evidence

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Background: Symptom management in rheumatoid arthritis (RA) remains a complex challenge. Widespread use of cannabis-based medicines for a myriad of symptoms has fostered rheumatology patients' interest. However, their safety and efficacy in RA remain unclear.

Objective: The aim of this study was to perform a structured summary of the body of evidence in order to determine whether cannabis, cannabis-derived products, and synthetic cannabinoids are an effective treatment for rheumatoid arthritis.

Methods: An electronic search in Epistemonikos database was performed to identify systematic reviews and their primary studies that addressed our clinical question. The body of evidence was collected in a pivot table in Epistemonikos. Information and data from the primary studies were extracted from the identified reviews. Finally, extracted data were reanalyzed, and a summary of findings table was generated using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: Twenty-six systematic reviews were identified which included in total only 1 randomized trial assessing our clinical question.

Conclusions: Cannabis, cannabis-derived products and synthetic cannabinoids may slightly reduce disease activity in patients with RA. Its use may result in little to no difference in pain reduction and may slightly increase nervous system adverse events. The evidence is very uncertain about the effect of cannabis, cannabis-derived products, and synthetic cannabinoids on serious adverse events risk.

Key Words: cannabinoids, cannabis, cannabis-derived products, Epistemonikos, GRADE, marijuana, medical cannabis, meta-analysis, rheumatoid arthritis, synthetic cannabinoids, systematic review

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Despite great advances in rheumatoid arthritis (RA) treatment, symptoms and disease burden still cause disability, poor quality of life, and significant excess mortality, which sometimes lead patients to seek therapeutic alternatives.[1–4] Although the mechanism of action of cannabis, cannabis-derived products, and synthetic cannabinoids in rheumatic diseases remains unclear, patient's interest in their medical use is rising.[5,6] This fact, along with the lack of a strong evidence support, has led physicians to face great uncertainty about the benefits and risks of their prescription.[7] The aim of this structured summary is to examine the therapeutic effects of cannabis, cannabis-derived products, and synthetic cannabinoids in rheumatoid arthritis.

MATERIALS AND METHODS

This article is a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), which main objective is to synthesize the body of evidence for a specific question, with a friendly format for clinical professionals. Its major resources are based on a matrix of evidence generated by Epistemonikos database software and an analysis of the body of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. It is elaborated with pre-established methods, following rigorous methodological standards and internal peer-review process. Further details of the methods for developing this FRISBEE are described elsewhere.[8–10]

Epistemonikos, the largest database of systematic reviews in health, was used as the primary source of information.[11] Epistemonikos database is maintained by systematically screening multiple information sources, including MEDLINE, EMBASE, and Cochrane, among others, to identify systematic reviews and their included primary studies.[12]

A highly sensitive electronic search was conducted in Epistemonikos database in order to obtain systematic reviews assessing our clinical question. Using automated and collaborative means, all the relevant evidence for the question of interest was collected and displayed as a matrix of evidence. An evidence matrix is a table that pools the cluster of systematic reviews sharing at least 1 included study and all studies included in those reviews. Subsequently, information and data from the primary studies were extracted from the identified reviews using standardized forms. With this information, a structured summary was generated following a pre-established format, including key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), a table with the characteristics of primary studies addressing the question of interest, meta-analysis of the whole studies when possible, a summary of findings (SoF) table using GRADE methodology, and a discussion about other considerations relevant for decision-making.

RESULTS

Twenty-six systematic reviews were included.[14–39] Only 1 primary study,[13] a randomized controlled trial included in all 26 reviews, answered the question of interest. Therefore, the information on the effects of cannabis, cannabis-derived products, and synthetic cannabinoids in RA is based on this single study (see Table 1,

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TABLE 1. Body of Evidence About Cannabis, Cannabis-Derived Products, and Synthetic Cannabinoids as a Therapeutic Alternative for Rheumatoid Arthritis (RA)

What is the evidence?	We identified 26 systematic reviews[14–39] including only 1 primary study[13] that answered the question of interest, which corresponds to a randomized controlled trial. The table and summary are based on the randomized trial, as no observational studies were found that answered the question of interest.
What types of patients were included?[a]	The trial included patients with active RA meeting the American College of Rheumatology criteria,[40] not adequately controlled by standard medication. DMARDs had to have been stabilized for 3 months prior to study enrolment, while in case of prednisolone and NSAIDs, a month of stable regimen was required. Exclusion criteria included a history of psychiatric disorders or substance misuse, severe cardiovascular, renal or hepatic disorder, or a history of epilepsy. The trial included 58 patients (79.3% female, mean age of 62.8 years), with a mean DAS28 of 5.9. Seropositivity, erosions, and disease duration were not described, and there were no race/ethnicity data. Setting: United Kingdom, multisite outpatient.
What types of interventions were included?[a]	The trial compared the use of the oromucosal spray nabiximols (2.7 mg of THC and 2.5 mg of CBD delivered with each activation [dose]) against placebo. Starting with 1 activation per evening, the dose was titrated every 2 days up to a maximum of 6 doses, according to individual response. Stable dosing was then maintained for a further 3-week period (mean dose of 14.58 mg THC and 13.5 mg CBD). DMARDs, NSAIDs, and prednisolone dosages were maintained constant throughout the study.
What types of outcomes were measured?	The trial reported several outcomes that were grouped by the systematic reviews as follows: ● Pain: morning pain on movement (0–10 NRS), morning pain at rest (0–10 NRS), total intensity of pain (score derived from 15 adjectives describing pain from the SF-MPQ), intensity of pain at present (VAS component from SF-MPQ), and pain at present (verbal rating scale extending from "none" to "excruciating" from the SF-MPQ). Patients completed a daily diary of pain outcomes. ● Morning stiffness. ● Quality of sleep (0–10 NRS). ● Disease activity (DAS28). ● Adverse effects, serious adverse effects, and withdrawal from the study due to adverse effects: the method used for adverse effect assessment was not detailed. Follow-up: 7–10 days.

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

CBD, cannabidiol; DMARDs, disease-modifying antirheumatic drugs; DAS28, 28-joint Disease Activity Score; NRS, numerical rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; SF-MPQ, Short-Form McGill Pain Questionnaire; THC, tetrahydrocannabinol; VAS, visual analog scale.

which illustrates the characteristics of the body of evidence assessing cannabis, cannabis-derived products, and synthetic cannabinoids therapeutic role in rheumatoid arthritis).[13]

The article included 58 patients and assessed pain on movement, pain at rest, total pain intensity, morning stiffness, sleep quality, disease activity, and adverse effects.[13] None of the identified systematic reviews reported physical disability or quality of life.[14–39]

The interactive version of the evidence matrix is available at the Epistemonikos web site https://www.epistemonikos.org/ under the title "Cannabis, Cannabis-Derived Products, and Synthetic Cannabinoids for Rheumatoid Arthritis."[41] The upper portion of the matrix will display a warning of "new evidence" if new systematic reviews are published after this structured summary.

Summary of Findings

The SoF is as follows:

- Cannabis, cannabis-derived products, and synthetic cannabinoids may slightly reduce disease activity.
- The evidence suggests that cannabis, cannabis-derived products, and synthetic cannabinoids result in little to no difference in pain reduction.
- No studies were found that examined physical disability.
- No studies were found that assessed quality of life.
- The evidence is very uncertain about the effect of cannabis, cannabis-derived products, and synthetic cannabinoids on serious adverse events risk.
- Cannabis, cannabis-derived products, and synthetic cannabinoids may result in a slight increase in the risk of nervous system adverse events.

Key information concerning the magnitudes of relative and absolute effects of the interventions examined, the amount of available evidence, and the certainty (or quality) of available evidence is shown in Table 2. The interactive version of the SoF table can be reviewed online at https://isof.epistemonikos.org/.[45]

DISCUSSION

The summary of the body of evidence reveals that many systematic reviews have encompassed or addressed in some way our clinical question. Nevertheless, the reviews have found only 1 trial evaluating medical cannabinoids prescription in RA.[13] The lack of articles on the topic contrasts with increasing interest of RA patients in medicinal cannabis and clinicians' need of a strong evidence base to properly address patients' questions.

The outcomes included in the SoF table are those considered critical for decision-making, according to the opinion of the authors of this summary, and in general coincide with the systematic reviews identified. However, physical disability and quality of life outcomes were not reported in these systematic reviews. The evidence suggests that cannabis, cannabis-derived products, and synthetic cannabinoids may slightly reduce disease activity. Nevertheless, given that the disease activity instrument used

TABLE 2. Summary of Findings Table: Cannabis, Cannabis-Derived Products, and Synthetic Cannabinoids as a Therapeutic Tool for Rheumatoid Arthritis

Patients	**Patients With Rheumatoid Arthritis**			
Intervention	**Nabiximols**			
Comparison	**Placebo**			
	Absolute Effect[a]			
Outcome	**Without Nabiximols**	**With Nabiximols**	**Relative Effect (95% CI)**	**Certainty of Evidence (GRADE)**
	Difference: Patients per 1000			
Disease activity (DAS28)[b]	5.9 points	5.0 points	—	⊕⊕○○[c,d] Low
	MD: 0.9 less (Margin of error: 1.23–0.57 less)			
Pain (SF-MPQ: PPI)[e]	3.3 points	2.6 points	—	⊕⊕○○[c,d] Low
	MD: 0.7 less (margin of error: 1.3–0.1 less)			
Physical disability	Not measured or reported by the systematic reviews		—	—
Quality of life	Not measured or reported by the systematic reviews		—	—
Serious adverse events	74 per 1000	13 per 1000	RR, 0.17 (0.01–3.49)	⊕○○○[c,f] Very low
	Difference: 61 less (margin of error: 73 less to 184 more)		—	—
Nervous system adverse events[#]	148 per 1000	419 per 1000	RR, 2.83 (1.05–7.65)	⊕⊕○○[c,d] Low
	Difference: 271 more (margin of error: 7 more to 985 more)			

Margin of error: 95% CI.

[a]The risk without nabiximols is based on the risk in the control group of the trials. The risk with nabiximols (and its margin of error) is calculated from relative effect (and its margin of error).

[b]The DAS28 is an instrument that measures activity in RA.[42] Its calculation includes the number of TJs, number of SJs, GH measured with a VAS, and inflammatory parameters (ESR or CRP).[42] This is calculated with the following formulas: DAS28 (ESR) = 0.56 * √(TJ28) + 0.28 * √(SJ28) + 0.014 * GH + 0.70 * ln(ESR) or DAS28 (CRP) = 0.56 * √(TJ28) + 0.28 * √(SJ28) + 0.014 * GH + 0.36 * ln(CRP + 1) + 0.96.[42] A DAS28 >5.1 implies active disease, <3.2 low disease activity, and <2.6 remission.[42] The MCID for this scale is a change from baseline >0.6 (>1.2 good response, >0.6 moderate response, ≤0.6 no response).[43]

[c]The certainty of the evidence was downgraded in 1 level for risk of bias because of unclear risk of bias related to blinding of participants and personnel.

[d]The certainty of the evidence was downgraded in 1 level because of imprecision as decisions at both ends of the confidence interval would vary.

[e]SF-MPQ: Short-Form McGill Pain Questionnaire.[44] The SF-MPQ has 3 components: total intensity of pain, intensity of pain at present, and the PPI.[44] Data shown are from the PPI component, a 6-point verbal rating scale that measures the patient's cognitive assessment of the pain. In this scale, patients choose the word that best describes the overall intensity of their pain: none (0), mild (1), discomforting (2), distressing (3), horrible (4), and excruciating (5).[44]

[f]The certainty of the evidence was downgraded in 2 levels for risk of bias because the trial had an unclear risk of bias related to blinding of participants and personnel.

[g]Nervous system adverse events include dizziness, light-headedness, drowsiness, and headache.

CI, confidence interval; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; GH, global health of the patient; MCID, minimally clinically important difference; MD, mean difference; PPI, present pain intensity; RR, risk ratio; SJ, swollen joint; SMD, standard mean difference, TJ, tender joint; VAS, visual analog scale.

includes both tender joints and patient's global health self-report in its calculation, the decrease in 28-joint Disease Activity Score may be exclusively due to a reduction in pain.

Because only 1 study evaluating nabiximols oromucosal spray was included in this summary, any extrapolation to other doses, compounds, therapeutic forms, and routes of administration might be premature. Accordingly, the results are applicable to patients with uncontrolled (active) RA and might not apply to patients with comorbidities such as psychiatric disorders, substance misuse, severe cardiovascular, renal or hepatic disorders, or a history of epilepsy, because they were excluded from the trial examined in this summary.[13]

It is not possible to make an adequate balance between benefits and risks because of the uncertainty about both. However, it is reasonable to estimate that the likelihood of a favorable balance is low. Furthermore, the follow-up period for the trial was relatively short, which is not informative in this chronic condition. In consideration of the previous information, the balance between benefits and risks should be individually assessed with patients.

Synthetic cannabinoids are generally expensive. In many countries, the use and commercialization of these drugs are not authorized, so the cost associated with the process of legalization, production, commercialization, and inspection is probably substantive. Nabiximols, in particular, has a high cost, but is available as a prescription medicine in the United Kingdom, Switzerland, Norway, Turkey, Australia, New Zealand, Israel, Brazil, Colombia, and Chile, whereas approval by the US Food and Drug Administration is still pending.[46]

Existing evidence should lead most patients and physicians to exercise caution in using this intervention. However, given the connotation of natural medicines of cannabis-derived products and cannabis in particular, it is likely that some clinicians and

patients might favor its use despite the information provided in this summary.

The American College of Rheumatology, European League Against Rheumatism, and international guidelines do not mention cannabis, cannabis-derived products, and synthetic cannabinoids for the treatment of patients with RA.[47–49] On the other hand, the College of Family Physicians of Canada recommends against the use of medical cannabinoids for pain due to rheumatologic conditions including RA,[50,51] whereas the Canadian Rheumatology Association position statement on medical cannabis use in rheumatic disease recognizes the lack of evidence for its use in rheumatology patients, but encourages patients to discuss benefits and risks with their physician.[52] The major part of the included systematic reviews was not specifically focused on patients with RA (e.g., noncancer chronic pain, rheumatic diseases), but most of those that made a declaration particularly for our population agreed that the evidence is insufficient to draw a conclusion.

The likelihood that the conclusions of this summary change with future evidence is high, given the scarcity of studies on the topic and the very low certainty of the evidence. Also, further research is needed addressing cannabis, cannabis-derived products, and synthetic cannabinoids other than nabiximols.

At least 3 ongoing studies that could provide relevant clinical information were identified; all of them were randomized clinical trials.[53–55] Ongoing primary studies and high-quality systematic reviews reanalyzing existing data could provide conclusions with higher certainty.

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