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Article type : Review article

A cautious hope for cannabidiol (CBD) in rheumatology care

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Category: Review article
No funding was provided for this manuscript

Conflict of interest:
MAF and WH report no conflict of interest.
DJC has performed consulting for Pfizer, Lilly, Zynerba, Aptinyx, Tonix, and Samumed and has received research funding from Pfizer and Aptinyx

No financial support or other benefits from commercial sources were obtained for the work reported in this manuscript,

All authors participated in the writing of this manuscriptRunning head: Cannabidiol in rheumatic disease

Keywords: rheumatic disease, cannabidiol

Word count: 3796 (allowed 3800)

Abstract (214 words)

Cannabidiol (CBD), a major metabolite of *Cannabis sativa,* is popularized as a medicinal product, with potential for analgesic, anti-inflammatory and antioxidant effects. CBD may hold promise as a treatment in rheumatic diseases, but evidence to date remains preclinical. Preclinical effects on pain and inflammation is encouraging, but clinical study is lacking with only a single study in knee osteoarthritis reporting promising effect on symptoms. CBD products are freely available over the counter and marketed as food supplements or wellness products. The World Health Organization has identified pure CBD as safe and without abuse potential, but products are not subject to drug regulatory standards leading to inconsistency in manufacturing practices and quality of products. Not only have molecular concentrations of CBD been identified as inaccurate, but there are concerns for contaminants including heavy metals, pesticides, microbes and mycotoxins, as well as added THC. Drug-drug interactions pose a potential risk due to metabolism via the CYP P450 enzyme pathway. Patients wishing to use CBD should obtain a product with certification of Good Manufacturing Practices, initiate treatment with a nighttime low dose and have defined outcome goals within a reasonable time frame. Treatments should not be managed by non-medical dispensary personnel. The hope that CBD may be a useful therapy must be substantiated by sound scientific study.

Significance and innovations

- Cannabidiol (CBD) has preclinical evidence for analgesic, anti-inflammatory and antioxidant effects, but without clinical evidence.
- Currently marketed as a natural food supplement, CBD is not subject to the stringent regulations applied to drugs, leading to concerns about the quality of products available.
- Metabolized via CYP 450 hepatic enzymes, CBD has potential for drug-drug interactions which could be detrimental to health.
- In the context of vigorous marketing as a "wellness" product, physicians must be knowledgeable of the current evidence for benefits and risks of CBD and advise patients reasonably.

Introduction

Pursuant to the concerns surrounding medical cannabis, patients and physicians are increasingly interested in cannabidiol (CBD) as a potential therapy (1, 2). Widely available in Canada, North America and Europe, there are health claims that CBD is a safe treatment option for many illnesses. Lacking the psychoactive effects of delta-9 tetrahydrocannabinol (Δ^9-THC), CBD is promoted for pain management, with this industry poised to grow impressively (3). Formally identified as nonmedical, CBD products are not subject to rigorous standardized procedures applied to drugs regarding accuracy of molecular content, production standards and labelling. In this setting of patients seeking advice about use or experimenting with use, as well as public and commercial enthusiasm, rheumatologists must be knowledgeable of the issues surrounding CBD. This review will examine the status of products that are available and may hold potential for medicinal effect in rheumatology patients.

A botanical understanding of cannabidiol

There is botanical complexity to the cannabis plant, with more than 1000 known strains, and dubbed "the plant of a thousand molecules". There are 18 different chemical classes present in the cannabis plant that include terpenes, flavonoids and alkaloids, and over 100 identified cannabinoid molecules (4). The composition of the various metabolites (molecules) in a specific strain of *Cannabis sativa* can be used to characterize a strain, but with molecular variation even within the same strain depending on growing characteristics, harvesting, storage, production and method of administration. Hemp refers to the varieties of *C. sativa* that contain <1% THC (with most countries requiring <0.3% THC), and with CBD the predominant cannabinoid molecule. Cannabinoids in the plant are inactive acidic molecules which require decarboxylation into the neutral active form by aging or heating as for commercial preparations.

CBD is extracted from the leaves and flowers and dissolved in an edible oil such as olive, coconut or hemp (3). Oil extracts from the dried plant are identified as the volume of oil extracted from 1 gram of dried product and can vary in concentrations of metabolites. Solvents used to extract CBD from the plant may be organic safe solvents such as ethanol or alcohol, harmful solvents such as petroleum-ether, butane or naphtha, or the currently preferred commercial method of extraction using carbon dioxide (3). During the extraction process, molecules other than CBD may be in the residue, and can be further extracted by "winterization" or cooling to precipitate substances with a higher melting point that can then be filtered. The

final CBD oil may contain other cannabis plant metabolites, including terpenes, flavonoids and small amounts of THC, depending on the strain used. There is however absence of equivalency between products of different growers due to lack of standardization of individual products. Potential contaminants of CBD products include heavy metals (cannabis is a hyperaccumulator of soil heavy metals), pesticides, microbes as well as microbial toxins. Hemp oil, extracted from hemp seed, is not synonymous with CBD oil and is poor in phytocannabinoid content, but rich in proteins and fatty acids.

Cannabidiol as a commercial product.

CBD is marketed with nomenclature nuances in different countries. In the United States (US), CBD is commercially and legally available as a hemp derived product in the "wellness" industry, although CBD derived from *C. sativa with greater than 0.3%* THC concentration is prohibited (5). In the European Union (EU) according to the Novel Food Catalogue, extracts of *C. sativa L.* are identified as novel foods, i.e. a food not previously consumed in significant amounts prior to 1997, and requires formal approval by the European Food Standards Agency (6). Even within the EU, regulations of individual countries can differ, for example in Germany CBD is available as a nutritional supplement, can be bought online, and can be prescribed by a physician with compounding by a pharmacy, but not reimbursed by insurers. To date the World Health Organization (WHO) has concluded that CBD is safe and without abuse potential, is not categorized as a drug, and is therefore not regulated according to requirements for drugs (7).

The legal status of CBD in the US is particularly complicated. According to the Controlled Substances Act (CSA), cannabinoids are classified as Schedule 1 drugs (psychoactive substances with abuse potential) (5). As Schedule 1 substances require dispensing only within the context of a research program, physicians in states with medical access may only recommend use for a specific condition, but not provide a formal prescription. CBD is listed as a "derivative" of marijuana (cannabis) (21 USC 803) and is not listed separately in the Code of Federal Regulations (CFR). In December 2018, the 2018 "Farm Bill" was signed into law. "Hemp" which is defined as any part of the cannabis plant with a THC content of less than 0.3%, is now no longer identified as a controlled substance under federal law (5). There still remains much ambiguity in US law regarding interstate commerce of CBD products (5).

Although CBD may be derived from any strain of *C. sativa* , the hemp varieties cultivated for fiber and seeds (high in protein, and oil extract high in Omega-3 and Omega-6 fatty acids), are the preferred strain, even though they contain relatively small amounts of cannabinoids (2-4% CBD, and <0.3% THC by dry weight) (3). Manufacturers can boost CBD content by an enrichment process. CBD wellness products are freely accessible over the counter (OTC) as liquids, capsules, topicals and oils, and can be bought at dispensaries, health food commercial enterprises, pseudo medical storefronts and via the internet. These artisanal preparations are not Food and Drug Administration (FDA) approved regarding efficacy or safety. There is also inconsistent quality control with different products containing varying amounts of CBD, at times even THC, and other additives for advertised therapeutic effects. As the amount of allowed psychoactive product in CBD products is minimal, a medical authorization is not required. Although often marketed as high-CBD and low-THC, there is no required standard for content, which can vary considerably. Regulations vary between US states, with some simply allowing possession for medical purposes, whereas others regulate the cultivation, manufacture,

distribution and possession by patients. In recent years the FDA has issued warnings to CBD vendors on a number of issues: medical claims not allowed for products without FDA approval; mislabeling of products regarding CBD and THC content; and marketing as a nutraceutical or dietary supplements which is not allowed when a product is under study as a pharmaceutical (5).

The physiologic and clinical effects of cannabidiol

CBD has potential for analgesic, anti-inflammatory, anxiolytic, antioxidant, anticonvulsant and cytotoxic effects. The signaling mechanism for CBD is complex and still poorly understood, but effects are not simply due to binding to CB1 or CB2 receptors. In fact, CBD has limited affinity for the cannabinoid receptors, may inhibit THC binding to receptors, can activate and silence classical cannabinoid receptors, and also has effect on non-cannabinoid receptors (8, 9). Furthermore, CBD has a multiplicity of other actions including being an indirect antagonist of CB1 and CB2 receptors, an inverse agonist of CB2 receptor, an inhibitor of endogenous cannabinoid uptake, can act as a full antagonist of the G-protein-coupled receptor 55(GPR55), and has activating effects (serotonin 1a receptor (5-HT_{1A}), G-protein-coupled receptor 18 (GPR18) and the transient receptor potential cation channel subfamily V member 1 (TRPV1)). These complex interactions may explain the reduced psychoactive effects of euphoria when CBD is co-administered with THC compared to the effect when the same amount of THC is administered alone. These many different actions may explain the suggested effects on various biological systems, with effect on pain and inflammation pertinent to the rheumatologist.

Attenuation of both pain and joint inflammation was achieved by locally administered CBD in a rat model of knee osteoarthritis (OA) (10). When prophylactically administered in the early stages of OA, CBD reduced joint pain and was neuroprotective by inhibiting saphenous nerve demyelination (10). In a small RCT in canine OA, CBD oil (2mg/kg orally bid) improved both pain and activity scores, but without changes in weight-bearing capacity (11).

The preclinical evidence for CBD is encouraging, but clinical study is lacking and extrapolation of preclinical science into the clinical setting lacks validity (12, 13). In a single placebo controlled RCT of transdermal synthetic CBD gel in 320 patients with OA knee, the primary end point of reduction in worst daily pain score was numerically but not significantly better than placebo (14). The secondary end point of a responder analysis (average weekly improvement in worst pain score of ≥30% and decrease in Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] physical function subscale of at least 20% at last observation) was significantly better for the active treatment. Men overall had a more robust favorable effect with the active treatment (14).

In light of the opioid epidemic in North America, interest in cannabis and CBD in particular has centered around possible effects in attenuating opioid dependence, as an alternative to opioid treatment and as a pain-relieving treatment (13). CBD is currently been studied as a treatment for opioid dependence. Although there were claims that medical cannabis was associated with reduced opioid overdose deaths, this finding has recently been refuted on the basis of ecological bias (15).

Methods of cannabidiol use

CBD can be administered by inhalation, oral or topical routes. When taken orally, absorption is erratic, and the pharmacokinetic profile is variable with a low bioavailability of about 6% (16). Reasons include incomplete absorption due to the lipophilicity of CBD, instability in the acid milieu of the stomach and high rate of first pass metabolism in liver. The extensive first pass hepatic metabolism for oral intake results in lower and delayed peak concentration compared to inhalation. CBD is rapidly distributed into well vascularized tissues, is highly protein bound and prolonged use results in adipose tissue deposition.

A transdermal route could be an attractive alternate delivery method to oral administration, but the highly lipophilic nature of CBD limits skin penetration. CBD accumulates in the skin stratum corneum with limited penetration to deeper layers unless facilitated by a carrier system (17). One such method uses ethosomal carriers, which are phospholipid nanovesicles that can encapsulate highly lipophilic molecules to achieve penetration to deeper tissues (18). In a murine model this mechanism provided significant accumulation of CBD in the skin and underlying muscle, achieved steady state plasma levels when applied to the abdomen, and reduced inflammation and edema in carrageenan induced inflammation (18).

Inhalation of CBD avoids first-pass liver metabolism, with systemic bioavailability about 31%, and peak concentration attained within 10 minutes (19). Bioavailability of inhaled CBD is influenced by characteristics of inhalation (depth, speed and amount of breath holding), device used, size of inhaled particles and site of deposition in the respiratory tract (20). Vaporizing CBD does not heat the product to the high temperatures achieved by smoking and there is therefore less risk from exposure to toxic products of combustion. However, patients should be cautioned about vaping until there is further knowledge of the exact causation of severe respiratory disease associated with vaping that has recently emerged (21). An oromucosal preparation of both THC and CBD, namely Sativex® (nabiximols) is rapidly absorbed by the oral mucosa, but some of the administered product could be swallowed and is absorbed by the gastrointestinal tract. The product is not available in the US and is expensive.

There is only one highly purified pharmaceutical grade CBD, with CBD content as high as 99.5% and with virtually no THC (CBD of GW Pharmaceuticals [Epidiolex™]). This agent has regulatory approval for treatment of some rare and severe resistant epilepsies in children in the US and is costly. The European Medicines Agency (EMA) has also given a positive recommendation for marketing of Epidiolex™ for additional treatment for specific seizure disorders.

Patients are currently mostly accessing CBD as OTC products marketed as wellness or dietary supplements, hemp oils and CBD enriched products. The artisanal production also provides additives such as cinnamon, turmeric, cloves, etc, which are marketed with advertised health effects. Other marketing ploys offer CBD as “pure” or “full-spectrum”, with the latter retaining other plant components such as terpenes and flavonoids with a theoretical synergistic therapeutic effect, named the entourage effect (13). The claimed benefits for CBD have not been substantiated and in the context of safety and efficacy place CBD products in an ambiguous zone between pharmaceutical products and foods. These OTC CBD products have labeled CBD concentrations generally up to 20%, but often with labelling inaccuracy (22). Furthermore, the

molecular content of the product, even within the same strain can differ considerably as described above. CBD products that are commercially available have concentrations considerably lower than amounts currently being investigated in clinical trials. Commercial oil products typically contain about 10 mg/ml of CBD, with patients using a few mg to 20 mg/day, whereas the trials use amounts ranging from a few mg to over 1000 mg/day (23).

Are there risks associated with cannabidiol?

There have been no safety studies on 'full-spectrum' CBD oils, although purified CBD has an excellent safety profile and is well tolerated at high doses in healthy persons and in childhood epilepsy (24). In the study of drug resistant seizures in children and young adults, with CBD administered in a dose of 20 mg per kilogram body weight a day, adverse events were reported as somnolence, gastrointestinal effects (reduced appetite, diarrhea, vomiting), fatigue, pyrexia, and abnormal liver function tests (24). The adverse events were judged to be mostly mild to moderate in severity. It is important to note that patients were receiving concomitant anti-seizure medication, with the potential for CBD to affect metabolism of these drugs. Concerns center more on the quality of the product that is currently marketed to the public. Studies in both Europe and North America have reported inaccuracy in the labelling of CBD products (3, 22, 25). When 84 commercial CBD products were analyzed, only 30% were accurately labelled, with 21% of products identified to contain THC (22). Vaporization CBD liquid was most often mislabeled (88% of products), whereas CBD oils were mislabeled for 55% of products. Under labeling of CBD content is less concerning, whereas the presence of THC could cause intoxication or adverse events, as has occurred in children (26). Since 2016 the FDA has issued numerous warning letters to companies marketing CBD products for the following reasons: inaccurate labelling, with some products containing almost no CBD, or variable amounts of THC; and products marketed as unapproved and unlawful new drugs advertised as treatments for illnesses (27). There have also been recent cases of vaping-related illnesses and deaths believed to be due to contaminated cannabis products. As CBD products will mostly contain a small amount of THC, patients could test positive for cannabis on drug screening. Another concern is the presence of contaminants which include microbes, mycotoxins, pesticides and heavy metals.

The potential for drug-drug interaction of cannabidiol

The major metabolic route for CBD is via the cytochrome (CYP) P450 oxidase enzyme pathway, a pathway critical for the metabolism of many drugs. The major hepatic isoenzymes involved are CYP2C19, and CYP3A4, but also CYP1A1, CYP1A2, CYP2C9 and CYP2D6 (16). Following hydroxylation to 7-hydroxy cannabidiol and after further hepatic metabolism, CBD is excreted mainly in the feces, but also with some urinary excretion. It is not known whether the metabolites of CBD are pharmacologically active in humans (28).

Little is known about clinically relevant drug-drug interactions of CBD and drugs that are commonly used by rheumatology patients, with potential interactions proposed on a theoretical basis with some potential areas of caution suggested (29). CBD is a potent inhibitor of CYP P450 enzymes including CYP3A, CPY2D6, CYP2C19, CYP3A4, CYP1A2, CYP2C8 and CYP2C9, with potential to increase concentrations of glucocorticoids, naproxen, various antidepressants such as amitriptyline, citalopram, sertraline, paroxetine, and mirtazapine, as well as gabapentin and pregabalin. The only disease modifying drug with similar metabolism is the Janus kinase inhibitor tofacitinib, metabolized by CYP3A and CYP2C19, with potential to

increase levels of tofacitinib in the presence of CBD. In a study of inhaled cannabis, CBD was shown to increase plasma concentrations of THC to almost the same level as was achieved with high concentration THC for inhaled cannabis of three different concentrations of THC and CBD (THC 22% and CBD < 1%; THC 6% and CBD 8%; THC < 1% and CBD 9%) (30).

What clinical guidance can be given to patients wishing to use cannabidiol?

Even in settings where sound clinical evidence is lacking, clinicians must provide valid and reasonable guidance to patients. CBD, when administered as a pure pharmaceutical grade product has a good safety profile. Concerns surround the unregulated, poorly standardized and untested products that are currently peddled OTC to vulnerable patients.

Patients should be encouraged to obtain a product with reasonable quality standards, including certification of Good Manufacturing Practices (GMP) from a national or international regulatory authority, information that the product has been assessed for contaminants, a THC content less than 0.3%, and to avoid purchasing from "cottage industry" suppliers. Be mindful that hemp seed oil alone does not contain phytocannabinoids or terpenes, but rather proteins and fatty acids (3). CBD containing food products such as sweets and cakes should be avoided, as this is not a medical treatment standard, as well as avoidance of smoking or vaporization.

The ideal dosage is unknown, with cost likely the most limiting factor. In a systematic review of CBD dosing in various patient populations, there was some improvement in primary outcome for studies in psychosis, epilepsy and anxiety with doses for epilepsy averaging 15 mg/kg/day, but without positive effect for other conditions including chronic pain with dose average of 2.4 mg/kg/day (31). The only study reporting on chronic pain used an 'N of I' study methodology in 24 patients using combined THC and CBD oral spray with approximate CBD daily dose of 22.5 mg (32). In this study with focus on multiple sclerosis, each individual patient represented a standalone study, with a double blind, placebo controlled crossover period of 8 weeks, following a 4 week baseline and run-in period (32). Therefore there is a wide dosage range for CBD across various diseases, between < 1 to 50 mg/kg/ day (31). Some patients anecdotally report benefit from very low doses (1-20mg/day), raising the question of a true therapeutic effect versus a placebo effect. A time period for a therapeutic trial should also be defined, with preset goals and objectives, and with critical assessment of the effects and costs of treatment before continuing use indefinitely. The respiratory route of administration should be avoided, especially since most rheumatologic conditions are chronic with little need for the rapid onset of action.

Safety concerns must be foremost for clinicians. Mislabeling of products, contamination by microbes, pesticides and heavy metals, and finally the financial burden for patients who are conned into believing unsubstantiated health benefit claims are current real-life concerns.

Conclusion

The CBD commercial industry has potential to be hugely lucrative in the coming years. Many of the health benefits that are currently promoted have yet to be confirmed by validated clinical study. In this era of sophisticated advertising and promotional strategies, the scientific community must move ahead with a strong research agenda regarding the effect of CBD and ensure that results of studies are presented in a clear and transparent manner. There is a hope that

CBD, a substance that is seemingly free of important adverse effects, could be a benefit for rheumatology patients, but this hope must be substantiated with valid science.

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