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REVIEW

The Elusive Truth of Cannabinoids for Rheumatic Pain

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Abstract

Purpose of Review Medical cannabis (MC) has entered mainstream medicine by a unique route. Regulatory acceptance as a medical product in many jurisdictions has bypassed the traditional evidence-based pathway required for therapies. Easier access to MC, especially related to recreational legalization of cannabis, has led to widespread use by patients for symptom relief of a variety of medical conditions and often without medical oversight. Musculoskeletal pain remains the most common reason for MC use. This review examines real-world issues pertaining to MC and offers some guidance for clinical care of patients with rheumatic diseases being treated with MC.

Recent Findings Controlled clinical studies of cannabis products in patients with rheumatic diseases have been small and tested a range of compounds, routes of administration, and clinical populations, limiting our ability to generate conclusions on MC's effectiveness in this population. Observational cohort studies and surveys suggest that use of MC and related products in patients with rheumatic diseases improves pain and associated symptoms but is commonly accompanied by mild to moderate side effects. Conflicting evidence contributes to practitioner and patient uncertainty regarding the use of MC for rheumatic disease-related pain.

Summary Despite promising preclinical and observational evidence that MC and cannabis-derived compounds are useful in the management of rheumatic disease-related pain, there remains limited high-quality clinical evidence to substantiate these findings. There are a significant number of clinical trials on this topic currently planned or underway, however, suggesting the next decade may yield more clarity. Nevertheless, given that many people with rheumatic diseases are using cannabis products, healthcare professionals must remain apprised of the evidence pertaining to cannabinoids, communicate such evidence to patients in a meaningful way that is free from personal bias and stigma, and maintain strong collaborative clinical care pertaining to MC.

Keywords Cannabinoids · Rheumatic disease · Regulations

Purpose of Review

Medicinal cannabis (MC) has a history that easily spans thousands of years yet many unanswered questions remain to this day. Following worldwide restrictive prohibition of cannabis in the twentieth century, the state of California was the first jurisdiction to allow medical use by passing the Compassionate Use Act in 1996. Thereafter, medical access to cannabis followed in various countries worldwide. Since the early/mid 1960's when the chemical structures of the two most abundant cannabinoids present in cannabis (cannabidiol and delta-9-tetrahydrocannabinol or CBD and THC, respectively) were reported, there has been explosive growth in our understanding of MC's pharmacological properties and clinical utility. Nevertheless, the medical community

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has rightly posed many questions about MC which we will endeavour to address in this review.

Persistent pain due to musculoskeletal conditions is a universal cause of personal suffering [1, 2]. Arthritis, a cause of chronic musculoskeletal pain, affects an estimated 23% of adults in the United States, with increasing prevalence as the population ages, and at least one rheumatic condition reported to affect 50% of adults aged over 65 years [3–5]. Treatment options for chronic rheumatic pain are suboptimal, with current medications providing only modest relief and side effects commonly outweighing benefits [6, 7]. Furthermore, pain does not occur in isolation and is associated with variable symptoms of sleep difficulties, mood disturbance and fatigue. It is therefore understandable that patients may seek treatment options that could better address the composite impact of chronic pain.

Cannabis has been popularized as a treatment for many conditions, with chronic pain cited as one of the most common reasons for use [8]. In North America the increase in use of MC has been particularly observed amongst those with musculoskeletal conditions, the elderly and persons with mood disorder [9–12]. Reports also indicate that patients are using MC to reduce or discontinue prescribed medications, in particular opioid-based medications, and often report an improved quality of life as a result [13–18].

This review will summarize the historical background and current regulatory framework for cannabis as a therapy, the science pertaining to the cannabis plant and the human endocannabinoid system, and the preclinical and clinical evidence for cannabis as a treatment of rheumatic pain. We will conclude with a presentation of clinical studies in the pipeline and examination of key real-world issues pertaining to MC.

The History of Medical *Cannabis*

Originating in the territories of central Asia, archaeobotanical research points to the human use of the plant *Cannabis sativa* for over 10,000 years [19]. With earliest use as a strong fibre and a food source, early medical use was recorded in the ancient Chinese Pharmacopoeia written in the first century BCE, named as a medicinal product in a compendium of natural herbs from the Han dynasty and remains today as one of 50 traditional herbs in Chinese medicine. Papyrus writings in ancient Egypt describe medical use for childbirth around 1500 BCE, and cannabis as a topical agent or treatment for arthritis is recorded in Assyrian clay tablets a century later [19]. The Greek historian Herodotus (484–425 BCE) alluded to the psychoactive effects as promoting "delight" for the Scythians. Beginning in the early nineteenth century, physicians in England and Europe proposed use of cannabis for rheumatism and painful pathologies with a report in *The Lancet* by Sir J Russell Reynolds, the personal physician to Queen Victoria [20]. In more recent times cannabis was available in the United States (US) in the early 1900's as an over-the-counter treatment for pain, inflammation and sleep disturbance.

During the early 20th Century, many countries formulated restrictive laws regarding the growth, commercialization and consumption of cannabis following the observation of potential risks of abuse and chemical dependency. These restrictive policies were reinforced with the 1961 United Nations Single Convention on Narcotic Drugs which gave cannabis the classification as a schedule I and IV substance [21, 22]. Cannabis however remained the most commonly used illicit drug worldwide, while research on cannabis, particularly patient-related clinical research, was greatly hindered by these restrictive policies.

Regulatory Standards

Beginning in the 1990's, with increasing advocacy for medical access to cannabis, California passed the Compassionate Use Act exempting certain patients and healthcare providers from liability for the possession of cannabis for medical use [23]. Thereafter decriminalization of medical use followed in other states and countries. In 2019, with recognition of the social injustices related to repressive cannabis policies and increasing worldwide medicinal use, the World Health Organization Expert committee on Drug Dependence recommended removal of cannabis from schedule IV, but retention of the schedule I designation [21]. This recommendation was accepted in December 2020. These revisions reflect the need for research to understand potential therapeutic uses and allow signatory countries to develop individual frameworks to address MC.

Globally diverse regulations regarding cannabis production, quality control, and medical or legal access amongst different countries have led to confusion and prompted a call for an international standard [24]. MC products are available in various forms in different countries and jurisdictions. Pharmaceutical products (e.g. nabilone, dronabinol, nabiximols) have regulatory approval based on evidence from randomized clinical trials (RCTs). In contrast, the plant product is often less rigorously regulated and generally available via an authorization from a healthcare professional.

In the US, MC programs differ between states with variable conditions for healthcare practitioner involvement and qualifying medical conditions [23]. There is state to state variation in cannabis products allowed, supply models, and rules regarding legal possession. As of 2024, MC is available in 38 US states and 4 territories, and the District of Columbia, and fully legalized for recreational use in 24 states. Still, cannabis remains a Schedule 1 drug in the US according to the US Controlled Substances Act and remains a federally illegal product [25]. With the passing of the "Farm Bill"

in 2018, hemp with a THC content of less than 0.3% is no longer a controlled substance. Canada has had MC available since 2001 and regulated recreational legalization in 2018. In Europe, various countries (e.g. the Netherlands, Denmark, Finland, Italy, Luxembourg, Norway, Malta, Portugal, Czech Republic and the United Kingdom) have legalized cannabis for medical use either with or without a list of eligible medical conditions and with variable access or prescription policies [26]. Some countries, such as Israel, Canada and the Netherlands have MC products that meet pharmaceutical standards regarding quality standards and purity, but regulatory standards generally remain uneven. Unfortunately, even with considerable progress and lifting of restrictions, unapproved cannabis products are used most commonly, according to a recent survey of 36 countries [21]. When identified as a novel food substance without medical claims as occurs in many countries, cannabis products are easily accessible. Notwithstanding the considerable regulatory barriers that have hindered effective study of cannabinoids in health and disease, scientific understanding has progressed sufficiently to hold promise for therapeutic effects when the endocannabinoid system is manipulated.

The Science of the Endocannabinoid System

Cannabis primarily exerts its physiological effects through modulation of the endocannabinoid system (ECS), which is comprised of endocannabinoids (i.e., endogenous cannabinoids), cannabinoid receptors (primarily CB_1 and CB_2), and enzymes (to synthesize and degrade endocannabinoids [27]). CB_1 receptors are primarily expressed in the central nervous system, and CB_2 receptors primarily in the peripheral nervous and immune systems [28]. However, both receptors are also distributed across the gastrointestinal tract, cardiovascular system, liver, adipose tissue, bone, and the reproductive systems [28], allowing for the diverse functions of the ECS (e.g., pain, mood, appetite, memory, sleep), and diverse effects of MC. Cannabinoids also exert their physiological effects via interactions with other G protein-coupled receptors (most notably GPR55 and GPR18, and members of the opioid, serotonin, muscarinic, dopamine, and adenosine families), transient receptor potential (TRP) channels, nuclear receptors (e.g., peroxisome proliferator-activated receptors [PPARs]), and ion channels, among others [29–34].

The Science of the *Cannabis* Plant

An appreciation of the complexity of the cannabis plant, dubbed the plant of 1000 molecules, helps to explain the challenges in understanding its potential therapeutic effects. There are two main subspecies of the cannabis plant, *Cannabis sativa* and *Cannabis indicia*, which contain cannabinoid and non-cannabinoid compounds. The two most abundant cannabinoids are delta-9-tetrahydrocannabinol (THC) – with psychoactive properties – and cannabidiol (CBD) – with anti-inflammatory properties [35, 36]. THC is a partial agonist of the CB_1 and CB_2 receptors and CBD is a partial agonist of the CB_2 receptor. Cannabis also contains cannabinoid metabolites, terpenes, flavonoids and alkaloids, all with various botanical properties but less understood therapeutic effects. [37] Some evidence suggests these molecules could potentiate CBD and THC's therapeutic effects (i.e., entourage effect) [38, 39]. The highest concentration of cannabinoids is found in the leaves and flowers of the plant, with concentration of THC varying from 3 to 30%, and CBD from < 1% to 13% [40, 41]. However, batch to batch differences in molecular content can occur even within a specific strain depending on growing, processing, storage and preparation conditions [42].

Plant cannabinoids are inactive acidic molecules that are decarboxylated to the neutral active form by aging or heating. Hemp refers to cannabis varieties that contain < 1% THC (with most countries requiring < 0.3% THC), and with CBD as the predominant cannabinoid. It is notable that hemp oil derived from hemp seeds is poor in phytocannabinoid content, but rich in proteins and fatty acids [43]. The sought after bioactive compounds are extracted from the plant material using a traditional solvent method or more recent greener methods such as ultrasonic-assisted, microwave-assisted, or pressurized liquid extraction processes. The product may then be reconstituted in a carrier liquid such as edible oils of olive, cocoFnut, or hemp [44]. The final product may contain other plant metabolites, including terpenes and flavonoids, depending on the strain used. Lack of standardization and absence of equivalency between non-regulated products, mostly those from the artisanal industry, has led to concerns about accuracy of chemical composition, quality, and safety, especially pertaining to CBD products [45].

Cannabinoid Products

While regulations across countries differ, cannabinoid products may generally be accessed as: 1) regulated pharmaceutical products; 2) MC products, or; 3) wellness products/nutritional supplements.

Pharmaceutical Products

Cannabinoid pharmaceuticals fall under the categories of extracts from the plant or synthetic products. There are currently four regulated pharmaceutical products available selectively in different countries, described in Table 1. Epidiolex is a highly purified CBD plant extracted product with approval in the US and some European countries for the

Table 1 Characteristics of pharmaceutical medical cannabis products

Generic name	Brand name	Formulation	Route
Cannabidiol	Epidiolex	CBD from plant extract	oral solution (100 mg/mL)
Nabiximols	Sativex	CBD ad THC from plant extract	oromucosal spray (2.5 mg CBD and 2.7 mg THC); maximum daily recommendation of about 30 mg for each molecule
Dronabinol	Marinol, Syndros	Synthetic THC	oral capsule (2.5 mg, 5 mg, 10 mg) or solution (5 mg/mL)
Nabilone	Cesamet	Sythetic cannabinoid similar to THC	oral capsule (1 mg, 2 mg)

treatment of severe epilepsy seen in Dravet Syndrome and Lennox-Gastaut Syndrome. Nabiximols (Sativex®) is a 1:1 CBD:THC oromucosal spray, approved in some countries for multiple sclerosis associated spasticity and pain. Dronabinol (Marinol, Syndros) is a synthetic form of THC [46] approved in the US, Australia, and some European countries for treating nausea associated with cancer chemotherapy and acquired immunodeficiency syndrome (AIDS). Nabilone (Cesamet) is a synthetic cannabinoid with a chemical structure slightly different from THC, giving it a higher bioavailability than dronabinol [47]. It is approved for the management of severe nausea associated with cancer chemotherapy [48] in the US, Canada, Australia, New Zealand, Mexico and some European countries. There is ongoing interest in pharmaceutical cannabinoids for treating neuropathic pain, spasticity-related pain, fibromyalgia (FM), osteoarthritis (OA), and post-operative pain, among others.

Plant-based Medical Cannabis Products

Regulations regarding products, specifications and access to plant-based MC products, which can include unprocessed plant products (e.g., dried plant) or basic extracts (e.g., oil), vary greatly amongst countries. Typically, a prescription or authorization is obtained from a healthcare provider, who may or may not require an authorizing license. Authorization may apply to a list of qualifying medical conditions, with a specified daily weight of dried cannabis allowed. In some countries, MC programs require dispensing by a licenced dispenser or a pharmacist, whereas others have more liberal access avenues.

Nutritional Supplements / Wellness Products

CBD products are mostly marketed as dietary supplements or health products and may contain variable amounts of plant isolates or other additives. As they are less rigorously regulated, there are concerns about accuracy of labelling and quality of product with regard to presence of contaminants [49, 50]. In the European Union, CBD is marketed as a "novel food", but with variations within countries. For example, in Germany CBD is a nutritional supplement, or can be prescribed by a physician and pharmacy compounded. Australia recently down scheduled CBD to a "pharmacist only" product with a maximum recommended dose of 150 mg/day. In Canada, CBD oil is classified as a cannabis product and is subject to the same restrictions as cannabis plant or THC oil.

Preclinical Studies

Preclinical studies have shown that exogenous cannabinoids are potential treatment options for pain disorders, specifically CBD with analgesic and anti-inflammatory properties. [51–53] Both CB_1 and CB_2 are involved in inflammatory hypersensitivity responses with inflammation attenuated via activation of CB_2 receptors and inhibition of inflammatory-promoting cytokines and immune cells.[54, 55] As summarized in a recent review, [56] in animal models of rheumatoid disease, CBD, THC, and related compounds (e.g., dimethylheptyl-THC-11-oic acid, tetrahydrocannabinolic acid) can prevent or alleviate induced arthritis [57–60].

The Evidence for Clinical Effect in Rheumatic Diseases

We focus on studies published since 2021 because several reviews summarize the literature up to 2020 [61–63].

Acute effects

Acute effects on pain and bone metabolism have been reported. Treatment-resistant neuropathic pain was decreased by low-dose vapourized THC (1.29%) and medium-dose THC (3.53%) for up to 4.5 h in a cross-over RCT of 39 patients [64]. In a cross-over RCT of a single vapor inhalation over 3 h in 20 FM patients, neither high THC, high CBD, nor balanced CBD:THC affected spontaneous pain scores, but increased pressure pain thresholds were noted for high THC and balanced CBD:THC [65]. Real-time data from a MC app (Strainprint®) has provided naturalistic insight into MC's effects on acute pain. Pain reporting up to 4 h after use of different MC products was recorded for over 131,000 sessions, with pain reduction of ≥ 30% reported for 60–70% of sessions. Pain rating did not differ by THC

or CBD content [66]. MC also has acute impacts on bone metabolism. After 7 days treatment with oral high-CBD or high-THC, a biomarker of bone resorption was decreased in 83 healthy humans, suggesting that MC may be bone protective [67].

Randomized controlled trials

Cannabinoids have been studied mostly in FM and OA. In patients with FM, a small ($n=17$ women) double-blind 8-week RCT of THC-rich cannabis oil (48:1 THC:CBD, starting dose 1.22 mg THC, mean final daily dose 4.4 mg THC) found that Fibromyalgia Impact Questionnaire scores were improved relative to placebo, with no intolerable adverse effects [68]. These results are generally aligned with improvements in pain and sleep in previous small RCTs testing the effect of THC or nabilone (synthetic THC) in FM [69–71]. There are 2 recent RCTs in patients with OA. In 86 participants with knee OA, CBD of 600 mg per day over 8 weeks provided no additional analgesic effect compared to placebo added to paracetamol, but with elevation of liver enzymes more commonly noted in the CBD group [72]. In 136 participants with hand OA or psoriatic arthritis, outcomes for pain, sleep quality, anxiety and depression did not differ for placebo or oral synthetic CBD (20–30 mg per day) over a 12 week RCT [73]. In older RCTs, topical transdermal synthetic CBD gel ZTN002 was examined over 12 weeks in 320 patients with knee OA. Published only as an abstract, there was no change from baseline in worst knee pain for ZYN002 250 mg, ZYN002 500 mg, or placebo divided over 2 daily doses, but secondary responder analysis and exploratory analysis in men was promising [74]. In an older blinded RCT of 58 patients with rheumatoid arthritis, 5 weeks of Sativex (oromucosal spray with 2.7 mg THC and 2.5 mg CBD) improved patients' pain with movement and rest, quality of sleep, and disease activity [75]. Overall, the few RCTs that have been conducted show inconsistent results, but also test a wide range of MC formulations (plant extracts vs. synthetics; cannabinoid content), doses, routes of administration in a variety of populations, impeding general conclusions.

Cohort studies

Cohort studies offer insight into the real-world use of MC in the absence of sufficient evidence from formal RCTs. A recent meta-analysis of patients with rheumatic disease (6 studies, $n=1{,}079$) reported cannabis consumption is associated with a decrease in pain (pain at baseline: 8.2 (2.9) mm *vs* pain over time: 5.6 (3.5) mm; $P<0.001$) [76]. Results from the following recent prospective, open-label, longitudinal cohort study is in line with these findings. In an observational study of 718 chronic pain participants (199 with arthritis) from Australian cannabis clinics at mean follow-up of 110 days, CBD dominant products were associated with reduced pain, while THC and CBD balanced products (but not the CBD or THC dominant product) was associated with significant improvement across most domains of the patient-reported outcomes measurement information system (PROMIS)-29 [77]. At least one adverse effect including dry mouth, somnolence, fatigue, nausea and balance problems was reported by 51% of 364 reporting participants.

Attrition rates in cohort studies of MC are high. With an attrition rate of 40% at 6 months, there was a decrease of average daily opioid consumption (in milligram morphine equivalents) from 18.2 mg to 9.8 mg for 40 OA patients after starting MC, with improved pain score from 6.6 to 5.4, but nearly half (43%) reporting feeling intoxicated [78]. A similar high attrition rate (over 75%) over 12 months was noted for a Canadian study of 323 FM participants [79]. In this study, cannabis initiation was associated with improved pain, which was partially explained by concurrent improvements in negative affect and sleep. In a United Kingdom study of 306 FM patients who were prescribed a variety of MC products with 12% followed for 12 months, improvements in quality of life, FM symptom severity, anxiety and depression, and pain was noted at 1, 3, and 6 months (but not 12 months). Opioid dose decreased from 24.0 mg morphine equivalents at baseline to 20.0 mg at the end of follow-up ($p=0.001$). Adverse events of mild to moderate severity were reported by 24% of patients [80]. A small ($n=30$) cohort of women with treatment-resistant FM, administered MC (20 g per month; various routes of administration) and followed for 30 days with no loss to follow-up, showed improvements from baseline in quality of life (1.47 ± 0.63 to 3.43 ± 1.07, $p<0.01$), pain and discomfort (3.77 ± 1.3 to 2.10 ± 1.18, $p<0.01$), sleep and rest (1.47 ± 0.82 to 3.53 ± 1.20, $p<0.01$) and dependence on medication (3.07 ± 1.74 to 3.73 ± 1.11, $p=0.05$), among other measures [81].

Overall, longitudinal studies suggest that MC can improve pain and related symptoms but decreases in opioid dose are likely not clinically significant. Conclusions are limited due to high rates of attrition, the absence of blinding or control groups.

Cross sectional survey data

Survey data provide insight into prevalence of MC use, substitution strategies regarding prescribed medications, adverse events and concomitant medical care.

Prevalence of Medical *Cannabis* Use

There is increasing use of MC for symptom relief, often accessed by patients as a self-management strategy,

promoted by the media, campaigns for cannabis decriminalization and legalization but with limited evidence for effect [9, 82, 83]. In a recent meta-analysis, 15% of rheumatology patients were currently taking cannabis (based on 5 studies, $n = 4{,}122$ patients) [76]. However, prevalence varies by rheumatic condition, [84, 85] legal status of MC, [86, 87] and has increased in recent years [87]. Pain intensity may be a driver for MC use [87]. In a meta-analysis of case/control studies, MC users reported higher pain scores (5.0 (2.4) vs 4.1 (2.6) mm; $P < 0.001$; 5 studies, $n = 1{,}257$) [76]. Almost three quarters of patients from rheumatology clinics indicate that MC is helpful or effective for pain [84, 87], with estimates of pain reduction of 57–83% and improved sleep of 71–87% [88]. Patients with spine pain estimate MC to be similarly effective (treats 54% of their pain) [89]. Thirty percent of patients with FM [83, 90] and 88% of patients with arthritis indicate that CBD improves their pain, as well as improving physical function [88, 90, 91].

Substitution of Medical *Cannabis* for Prescribed Medications

Decreased use of prescription medication, such as opioids, antidepressant, anxiolytics, benzodiazepines, and non-opioid analgesics is often reported when MC is used. This reduction in medication use was reported in a scoping review of 19 of 20 studies of MC use in in patients with chronic musculoskeletal pain [92], and 72% of patients with FM in a large online survey [16].

Adverse Event Reporting

Although serious adverse events are rare – reported by only 1.2% (95% CI 0.1% to 3.1%) of 12,143 patients with chronic pain who use MC in a meta-analysis of 39 studies – 26% (95% CI 2.6% to 30.6%) experienced some adverse event, usually not leading to discontinuation [93]. Among FM patients using CBD, 50% report side effects, most of which are minor [90]. Similarly, 40% of patients using CBD for arthritis pain report a side effect, but the vast majority were mild (84%) or moderate (14%) [91].

Studies in the pipeline

Table 2 lists RCTs of MC in rheumatic conditions currently underway. Of the 16 identified, most are in FM or OA, with relatively small sample sizes (median 52), and treatment duration ranging from 1 day (for mechanistic studies) to 24 weeks. All but one uses lower risk routes of MC administration (oral, topical), and all but one study tests CBD, often combined with THC. While it is encouraging to note ongoing RCTs, sample sizes are often inadequate to thoroughly examine effects of MC.

The Current Real-world of Medical *Cannabis* and the Way Forward

Lifting of restrictions on cannabis worldwide, reduced stigma, and increased commercialism, advocacy and media promotion have all contributed to growing patient willingness to explore MC as a treatment option for an array of complaints. In contrast to the generally favourable view of the public, the medical community remains cautious. Rheumatologists are uncomfortable authorizing MC due to concerns about general lack of knowledge, paucity of evidence for effects, and often poor product standardization [84]. Medical oversight is however critical when patients use a product for therapeutic reasons. It is therefore concerning that only 33% of FM patients sought medical advice about CBD, with patient choices more based on personal research (63%) than medical advice (16%) [16, 90]. Patient knowledge of the cannabis product used is often lacking; 1 in 3 patients did not know their dose of CBD [16]. These issues seem to be exacerbated in areas without MC legalization; US patients are more likely than Canadian patients to engage in higher-risk cannabis use (e.g., inhalation, higher THC:CBD ratios) and less likely to receive physician guidance [94]. This breakdown in a trusted therapeutic relationship of patient and healthcare provider will compromise clinical care. Simply agreeing to a patient's wishes, or alternately, discounting MC for various reasons, including personal biases, does not constitute collaborative clinical care and must be discouraged.

We emphasize that any authorization for MC must come from a healthcare professional with a comprehensive knowledge of a patient's medical, psychological and psychosocial condition, and with appropriate follow up care according to good clinical practice. It is not recommended that MC be prescribed by individuals who devote their practice predominantly to the prescription of cannabis. Although optimal dosage regimens for MC are not yet known, ideally MC should not be inhaled, and use of edibles (gummies, cookies) should be discouraged as this detracts from the concept of a therapeutic product. There is an emerging impression that CBD alone or CBD dominant products may not be as effective for pain management as those containing at least some THC, supported by a recent study of symptom relief and potential disease modifying effect in an animal OA model, although anecdotally there are patient reports of efficacy with CBD products for pain relief [95].

Table 2 Characteristics of current RCTs testing the effects of medical cannabis products in rheumatology patients (accessed 1st April, 2024)

Registration number	Study title	Conditions	*N*	Treatment duration	Route	Interventions
NCT03215940	Treatment of Chronic Pain With Cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC)	Chronic musculoskeletal and joint pain	75	5 days	oral	high THC/low CBD, low THC/high CBD, placebo
NCT05052541	Safety and Efficacy of Oral Cannabis in Chronic Spine Pain	Non-radicular spine pain	157	6 weeks	oral	THC/CBD, THC, placebo
NCT04729179	Cannabidiol for FM (The CANNFIB Trial)	FM	200	24 weeks	oral	CBD, placebo
NCT05283161	CBD (Cannabidiol)/THC (Tetrahydrocannabinol) Solution as a Pharmacological Strategy for Patients With FM (FibroCann)	FM	40	120 days	oral	CBD/THC, placebo
NCT05644054	The Impact of THC on Pain Modulation in FM	FM	40	1 day	oral	THC (Aximan), placebo
NCT04239469	Phase II Clinical Trial, Use of KL16-012 in Women With FM Refractary to Conventional Treatment	FM	44	3 months	oral	THC/CBD (KL16-012), Placebo
EU TRIAL REGISTER 2019–001861–33	Cannabis-opioid interaction in the treatment of FM pain – an open label proof-of-concept study	FM	60	6 weeks	inhaled	THC/CBD, oxycodone, combined
NCT05020028	Cannabidiol (CBD) in Pain Reduction for Knee OA	Knee OA	100	84 days	oral	CBD, placebo
NCT04992962	Cannabinoid Tablets for the Treatment of Pain From OA of the Knee	Knee OA	66	28 days	oral	CBD/CBN, CBD/THC, Placebo
NCT04992624	Cannabinoid Interactions With Central and Peripheral Pain Mechanisms in OA of the Knee	Knee OA	200	16 weeks	oral	CBD (Epidiolex), THC (Marinol), THC/CBD, placebo
NCT04195269	OA of the Knee Pain Study Using a CBD and THC Sublingual Tablet	Knee OA	30	30 days	oral	THC/CBD
NCT04611347	Topical CBD in Joint Arthritis	Hand OA	40	2 weeks	topical	CBD
NCT05942911	Safety and Effect on Pain and Function According to RAPID-3 of IHL-675A in Patients With Rheumatoid Arthritis	Rheumatoid Arthritis	128	24 weeks	oral	CBD/hydroxychloroquine (IHL-675A), CBD, hydroxychloroquine, placebo
NCT06108349	Topical Cannabidiol for Treating Carpal Tunnel Syndrome	Carpal Tunnel Syndrome	20	2 weeks	topical	CBD, placebo
NCT05562635	CBD (Cannabidiol) Intraoral Application and TMD (Temporomandibular Disorders)	Temporomandibular disorder	30	30 days	oral topical	CBD, CBD, placebo

Table 2 (continued)

Registration number	Study title	Conditions	*N*	Treatment duration	Route	Interventions
NCT04609748	Comparative Analysis of the Effectiveness of the Use of Nimesulide and CBD Oil in Patients With Pain in the Preauricular Region Due to the Pain-dysfunctional Syndrome of the Temporomandibular Joint	Temporomandibular disorder	30	15 days	oral topical	CBD, Nimesulide

Conclusion

Given the public embrace of cannabis as a treatment modality for may chronic diseases, it is imperative that healthcare professionals remain appraised of up-to-date evidence pertaining to cannabinoids, and that regulatory authorities and industry promote and support conduct of high-quality scientific study. By keeping abreast of current knowledge through personal study, reference to high quality publications or participation in accredited professional development courses (such as the Canadian Cannabis Syllabus, https://ccic.net/accredited-program/), physicians will be better able to engage in thoughtful discussions when a patient broaches the subject of MC. A trial of a MC within a healthcare setting provides a secure safety net that is superior to patient experimentation and self-administration. It can be anticipated that the science of MC will rapidly evolve over the next decade and that many of the elusive truths will become more evident. Until such time, physicians must maintain strong collaborative clinical care pertaining to MC and provide patients with meaningful information from a trustworthy source that is free from personal bias and stigma.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

MF was a Core member of the Health Canada Science Advisory Committee on Health Products Containing Cannabis (SAC-HPCC) 2020–2022; lead on the Canadian Rheumatology Association position statement on cannabis for the rheumatology patient.

Competing Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and were in compliance with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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