Arthritis Care & Research
Vol. 68, No. 5, May 2016, pp 681–688
DOI 10.1002/acr.22727

ORIGINAL ARTICLE

Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials

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Objective. **To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases.**

Methods. **Multiple databases, including Medline, Embase, and CENTRAL, were searched. Randomized controlled trials with outcomes of pain, sleep, quality of life, tolerability (dropouts due to adverse events), and safety (serious adverse events), with comparison of cannabinoids with any type of control, were included. Study methodology quality was evaluated with the Cochrane risk of bias tool.**

Results. **In 4 short-term studies comprising 203 patients (58 with rheumatoid arthritis, 71 with fibromyalgia, and 74 with osteoarthritis [OA]), cannabinoids had a statistically significant effect on pain in 2, sleep in 2, and improved quality of life in 1, with the OA study prematurely terminated due to futility. The risk of bias was high for all 3 completed studies. Dizziness, cognitive problems, and drowsiness, as well as nausea, were reported for almost half of the patients. No serious adverse events were reported for cannabinoids during the study duration. No studies of herbal cannabis were identified.**

Conclusion. **Extremely small sample sizes, short study duration, heterogeneity of rheumatic conditions and products, and absence of studies of herbal cannabis allow for only limited conclusions for the effects of cannabinoids in rheumatic conditions. Pain relief and effect on sleep may have some potential therapeutic benefit, but with considerable mild to moderate adverse events. There is currently insufficient evidence to recommend cannabinoid treatments for management of rheumatic diseases pending further study.**

INTRODUCTION

Rheumatic diseases are an important cause of chronic pain, with an imperfect response to current analgesic pharmacologic treatments. Recent research has identified an extensive endocannabinoid system in the animal kingdom, comprised of endogenous ligands and receptors throughout the organism, but with important localization to nervous tissue. The primary function of this system in the developed human being is to maintain homeostasis, which includes modulation of pain and inflammation (1). Exogenous molecules with cannabinoid properties may therefore also function to engage this system, with particular interest in the effects on pain. Originally available as the herbal preparation derived from the hemp plant *Cannabis sativa*, cannabinoids have been used through the ages for alleged therapeutic effects. Currently, musculoskeletal pain is a common reason why persons use herbal

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Submitted for publication June 23, 2015; accepted in revised form September 8, 2015.

Significance & Innovations

- The human endocannabinoid system modulates the body toward homeostasis with effects on pain, inflammation, and sleep.
- There are limited studies of the effects of exogenous cannabinoids in the management of symptoms of rheumatic diseases.
- The existing evidence for effects on pain and sleep is poor, although cannabinoids may hold potential pending further study. Neurocognitive and gastrointestinal adverse effects may limit use.

cannabis for medicinal reasons (2–5). With use of the herbal product as a means of self-medication by up to 10% of persons with chronic noncancer pain in Canada, pharmaceutical preparations have been developed and are now available for certain indications in some countries (6). Therefore, it is timely to examine the evidence for effect of the various cannabinoid molecules in persons with rheumatic diseases (7).

Cannabinoids exist as endocannabinoids, which are natural regulatory molecules produced in our bodies; as phytocannabinoids derived from the plant material; or as synthesized pharmaceutical preparations, synthetocannabinoids (8). The effects of herbal cannabis are mediated via plant alkaloids with two molecules, specifically Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), having particular interest for therapeutic effects (9–11). Analogs of mostly THC have been synthesized, allowing for administration of defined amounts, compared to the variable composition of naturally occurring herbal products. Current preparations are available as 4 products: the herbal product administered by a weight measurement in grams, and 3 pharmacologic preparations, including 2 synthetic oral agents, dronabinol, a stereoisomer of Δ^9-THC, and nabilone, a synthetic analog of Δ^9-THC, and an oromucosal spray of cannabis extract, nabiximol, a combination of Δ^9-THC and CBD as well as trace amounts of minor phytocannabinoids (7). Several drugs under development manipulate the endocannabinoid system by inhibiting enzymes that hydrolyze endocannabinoids and thereby boost the levels of the endogenous molecules. Blockade of the catabolic enzyme fatty acid amide hydrolase (FAAH) elevates anandamide levels and elicits antinociceptive effects, without the psychomimetic side effects associated with Δ^9-THC (12).

Since this class of molecules may hold potential for symptom relief of pain related to rheumatic conditions, we have examined the literature for evidence of effects of cannabinoids as a therapy for patients with rheumatic diseases, including inflammatory arthritis, peripheral osteoarthritis (OA), soft tissue rheumatism, and fibromyalgia (FM).

MATERIALS AND METHODS

The Canadian Rheumatology Association (CRA), in response to the Government of Canada's decision to revise its herbal cannabis for medicinal use policies, mandated this systematic review to better understand the use of cannabinoids pertaining to the management of persons with rheumatic diseases. Rheumatic diseases were defined as conditions affecting the musculoskeletal system, including systemic rheumatic diseases, OA of peripheral and spinal regions, soft tissue rheumatism, and FM. As a preliminary step, the CRA convened a working group to conduct a needs assessment concerning rheumatologist confidence regarding cannabinoid preparations in general and herbal cannabis in particular. Rheumatologists reported considerable lack of confidence in their knowledge of cannabinoids in general and in their ability to provide advice regarding use of cannabinoids for rheumatology patients in general (13). Thereafter, a librarian from the McGill University Health Centre (TL) conducted the literature search.

Identification of studies. A comprehensive literature search of the following databases was conducted in September 2013 and further updated in January 2015: Medline (via OvidSP from 1946 to September 25, 2013 and via PubMed from 1946 to September 26, 2013), Embase Classic and Embase (via OvidSP from 1947 to September 24, 2013), BIOSIS Previews (via OvidSP from 1969 to week 43, 2013), Web of Science (via Thomson Reuters from 1996 to September 29, 2013), Scopus (via Elsevier from 1996 to September 26, 2013), CENTRAL (via Cochrane Library to issue 9 of 12, 2013), DARE (via Wiley to issue 3 of 4, July 2013), CINAHL (via EBSCO to September 29, 2013), PsycINFO (via OvidSP from 1806 to September week 4, 2013), and AMED (via OvidSP from 1985 to September 2013). Searches for ongoing clinical trials were also run in ClinicalTrials.gov (www.clinicaltrials.gov, 12/05/2013), International Clinical Trials Registry Platform (http://apps.who.int/trialsearch, 12/05/2013), Current Controlled Trials (http://www.controlled-trials.com, 05/12/2013), and Natural Medicines (https://naturalmedicines.therapeuticresearch.com, 12/05/2013), as well as various drug and device regulatory approval sites. Further studies were identified in Web of Science and Scopus (to March 18, 2014) by carrying out citation searches for studies citing included studies, as well as by examining their reference lists. The search strategy outlined in Supplementary Figure 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22727/abstract) combined the following 2 concepts: cannabinoids and rheumatic diseases, using text words and relevant indexing. The full Medline strategy was applied to all databases, with modifications to search terms as necessary.

Inclusion and exclusion criteria. Randomized controlled trials (RCTs) that assessed at least one outcome of pain, sleep disturbance, and/or quality of life in rheumatic diseases, with comparison of a cannabinoid with placebo or an active control, were included, without limitations for study duration and patients included per treatment arm. Only articles with full text in either English or French were included.

Quality assessment. Risk of bias in included studies was assessed independently by 2 authors (M-AF and PAS-

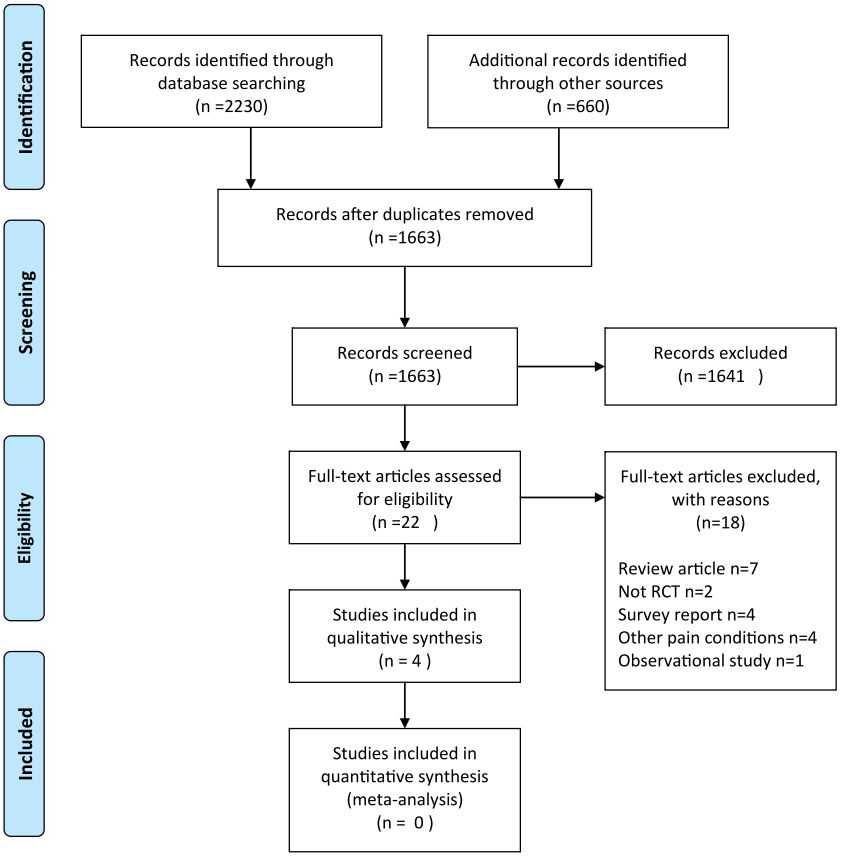

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. RCT = randomized controlled trial.

M) using the criteria outlined in the "Risk of bias" tool in the Cochrane Handbook for Systematic Reviews of Interventions and adapted from those used by the Cochrane Pregnancy and Childbirth Group (14). We resolved any disagreement by discussion. The following were assessed for each study: 1) random sequence generation (selection bias), 2) allocation concealment (selection bias), 3) blinding of outcome assessment (detection bias), 4) incomplete outcome data (attrition bias due to amount, nature, and handling of incomplete outcome data), and 5) size (possible bias confounded by small size, with low risk of bias if there were >200 participants, unclear risk with 50–200 participants, and high risk if there were <50 participants). Risk of bias within each study was assessed as low (when there was low risk for all domains), unclear (if there was unclear risk for one or more domains), and high (if there was high risk for one or more key domains). Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to rate the overall quality of the evidence, with GRADE ratings of very low-, low-, moderate-, or high-quality evidence reflective of the extent to which we were confident in the overall effect of a treatment (15).

Data extraction. Data were recorded on a standardized form by 2 of the authors (M-AF and PAS-M). The following information was recorded for each study: first author, year of publication, specific agent studied, study design, sample size, specific disease studied, and outcome measurements reported. Where possible, data on the following outcomes were recorded: pain intensity, sleep quality, and health-related quality of life. Adverse events reported for each study were recorded with attention to the following: somnolence, cognitive symptoms, and gastrointestinal symptoms. The number of patients dropping out due to adverse events (tolerability), as well as the total number of severe adverse events, including deaths (safety), was recorded for each study.

RESULTS

Literature search. The electronic database search and initial screening for eligible studies yielded 1,663 articles after removal of duplicates, with 22 studies selected for full-text review (see Figure 1 for a PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] flow diagram). Excluded were survey reports, observational studies, case series, case reports, and commentaries, with 8 remaining articles (16–23). Of these, 4 were excluded: 2 included patients with pain due to causes other than rheumatic diseases, 1 was an open-label study examining the effect of product Δ^9-THC on experimentally induced pain, and the other was an open-label report of cannabis use in patients with FM (16–19).

Table 1. Randomized controlled trials assessing cannabinoids in the treatment of rheumatic conditions*

Author, year (ref.)	Agent (control group)	Population	Outcome measure	Duration of treatment	Efficacy	Safety	Risk of bias and comments
Blake et al, 2006 (20)	Nabiximols (placebo)	RA (n = 58)	Primary Morning pain on movement (VAS) Secondary Morning pain at rest (VAS) Sleep quality (VAS) Morning stiffness (VAS) SF-MPQ DAS28	5 weeks	Improved pain on movement, pain at rest, sleep quality, DAS28, and SF-MPQ	2 serious AEs in placebo group No withdrawals due to AEs in treatment group Dizziness, dry mouth, lightheaded, nausea, falls	High risk of bias No comment regarding RA disease-modifying treatment
Skrabek et al, 2008 (22)	Nabilone 0.5–1 mg bid (placebo)	FM (n = 40)	Primary Pain (10-cm VAS) Secondary Tender points Tender point threshold FIQ depression FIQ fatigue FIQ anxiety FIQ total score	8 weeks	Improved pain, FIQ anxiety, and FIQ total score	No serious AEs 3 withdrawals due to AEs in treatment group Drowsiness, dry mouth, vertigo, cognitive effects	High risk of bias No difference from placebo at 2 weeks
Ware et al, 2010 (23)	Nabilone 0.5–1 mg (amitriptyline 10–20 mg)	FM (n = 31)	Primary Quality of sleep (ISI and LSEQ) Secondary MPQ Profile of Mood States FIQ Global satisfaction with treatment	2 weeks each study period and 2 weeks washout	Improved ISI No differences for LSEQ, MPQ, mood, FIQ	No serious AEs 1 withdrawal due to AE in treatment group Dizziness, drowsiness, nausea, dry mouth	High risk of bias Nabilone judged noninferior to amitriptyline
Huggins et al, 2012 (21)	PF-04457845 (placebo or naproxen 500 mg bid vs. placebo)†	Knee OA (n = 74)	WOMAC pain WOMAC stiffness WOMAC physical function WOMAC total score Daily pain Use of rescue medication	2 weeks	Study stopped at interim analysis due to futility	No serious AEs	Risk of bias not applicable as study stopped at interim due to futility

* RA = rheumatoid arthritis; VAS = visual analog scale; SF-MPQ = short form McGill Pain Questionnaire; DAS28 = Disease Activity Score in 28 joints; AEs = adverse events; bid = twice a day; FM = fibromyalgia; FIQ = Fibromyalgia Impact Questionnaire; ISI = Insomnia Severity Index; LSEQ = Leeds Sleep Evaluation Questionnaire; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845.

Table 2. Risk of bias assessment for randomized controlled trials of cannabinoids for rheumatic diseases*

Author, year (ref.)	Random sequence	Allocation concealment	Blinding outcome	Incomplete outcome data	Size
Blake et al, 2006 (20)	Low	Unclear	High	High	High
Ware et al, 2010 (23)	Low	Low	Unclear	High	High
Skrabek et al, 2008 (22)	Unclear	Low	Unclear	High	High
Huggins et al, 2012 (21)	Low	Low	Low	NA	High

* NA = not applicable.

Characteristics of included studies. There were 4 controlled studies that met the inclusion criteria, but because the studies included patients with different rheumatic diseases and different products were used as treatments, the existing information did not allow for meta-analysis, and therefore is reported only as a qualitative (narrative) review. The 4 studies comprised 201 patients with rheumatic diseases, of which 58 patients had rheumatoid arthritis (RA), 71 had FM, and 74 were diagnosed with OA. A single study examined the effect of nabiximols in RA, 2 studies examined nabilone in FM, and 1 study reported on the effect of an FAAH inhibitor in OA (Table 1). The single study of an FAAH inhibitor was stopped at interim analysis for futility. For the remaining 3 completed trials, duration was from 5–8 weeks (20,22,23). All 3 completed studies had at least 2 of the 5 key domains assessed as having a high risk of bias, with the conclusion that all studies had an overall high risk of bias (Table 2).

Specific cannabinoid preparations *Nabiximols.* A single study examined the effect of nabiximols, phytocannabinoids extracted from cannabis and supplied as an oromucosal spray, compared to placebo in RA (20). This study had a high risk of bias for 3 of the 5 key domains assessing risk for bias. In this double-blind randomized trial of 58 patients with RA, over a 5-week period, improvements in pain, sleep quality, and Disease Activity Score in 28 joints were observed. A total of 4 patients withdrew from the study, 1 from the active treatment group for an unrelated surgery, and 3 from the placebo group due to adverse events (2 serious not further characterized and 1 not described). Adverse events were more commonly reported for the active treatment group, with dizziness in 26%, dry mouth in 13%, lightheadedness in 11%, and nausea and falls in 6%, and less frequent reports of constipation, arthritis pain, and headache. Constipation and malaise were identified as severe for each of the 2 patients in the active treatment group reporting this adverse effect.

There have been no RCTs of nabiximols in patients with other inflammatory rheumatic condition, OA, soft tissue rheumatism, or FM.

Nabilone. There are 2 trials of nabilone for the treatment of symptoms of FM that included a total of 71 patients (22,23). In the first study of 40 FM patients observed over an 8-week period with a 4-week active treatment phase, nabilone was associated with statistical improvement in pain and the quality of life measurement, the Fibromyalgia Impact Questionnaire (FIQ) (22). Nabilone was initiated at 0.5 mg at bedtime and could be titrated up to 1 mg twice a day. Seven patients withdrew from the study, 5 in the treatment group (2 without reason; 2 dizziness and/or disorientation, nausea, and headache; and 1 drowsiness and fatigue) and 2 in the placebo group (1 without a reason and 1 headache). Risk for bias was assessed as high for 2 of 5 key domains assessing bias. With no differences in effect observed between the groups at the 2-week assessment, the treatment group showed statistically improved pain and FIQ score at 4 weeks. Side effects were more common for the active treatment group throughout the study period, with drowsiness reported by almost one-half on active treatment, dry mouth in one-third, vertigo and ataxia in one-fifth, and fewer reporting confusion, poor concentration, headache, anorexia, and dysphoria or euphoria. There were no serious adverse events reported for the study.

The second study was a randomized, double-blind, crossover study examining the effect of nabilone compared to amitriptyline on sleep disturbance in 31 FM patients (23). Conducted over a 6-week period, with each subject receiving each drug for a 2-week period with a 2-week washout period, noninferiority of nabilone compared to amitriptyline was observed for some sleep measures. Nabilone was initiated at 0.5 mg/day with the option to increase to 1 mg/day, and amitriptyline was initiated at 10 mg/day with the option to increase to 20 mg/day. Three patients withdrew from the study, 1 for noncompliance with study protocol, 1 for lack of effect, and 1 for side effects of edema, dizziness, nausea, and insomnia after a single dose. Risk of bias was high for 2 of the 5 key domains assessed. With both agents showing a positive effect on sleep, nabilone showed a marginal advantage when sleep was assessed by the Insomnia Severity Index, but not for the Leeds Sleep Evaluation Questionnaire (23). There were no significant differences between treatments for effect on pain or quality of life. Adverse events of dizziness, drowsiness, nausea, and dry mouth were more frequently reported in the nabilone treatment group. There were no serious adverse events.

There have been no studies of nabilone in patients with inflammatory rheumatic conditions, OA, or soft tissue rheumatism.

FAAH inhibitor. A single study of 74 patients with OA examined the effect of an FAAH inhibitor, PF-04457845, compared to naproxen as an active comparator (21). This study was stopped at the interim analysis for futility.

While naproxen showed reduction in pain compared to placebo, the FAAH-1 inhibitor did not demonstrate difference from placebo, although the agent was well tolerated, with a safety profile similar to placebo. There have been no studies of any similar agent used in inflammatory rheumatic conditions, soft tissue rheumatism, or FM.

Dronabinol. There have been no studies of dronabinol in patients with any rheumatic disease.

Herbal cannabis. There have been no studies of herbal cannabis administered in any form in patients with any rheumatic disease.

DISCUSSION

This systematic review has revealed a dearth of studies examining the effects of cannabinoids in a small number of patients with rheumatic diseases. Among a vast array of rheumatic conditions, cannabinoid effects have been studied only in RA, FM, and OA, with the latter study prematurely terminated due to lack of efficacy. All studies included in this analysis were assessed as having a high risk of bias, with particular note that all studies comprised extremely low numbers of participants, leading to the possibility that results may be completely random. While statistical improvements in pain and effect on sleep were observed, troublesome quasi-neurologic side effects of altered perception, dizziness, and drowsiness, as well as gastrointestinal effects, were common. With only pharmaceutical preparations studied to date, and without any formal study of herbal cannabis preparations, no comment can be made regarding effects for herbal cannabis preparations in patients with rheumatic diseases. Based on the GRADE approach, there is low-quality evidence suggesting that cannabinoids may be associated with improvements in pain and sleep quality in RA and FM.

Clinically positive effects for the studies assessed in this review must be balanced by the reported adverse events. For the study of nabiximols in RA, the selected primary outcome measure of improved morning pain on movement was achieved, as well as some other secondary outcome measures of morning pain at rest, sleep quality, and a global disease activity score, but measures of pain intensity were unchanged (20). The authors further stated that although the differences observed were small and also variable across the population, they represent "benefits of clinical relevance." These selected measurements of change in pain and sleep quality are unique and not the usual standard for measurements of pain response or change in sleep. Other than limited demographic information, no other information is provided regarding RA disease status, such as duration of disease or concomitant treatments for disease modification or pain management, which further complicates interpretation of the results. Similarly, the 2 studies of nabilone effect in FM, while reaching statistical significance, may have less clinically meaningful effect when efficacy and side effects are weighed simultaneously (22,23). Although reported as significant, a 1.43-cm change in pain from baseline (on a 10-cm visual analog scale) and a 10.76 (16%) change in the FIQ score are of questionable meaningful clinical effect (22). The 16% reduction in FIQ total score does, however, exceed the reported minimum important difference for a change of 14% in the FIQ total score (24). In the second study, nabilone had a marginally better effect on sleep compared to amitriptyline, but with effects on pain, mood, and quality of life that were similar, but not superior, to those observed for amitriptyline (23).

Adverse events related to pharmaceutically prepared cannabinoid treatments were common, but although not serious, may be sufficiently troubling to impact well-being. For all 3 studies, between one-quarter and one-half of subjects reported side effects with quasi-neurologic effects of dizziness and drowsiness, and some form of cognitive effect was reported for all subjects. Gastrointestinal effects of dry mouth, nausea, and constipation were also reported in each of the studies. The frequency of side effects noted in the placebo-controlled study of nabilone prompted the authors to suggest that a gradual introduction and titration of nabilone should be considered for future studies (22). It is, however, reassuring to note that there were no active treatment-related serious adverse events reported for any of the studies.

Two recent systematic reviews that examined the effect of cannabinoids for treatment of chronic noncancer pain reported superiority of cannabinoids to placebo for analgesic effect, with some studies also showing improvement in sleep (25,26). Notably, neuropathic pain was the most commonly identified pain mechanism, rather than a specific musculoskeletal symptom. It is, however, increasingly appreciated that many musculoskeletal pain conditions have a considerable overlap of neuropathic pain mechanisms (27). Any therapeutic effect must, however, be balanced with adverse effects, with numbers needed to harm calculated to be between 5 and 8 for events affecting motor function, altered perception, and altered cognition, emphasizing the narrow therapeutic window associated with currently available pharmaceutically prepared cannabinoid treatments.

There are no RTCs examining the effect of herbal cannabis in patients with rheumatic diseases. The lack of research into using herbal cannabis may be attributed to the contentious status of cannabis as a highly controlled substance, with strong restrictions to access for research purposes, and as such, access to herbal cannabis for therapeutic use has been primarily driven by patient-led initiatives at the legal and political levels. Physicians are therefore reliant on extrapolation from studies in other conditions. Information about herbal cannabis for the management of rheumatic symptoms may be derived from small population surveys of persons with chronic pain conducted in the UK, Canada, and Australia (3–5). Musculoskeletal or arthritis symptoms by self-report are identified for between 15% to almost 40% of subjects, with variable outcome measures used. A single study reported dosing of 2 gm of herbal cannabis use per day for approximately 40% of subjects, but without report of concomitant treatments for any of the studies (3–5). Although these studies did not disaggregate respondents reporting rheumatic conditions, across all 3 studies the majority of patients perceived herbal cannabis to be therapeutically effective. Recreational use of cannabis either before medicinal use or concurrently

was common for all 3 studies. Therefore, on the strength of the evidence for the published literature, no conclusions for efficacy or safety of herbal cannabis in rheumatic conditions can be made. However, the safety profile of cannabis may compare favorably to current available therapies to treat rheumatic pain.

In total, there is currently no sound evidence on which to base any recommendation for use of cannabinoids for symptom relief in the rheumatic conditions. As one may expect, this lack of evidence translates into the lack of confidence expressed by Canadian rheumatologists regarding their knowledge of cannabinoids in general (13). In light of the extensive scientific but limited clinical evidence, patients may have numerous reasons to advocate for use of cannabinoids in general and herbal cannabis in particular. These include the poor performance of current available pain therapies, skepticism about the pharmaceutical industry, anecdotal and media reports attesting to the efficacy of herbal cannabis, familiarity with the agent because of past recreational use, and knowledge that cannabis has been used for millennia for various reasons, including medicinal relief.

Findings on efficacy and tolerability issues can also be found in uncontrolled trials of cannabinoids. Problems with tolerability are, however, commonly reported for all current analgesic agents. In a study of 9 patients with FM, orally administered Δ^9-THC reduced electrically induced pain as well as daily pain report, with 5 of the 9 subjects withdrawing due to treatment-related side effects (17). In a second uncontrolled study comparing FM patients who used (28 patients) or did not use (28 patients) cannabis for therapeutic effect, users reported reduction in pain scores 2 hours after herbal cannabis use (19). Whether patients were regular users of medicinal cannabis or nonusers did not influence measurements of function by the Short Form 36 health survey physical component summary score or the FIQ at baseline (19).

The conclusions of this systematic review for cannabinoid use in rheumatology practice are limited by the weakness of the evidence available. Although 4 RCTs were identified, the studies were extremely small, were of short duration, and only included patients with RA, FM, and OA. Small sample size introduces a high risk of bias for all 3 completed studies and represents the most important limiting factor for interpretation of the results. There has been only a single study that has examined the effect of modulation of the endocannabinoid system in a homogenous patient group with knee OA, without any difference from placebo for either efficacy or side effects (21). Our search strategy was comprehensive and conducted by a qualified librarian to ensure that all of the current available studies were accessed.

In view of the considerable limitations of the studies examined in this review, including small sample sizes, short duration, only modest efficacy, and a high rate of mild to moderate adverse effects, it is not currently possible to recommend this category of treatments as therapy for patients with rheumatic diseases. Any conclusions based on these studies remain tenuous and call for larger, well-controlled clinical trials to better understand potential benefits and risks as pertaining to rheumatic conditions. In addition, the absence of any study of herbal cannabis in rheumatic diseases precludes any recommendation for use, with particular policy implications as governments worldwide, responding to patient demand for access, expand the authorized medical use of herbal cannabis, with rheumatic diseases commonly cited as a reason for use. Further research is clearly needed to improve our understanding of the therapeutic potential and limitations of cannabinoids for the treatment of rheumatic disorders.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms Fitzcharles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Fitzcharles, Ste-Marie, Häuser, Clauw, Jamal, Karsh, Landry, LeClercq, McDougall, Shir, Shojania, Walsh.
Acquisition of data. Fitzcharles, Ste-Marie, Häuser, Clauw, Jamal, Karsh, Landry, LeClercq, McDougall, Shir, Shojania, Walsh.
Analysis and interpretation of data. Fitzcharles, Ste-Marie, Häuser, Clauw, Jamal, Karsh, Landry, LeClercq, McDougall, Shir, Shojania, Walsh.

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