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COMPLEMENTARY AND INTEGRATIVE MEDICINE (C WANG, SECTION EDITOR)

Cannabidiol (CBD) in Rheumatic Diseases (Musculoskeletal Pain)

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Abstract

Purpose of Review This review will address the many uncertainties surrounding the medical use of cannabidiol (CBD). We will begin with an overview of the legal and commercial environment, examine recent preclinical and clinical evidence on CBD, explore questions concerning CBD raised by healthcare professionals and patients, investigate dosing regimens and methods of administration, and address current challenges in the accumulation of sound evidence.

Recent Findings CBD has potential for relief of symptoms of pain, sleep, and mood disturbance in rheumatology patients, but sound clinical evidence is lacking. CBD is safe when accessed from a regulated source, whereas wellness products are less reliable regarding content and contaminants. Dosing for symptom relief has not yet been established.

Summary As many rheumatology patients are trying CBD as a self-management strategy, the healthcare community must urgently accrue sound evidence for effect.

Keywords Cannabidiol rheumatic disease · Musculoskeletal · Pain

Introduction

Will cannabidiol (CBD) be used to treat symptoms of pain, mood disturbance, and sleep problems among patients with rheumatic complaints in decades to come? We introduce our review with this pressing question given the many legal and pharmacological uncertainties regarding CBD.

Following the recent wave of medical and recreational cannabis legislation, CBD has exploded onto the commercial market. Marketed as a non-intoxicating cannabinoid, CBD is promoted as a safer alternative to many medications for managing an array of symptoms (pain, mood disorders, sleep disturbance) commonly experienced by rheumatology patients. This notion of safety has been reinforced by the World Health Organization (WHO) statement that pure CBD is safe and without abuse potential, even in high doses for children with uncontrolled epilepsy [1].

Before rheumatologists can fully embrace CBD as a treatment strategy, evidence for efficacy and risk must be grounded in sound science. The preclinical science has compelling evidence for CBD effect on pain, sleep disturbance, and anxiety, symptoms commonly experienced by rheumatology patients, but to date the clinical evidence for these effects remains limited mostly due to lack of study. Nevertheless, clinicians require knowledge and guidance to facilitate patient care. With these points in mind, the objective of this review will be to examine the current science regarding CBD, offer critical interpretation of the literature, and endeavor to fill the bench to bedside gap [2]. Regulatory authorities must control indiscriminate sale of non-standardized products and health authorities must commit to undertake effective surveillance programs. As such, the purpose of this review is to provide an overview of the legal and commercial environment, examine recent preclinical and clinical evidence on CBD, explore

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questions concerning CBD raised by healthcare professionals and patients, investigate dosing regimens and methods of administration, and identify controversies to be addressed by future research.

The Legal Overview and International Commercial Landscape of CBD

Regulatory Differences

CBD is extracted from *Cannabis sativa*, a plant used for thousands of years for religious, recreational, and therapeutic purposes [3]. *Cannabis sativa* contains more than 100 cannabinoid molecules, of which CBD and delta-9-tetrahydrocannabinol (THC) have been best investigated for therapeutic effects. Hemp, in most countries, refers to *C. sativa* with < 0.3% THC.

While regulations across countries differ, CBD may generally be accessed as (1) regulated pharmaceutical products, (2) medical cannabis products, or (3) wellness products/nutritional supplements. Regulations regarding marketing of CBD vary among countries, with some applying loose directives and others with stricter marketing rules. In the United States (US), according to the Controlled Substances Act, all cannabinoids are schedule 1 drugs (psychoactive substance with abuse potential), dispensed only in a research program, or recommended by physicians who are not permitted to provide a prescription [4, 5]. According to the "Farm Bill" of 2018, hemp products with ˂0.3% THC are not governed by the Controlled Substances Act, effectively legalizing hemp-derived CBD. The resulting proliferation of CBD products of variable quality has caused the Federal Drug Agency (FDA) to issue warnings to vendors regarding mislabelling, illegal medical claims for non-FDA-approved products, and has prohibited marketing as a nutraceutical or dietary supplement [6]. Inaccuracy in CBD product labeling calls for a more regulated industry. Indeed, studies have shown that CBD products purchased online or from commercial outlets are generally inaccurately labeled for CBD content, with some also containing THC [7, 8].

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. Canada has established medical cannabis access and is considering allowing CBD as an over the counter (OTC) product in pharmacies.

Pharmaceutical Products

The two pharmaceutical CBD-containing products have specific indications for neurological conditions. Epidiolex is a CBD product containing 100 mg/mL oral solution and approved in the US and by the European Commission for 27 countries of the European Union for Dravet Syndrome and Lennox-Gastaut Syndrome. Nabiximols (Sativex®), a 1:1 CBD:THC oromucosal spray, is approved in some jurisdictions for multiple sclerosis-associated spasticity and pain. Each spray contains 2.5 mg CBD and 2.7 mg THC with a daily recommended maximum of about 30 mg for each molecule. These agents are costly and mostly unavailable for off-label use.

Medical Cannabis Products

In jurisdictions where medical cannabis is legal and regulated, patients obtain medical authorization for access. Rheumatic complaints, such as chronic pain, typically fall under qualifying conditions for cannabis licensure in North America [9], but with variable indications in European countries [10]. While many medical cannabis products are THC dominant, products may contain either CBD with no THC, CBD with small amounts of THC (e.g., 10:1 CBD:THC ratio), or substantial quantities of THC (e.g., 1:1 CBD:THC ratio). These products typically have some degree of regulation on potency and contaminant testing, although not the standard of pharmaceutical manufacture. Formulations include (1) isolates (CBD alone), (2) "full-spectrum" with minor cannabinoids and plant components such as terpenes and flavonoids, and (3) enriched products containing additives such as cinnamon, cloves, arnica, or turmeric.

Nutritional Supplements/Wellness Products

There is a thriving market of CBD products marketed as dietary supplements or health products. These artisanal products may also be isolate or "full-spectrum," and often contain other additives. These products are of most concern from a regulatory and medical perspective, as they are minimally regulated, are often inaccurately labeled, and may be contaminated with pesticides, mycotoxins, residual solvents, and heavy metals [8, 11].

The Physiologic Effects of CBD

Cannabinoids are exogenous ligands that interact with the endocannabinoid system (ECS), a modulator of many physiological and neuronal processes involved in the immune

response, pain sensation, mood, memory and motivation, among others. The ECS comprises receptors and endogenous ligands. Initially believed to have effect primarily on the ECS, CBD is now known to have a complex signaling mechanism not yet fully understood [12, 13]. Despite their similar molecular structure, THC has affinity for the two well-characterized cannabinoid receptors, cannabinoids receptors 1 and 2 (CB_1 and CB_2, respectively), while CBD has limited affinity for these receptors [12, 13]. Indeed, CBD can activate and silence classical receptors, has effect on non-cannabinoid receptors, and may inhibit endogenous cannabinoid uptake and THC receptor binding—possibly through negative allosteric modulation of CB_1 [14]. CBD's effect on non-cannabinoid receptors is wide-ranging and includes activating receptors associated with the anti-inflammatory pathway [15]. CBD also targets transient receptor potential channels involved in modulation of intracellular calcium and relevant to analgesic effects [16]. The lipophilic nature of CBD allows for easy access to intracellular sites with effects on calcium homeostasis, a feature that may facilitate neuroprotection. Even at low concentrations, CBD decreases G-protein activity that function as molecular switches transmitting signals from outside stimuli into cells [16]. Collectively, these effects demonstrate CBD's promise as pain and inflammation modulators.

Recent Preclinical Evidence for CBD Effects in Rheumatic Complaints

Preclinical evidence suggests that CBD has anti-inflammatory, analgesic, and antioxidant effects [17], all of which are relevant for rheumatology care. In a rat model of knee osteoarthritis (OA), topical application of CBD was associated with reduced pain and inflammation [18]. In a study of rodent inflammatory and non-inflammatory pain models, high doses (5–40 mg/kg) of CBD alone or in combination with standardized bioflavonoid compositions, either orally administered or applied topically, provided pain reduction [19].

These rodent findings have been confirmed in canine and equine models. For example, 2 mg/kg of oral CBD oil given b.i.d. improved pain and activity scores among dogs with OA [20]. Pain relief was similar for a lower dose of oral liposomal encapsulated CBD (20 mg/day) compared to a higher dose of naked CBD (50 mg/day) in a randomized controlled trial (RCT) with 20 large domestic dogs with OA [21]. Oral transmucosal CBD (2 mg/kg) every 12 h added to a therapeutic protocol of anti-inflammatory drugs, gabapentin, and amitriptyline reduced pain severity and interference, and improved Quality of Life Index in 21 dogs with OA [22]. In a pharmacokinetic study of CBD in horses, once daily dosing of CBD at 0.35 and 2.0 mg/kg was well tolerated, this led to a rapid plasma elevation then a rapid decline and a more prolonged elimination half-life. Of note, although the product for this study was hemp pellets containing 10 mg of CBD and THC lower than the limit of detection per gram of pellets, measurable levels of THC were found in plasma [23].

Taken together, these results align with conclusions from the systematic review on the preclinical literature by the recent International Association for the Study of Pain Presidential task force on Cannabis and Cannabinoid Analgesia: There is significant evidence suggesting that CBD may be analgesic in preclinical studies [17].

Recent Human Studies for CBD Effects in Rheumatic Complaints

Pain

Randomized Controlled Trials

Osteoarthritis or Inflammatory Arthritis The only randomized controlled trial investigating topical CBD in knee OA has been published as an abstract but has not undergone peer review [24]. Topical synthetic CBD gel was examined in a 12-week RCT in 320 subjects (mean age 62, mean worst pain 6.9/10 cm). Subjects were randomized to 3 treatment arms (placebo, 250 mg/day, and 500 mg/day of 4.2% CBD gel). At study conclusion, there was no difference in the primary endpoint of pain reduction between groups. A secondary responder analysis endpoint (average weekly reduction in worst pain of $\geq 30\%$, and a reduction in WOMAC physical function subscale of at least 20%) was met for CBD 250 mg vs. placebo arm, 53% vs. 34% ($p = 0.016$). Men responded better than women, and side effects of dry skin and headache were minimal.

Oral, synthetic CBD (20–30 mg/day) was assessed as a pain treatment for patients with hand OA or psoriatic arthritis in an RCT of 136 subjects over 12 weeks [25]. There were no statistically significant differences from placebo for pain, sleep quality, anxiety, depression, or pain catastrophizing.

CBD alone has not been studied in any inflammatory rheumatic condition. A single study examined oromucosal nabiximols (Sativex®), with a mean daily dose of about 14 mg CBD and 15 mg THC, in 58 subjects with rheumatoid arthritis [26]. The active treatment produced improvements in pain at rest and on movement, quality of sleep, and in the 28-joint disease activity score (DAS28). The results of this study cannot however be attributed to a CBD effect alone.

In a study of 100 patients presenting with acute low back pain to an emergency department, a single dose of CBD

400 mg was not better than placebo when studied as an adjunct treatment to standard care [27].

Fibromyalgia One clinical trial investigated CBD among people with fibromyalgia. Inhaled cannabis with varying concentrations of THC and CBD was administered to 20 women with fibromyalgia to assess pain responses [28]. Following a single inhalation of three cannabis products (22% THC, ˂1% CBD; 6.3% THC, 8% CBD; 9% CBD, ˂ 1% THC; and placebo without THC or CBD), none of the active treatments had an effect that was greater than placebo on spontaneous pain or electrical pain response. More subjects showed a 30% reduction of pain scores compared to placebo for the balanced THC:CBD product. The high concentration of CBD 9% with THC ˂1% had no effect on spontaneous or evoked pain. The authors concluded that single inhalation of various cannabis concentrations provided only a small analgesic response and that a "drug high" correlated with reduced spontaneous pain suggesting a role of psychotropic symptoms in pain relief.

Observational Literature

Fibromyalgia With limited information from RCTs, the medical community is turning to information gleaned from observational studies. Boehnke et al. surveyed the use of CBD products in 2700 participants with self-reported fibromyalgia in the US [29]. Two-thirds of participants had ever used CBD, with 1/3 continuing use. CBD use was associated with past year cannabis use and the number of medical conditions present. There was a moderate effect across all symptom domains, and side effects were minor. Discontinuation of CBD was due to safety concerns, lack of effect, and cost. Although two-thirds disclosed CBD use to their treating healthcare professional, medical advice was only sought by one-third.

Numerous authors have concluded that although the animal models for effect of CBD on pain and inflammation are compelling, there is currently insufficient evidence from high-quality research for effect on human pain or musculoskeletal disease [15, 30, 31].

Anxiety

Anxiety occurs commonly in patients with rheumatic complaints. As reported in several systematic reviews, CBD may hold some promise for anxiety disorders and symptoms. In a systematic review of 6 small RCTs, 1 case series, and 1 case report, Skelley et al. reported that CBD in doses of 6–400 mg per dose appeared to consistently improve anxiety, and was generally well tolerated [32]. Sharpe et al. reported that acute doses of CBD reduced anxiety in both animals and humans, without having anxiogenic effects at higher doses [33]. A recent clinical trial of teenagers with social anxiety disorder ($n = 37$) showed that 300 mg/day of CBD resulted in lower anxiety scores than placebo [34]. Larsen et al. reported on 22 controlled trials (833 subjects from five countries) that examined CBD in doses from 20 to 1000 mg/day as a treatment for somatic and psychiatric disorders [35]. Although studies were assessed as heterogenous and with a substantial risk of bias, there was generally improvement in anxiety, but with wide variations in formulations and dosage schemes. In sum, while more research is needed, CBD has potential as either a treatment or adjunctive treatment for anxiety.

Sleep

Sleep disturbance is commonly cited as a reason that patients try CBD. A systematic review of cannabinoid therapies (THC and CBD), which included 14 preclinical and 12 clinical studies, assessed that there is insufficient evidence to currently recommend cannabinoids for sleep disorders, but promising preliminary evidence requires further study [36]. CBD has differential effects on sleep according to dosage, with low doses being stimulating and higher doses are more sedating. The stimulating effect of CBD may be due to a negative allosteric modulation of the CB_1 receptor [37]. In a narrative literature review published in 2017, Babson et al. concluded that CBD may have therapeutic potential for the treatment of insomnia [38]. In a study among 15 individuals with insomnia, results suggested that administration of 160 mg/day of CBD increased total sleep time and decreased the frequency of arousals during the night, but with somnolence reported by some [39]. In a retrospective case series examining the effect of CBD (as an adjunct to usual treatment) in 72 adults for anxiety and sleep, anxiety scores decreased within 1 month in 57 (79%) and remained reduced; sleep scores improved in 48 (67%) but fluctuated over time. Limitations of this study include an open-label design, absence of a control group, and unspecified reasons for attrition [40]. Therefore, although there is prevalent use of CBD for the management of sleep disorders, especially insomnia, sound evidence is lacking.

Upcoming Clinical Trials

There are currently five registered and recruiting clinical trials for rheumatic conditions (osteoarthritis) and cannabidiol (Table 1) [41].

Table 1 Recruiting studies with cannabidiol for rheumatic diseases registered in the database of the National Institutes of Health (date of search January 30, 2022)

Title of the study	Phase of the study Duration active treatment Estimated Number of participants	Country of the study Sponsor	Dosage of CBD mg/d	ClinicalTrials.gov identifier
Cannabidiol for bilateral total knee arthroplasty	Phase 2 36 First 72-h postoperative	USA Hospital for Special Surgery, New York	400 and 800 mg	NCT04749628
Topical CBD in joint arthritis	Not reported 40 4 weeks	USA University of Virginia	Not reported	NCT04611347
Cannabinoid tablets for the treatment of pain from osteoarthritis of the knee	Phase 2 66 4 weeks	USA Pure Green Pharmaceuticals	30 mg CBD and 15 mg THC	NCT04992962
Osteoarthritis of the knee pain study using CBD and THC in rapidly dissolvable sublingual tablet	Phase 2 30 4 weeks	USA Pure Green Pharmaceuticals	20 mg CBD and 20 mg THC	NCT04195269
Efficacy of cannabidiol in knee osteoarthritis	Phase 2 86 7 weeks	Austria University of Vienna	Up to 600	NCT04607603

Administration of CBD

While pharmaceutical CBD products have standardized dosing (quantity and route of administration) for designated indications, medical cannabis and wellness CBD products are widely variable. Furthermore, the ideal dosing of CBD for pain or rheumatic symptoms is unknown. The onset and duration of administration routes have been summarized by MacCallum and Russo [42]. Briefly, when *smoked or vaporized*, onset is 5–10 min and effects last 2–4 h. *Oral* products (e.g., edibles) cause effects in 1–3 h and last for 6–8 h or more. When held under the tongue for 1–2 min, s*ublingual* products (e.g., tinctures or oils) typically take effect in 15–45 min and last 6–8 h, with variability depending on the carrier oil and other additives (e.g., ethanol). *Topically applied* products (e.g., creams or salves) have inconsistent effects either locally or systemically due to variable formulations and additives. Based on observational studies of naturalistic use, the majority of CBD use appears to be in the form of tinctures, edibles, and topical products [43].

Oral bioavailability of CBD is low at 6% for several reasons: erratic absorption due to the lipophilic nature of CBD; instability in the stomach acidic environment; and high 1st pass liver metabolism. Bioavailability of inhaled CBD is in the order of 31%, but dependent on inhalation method, depth and speed of breathing, and duration of breath holding [44, 45]. Administration via the transdermal route results in accumulation in the upper skin stratum corneum, unless absorption of the lipid CBD is facilitated by a carrier system to allow penetration to the deeper tissue layers [46].

There are two aspects to CBD dosing that require consideration: what doses patients self-administer, and what doses have been used in clinical studies. In a survey of 878 fibromyalgia patients, the reported average dose of CBD was 16–27 mg/day, although 1/3 did not know the daily amount of CBD used [43]. Millar et al. investigated doses of CBD administered as an oral solution, capsule, or sublingual spray in various clinical populations with 35 included studies, with most studies reporting doses ranging from ˂1 to 20 mg/kg/day [47]. Most higher doses were used in neurological conditions (e.g., Dravet Syndrome), with higher doses typically unaffordable for off-label use.

Serum concentration of CBD is dose dependent, without accumulation with regular dosing. In a systematic review of 24 studies, the pharmacokinetics of commonly used OTC doses of CBD (5–20 mg/day) was assessed [48]. Oral administration of a single dose of CBD of 5.4 and 10 mg achieved a peak serum concentration (C_{max}) of 0.9 and 2.5 ng/mL. The time to maximal concentration was about 1 h, with a half-life between 1 and 3 h. As CBD is highly lipophilic, oral bioavailability is dependent on coadministration of high fat food.

Risks Associated with CBD

CBD has no known abuse potential [1]. CBD is considered safe when used in a daily low dose, with most commonly reported side effects of drowsiness and fatigue, dry mouth, nausea, reduced appetite, and diarrhea [35]. The Australian Therapeutic Good Administration has determined that up to

60 mg/day, with a maximum of 150 mg/day, is sufficiently safe as a non-prescription OTC product with pharmacist oversight [49]. A recent review has concluded that there is a low risk for adverse hepatic effects, especially for the low doses in dietary supplements and food products [50].

Most drug-drug interactions of CBD are theoretical [51], although CBD is known to interact with valproate and other anticonvulsant medications [52]. CBD is metabolized via the cytochrome P450 enzyme system and inhibits CYP2D6. CBD is a substrate for CYP2C19 and CYP3A4 with potential to increase serum concentrations of antidepressants, tofacitinib, and reduce concentrations of clopidogrel. Inhaled CBD can boost serum THC concentration, potentially resulting in increased psychoactive effects [28]. In a recent study of CBD administered to 120 frontline healthcare professionals who experienced burnout related to COVID-19, adverse events of increased liver function tests were observed in 4 of the 59 subjects receiving CBD 150 mg twice daily over a period of 28 days [53]. About 20% of the cohort were on psychiatric medications or used weekly alcohol, but not further specified.

Although CBD does not have intoxicating effects, analysis of studies of magnetic resonance imaging found that CBD alone induces significant alterations in brain activity and connectivity patterns in the resting state and during performance of cognitive tasks in both healthy volunteers and patients with psychiatric disorders [54]. These findings point to the potential that neurological symptoms or side effects can occur with any dose of CBD.

The current greatest risks for CBD use continue to be the poor reliability of market products, which include inaccuracy in labeling, unsafe contaminants (e.g., heavy metals, pesticides, metals) [8, 11], and extravagant health claims that may direct patients away from evidence-based and useful treatments.

Insights for Patient Care

CBD is often seen as a new "go to" harmless treatment option for many symptoms experienced by patients with rheumatic complaints. As with medical cannabis, harm reduction is key for people using CBD. Fibromyalgia patients often report substituting CBD for pain medications, including opioids, because of fewer side effects [55]. Similarly, in a German study of consumer reports, fibromyalgia patients are wary of the harmful effects of pharmaceutical drugs and are open to seek alternative products [56]. Although there are currently no studies reporting on continuous relevant symptom relief in rheumatology patients, we believe anecdotal reports should prompt rigorous research and be considered when acting in the model of patient-centric care.

Patients must be evaluated with attention to co-morbidities and concomitant medications and should be managed by a healthcare team that is fully knowledgeable of their medical condition. Any advice about use of a therapeutic product would ideally be communicated to patients by healthcare professionals who are best placed to be knowledgeable of the current science of CBD. Advice should be balanced, honest, and free from personal bias or financial interests. Lack of education about medical cannabis products (including CBD) may deter many healthcare providers from providing advice [57], highlighting the need for continued training specifically related to CBD and cannabis. Dispensary staff often fill this gap but are not trained to advise and manage patients. Indeed, a survey of 434 staff from US cannabis dispensaries found that only 18% were identified as healthcare professionals. Although customers were often counseled on safe storage and commonly reported side effects, seldom were risks such as mental health effects or motor vehicle crashes discussed [58].

As such, we urge physicians to work collaboratively with patients who wish to trial CBD for symptom relief. Product(s) should have a certificate of Good Manufacturing Practice, contain < 0.3% THC, and be obtained from a manufacturer not advertising health benefits. As inhalation causes respiratory damage, we counsel the use of oral or mucosal preparation. Patients should "start low and go slow," beginning with a small nighttime dose ~ 2.5 mg, with a gradual titration up to 30–50 mg/day [42, 59, 60]. Physicians should explain and monitor for potential drug interactions, especially anticoagulants (e.g., warfarin), anti-convulsants (e.g., valproate), and tofacitinib which are metabolized by similar enzyme systems to CBD. A treatment trial should last for a defined period of time, e.g., ≤ 3 months, and in the event of poor effect or adverse effect, CBD should be discontinued. Patients should not be financially compromised to continue a treatment with questionable effects indefinitely. Lastly, patients should be aware that even legal CBD products may cause a positive drug screen for THC. A small clinical trial of a hemp-derived CBD product with 0.02% THC ($n = 14$ participants) showed that 50% were positive for THC metabolites after 4 weeks of dosing at 3 mL per day—an average daily dose of ~ 30 mg CBD and < 1 mg THC [61].

Controversies and Significant Trends and Developments

We highlight two significant and interrelated controversies regarding appropriate clinical use of CBD products and CBD research. The first relates to use of CBD isolate vs. full-spectrum products. The rationale for full-spectrum products is the "entourage effect," the idea that co-occurring cannabinoids, terpenes, and flavanoids do have analgesic and

anxiolytic effect that may enhance CBD's therapeutic effect [62]. While there is a dearth of human studies comparing full spectrum and isolate products, some preclinical data suggest that full-spectrum preparations may be more useful. Indeed, in a rodent model, Galilly et al. show that a CBD-dominant whole-plant cannabis preparation provided greater anti-inflammatory effect and widened the therapeutic window of CBD compared to isolate [63]. The second relates to proper dosing. Indeed, acute dosing studies show that synthetic CBD effects follow an inverted *u*-shape curve, in which middling doses result in preferential outcomes [64]. Notably, the Galilly et al. rodent study also showed that while the isolated CBD showed the classic inverted *u*-shaped curve, the whole-plant preparation did not. Future clinical trials should investigate these effects.

Conclusions

CBD alone is considered safe, although it may have several drug-drug interactions. Preclinical evidence suggests analgesic, anti-inflammatory, and antioxidant effects, but clinical evidence is limited for these symptoms or for effects on underlying rheumatic diseases. When marketed as a wellness product, CBD is not subject to stringent regulations, with concerns about inconsistent quality of products. When CBD is used as a therapeutic agent, clinical care should be by the healthcare team and not cannabis dispensary staff. To counterbalance the vigorous marketing of CBD as a "wellness" product, patients should be fully informed of the current scientific evidence for both positive and negative effects.

Author Contribution All authors participated in the writing of this manuscript.

Declarations

Conflict of Interest KB sits on a data safety and monitoring commitee for Vireo Health in an unpaid capacity. MAF and WH report no conflict of interest involving the work under consideration.

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References

1. WHO. Cannabidiol (CBD) Critical review report 2018 [22 Sept 2019]. Available from: https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf.
2. Fitzcharles MA, Clauw DJ, Hauser W. A cautious hope for cannabidiol (CBD) in rheumatology care. Arthritis Care Res (Hoboken). 2020. (online ahead of print).
3. Bonini SA, Premoli M, Tambaro S, Kumar A, Maccarinelli G, Memo M, et al. Cannabis sativa: a comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol. 2018;227:300–15.
4. Mead A. The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. Epilepsy Behav. 2017;70(Pt B):288–91.
5. Mead A. Legal and regulatory issues governing cannabis and cannabis-derived products in the United States. Front Plant Sci. 2019;10:697.
6. Wagoner KG, Lazard AJ, Romero-Sandoval EA, Reboussin BA. Health claims about cannabidiol products: a retrospective analysis of U.S. Food and Drug Administration Warning Letters from 2015 to 2019. Cannabis Cannabinoid Res. 2021;6(6):559–63.
7. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. JAMA. 2017;318(17):1708–9.
8. Gurley BJ, Murphy TP, Gul W, Walker LA, ElSohly M. Content versus label claims in cannabidiol (CBD)-containing products obtained from commercial outlets in the state of Mississippi. J Diet Suppl. 2020;17(5):599–607.
9. Boehnke KF, Gangopadhyay S, Clauw DJ, Haffajee RL. Qualifying conditions of medical cannabis license holders in the United States. Health Aff (Millwood). 2019;38(2):295–302.
10. Krcevski-Skvarc N, Wells C, Häuser W. Availability and approval of cannabis-based medicines for chronic pain management and palliative/supportive care in Europe: a survey of the status in the chapters of the European Pain Federation. Eur J Pain. 2018;22(3):440–54.
11. Wakshlag JJ, Cital S, Eaton SJ, Prussin R, Hudalla C. Cannabinoid, terpene, and heavy metal analysis of 29 over-the-counter commercial veterinary hemp supplements. Vet Med (Auckland, NZ). 2020;11:45–55.
12. McCarberg BH, Barkin RL. The future of cannabinoids as analgesic agents: a pharmacologic, pharmacokinetic, and pharmacodynamic overview. Am J Ther. 2007;14(5):475–83.
13. Pacher P, Kogan NM, Mechoulam R. Beyond THC and endocannabinoids. Annu Rev Pharmacol Toxicol. 2019.
14. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol. 2015;172(20):4790–805.
15. Urits I, Gress K, Charipova K, Habib K, Lee D, Lee C, et al. Use of cannabidiol (CBD) for the treatment of chronic pain. Best Pract Res Clin Anaesthesiol. 2020;34(3):463–77.
16. De Petrocellis L, Ligresti A, Moriello AS, Allarà M, Bisogno T, Petrosino S, et al. Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol. 2011;163(7):1479–94.
17. Soliman N, Haroutounian S, Hohmann AG, Krane E, Liao J, Macleod M, et al. Systematic review and meta-analysis of cannabinoids, cannabis-based medicines, and endocannabinoid system modulators tested for antinociceptive effects in animal models of injury-related or pathological persistent pain. Pain. 2021;162(Suppl 1):S26-s44.
18. Philpott HT, O'Brien M, McDougall JJ. Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. Pain. 2017;158(12):2442–51.
19. Yimam M, O'Neal A, Horm T, Jiao P, Hong M, Rossiter S, et al. Antinociceptive and anti-inflammatory properties of cannabidiol alone and in combination with standardized bioflavonoid composition. J Med Food. 2021;24(9):960–7.
20. Gamble LJ, Boesch JM, Frye CW, Schwark WS, Mann S, Wolfe L, et al. Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. Front Vet Sci. 2018;5:165.
21. Verrico CD, Wesson S, Konduri V, Hofferek CJ, Vazquez-Perez J, Blair E, et al. A randomized, double-blind, placebo-controlled

study of daily cannabidiol for the treatment of canine osteoarthritis pain. Pain. 2020;161(9):2191–202.
22. Brioschi FA, Di Cesare F, Gioeni D, Rabbogliatti V, Ferrari F, D'Urso ES, et al. Oral transmucosal cannabidiol oil formulation as part of a multimodal analgesic regimen: effects on pain relief and quality of life improvement in dogs affected by spontaneous osteoarthritis. Animals. 2020;10(9).
23. Williams MR, Holbrook TC, Maxwell L, Croft CH, Ientile MM, Cliburn K. Pharmacokinetic evaluation of a cannabidiol supplement in horses. J Equine Vet Sci. 2021;110: 103842.
24 Hunter DOG, Tich N, Messenheimer J, Sebree T. Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis. Osteoarthritis Cartil. 2018;26:10–59.
25. Vela J, Dreyer L, Petersen KK, Lars AN, Duch KS, Kristensen S. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. Pain. 2021.
26. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology. 2006;45(1):50–2.
27. Bebee B, Taylor DM, Bourke E, Pollack K, Foster L, Ching M, et al. The CANBACK trial: a randomised, controlled clinical trial of oral cannabidiol for people presenting to the emergency department with acute low back pain. Med J Aust. 2021;214(8):370–5.
28. van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. Pain. 2019;160(4):860–9.
29. Boehnke KF, Gagnier JJ, Matallana L, Williams DA. Cannabidiol use for fibromyalgia: prevalence of use and perceptions of effectiveness in a large online survey. J Pain. 2021;22(5):556–66.
30. Svensson CK. CBD for the treatment of pain: what is the evidence? J Am Pharm Assoc (2003). 2020;60(6):e80-e3.
31. Gusho CA, Court T. Cannabidiol: a brief review of its therapeutic and pharmacologic efficacy in the management of joint disease. Cureus. 2020;12(3): e7375.
32. Skelley JW, Deas CM, Curren Z, Ennis J. Use of cannabidiol in anxiety and anxiety-related disorders. J Am Pharm Assoc (2003). 2020;60(1):253–61.
33. Sharpe L, Sinclair J, Kramer A, de Manincor M, Sarris J. Cannabis, a cause for anxiety? A critical appraisal of the anxiogenic and anxiolytic properties. J Transl Med. 2020;18(1):374.
34. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. Front Psychol. 2019;10:2466.
35. Larsen C, Shahinas J. Dosage, efficacy and safety of cannabidiol administration in adults: a systematic review of human trials. J Clin Med Res. 2020;12(3):129–41.
36. Suraev AS, Marshall NS, Vandrey R, McCartney D, Benson MJ, McGregor IS, et al. Cannabinoid therapies in the management of sleep disorders: a systematic review of preclinical and clinical studies. Sleep Med Rev. 2020;53: 101339.
37. Tham M, Yilmaz O, Alaverdashvili M, Kelly MEM, Denovan-Wright EM, Laprairie RB. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. Br J Pharmacol. 2019;176(10):1455–69.
38. Babson KA, Sottile J, Morabito D. Cannabis, cannabinoids, and sleep: a review of the literature. Curr Psychiatry Rep. 2017;19(4):23.
39. Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol. 1981;21(S1):417s-s427.
40. Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in anxiety and sleep: a large case series. Permanente J. 2019;23:18–041.
41. Clinicaltrials.gov. 2022.
42. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12–9.
43. Boehnke KF, Gagnier JJ, Matallana L, Williams DA. Cannabidiol product dosing and decision-making in a national survey of individuals with fibromyalgia. J Pain. 2022;23(1):45–54.
44. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet. 2003;42(4):327–60.
45. Solowij N, Broyd SJ, van Hell HH, Hazekamp A. A protocol for the delivery of cannabidiol (CBD) and combined CBD and 9-tetrahydrocannabinol (THC) by vaporisation. BMC Pharmacol Toxicol. 2014;15:58.
46. Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E. Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model. J Control Release. 2003;93(3):377–87.
47. Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. Br J Clin Pharmacol. 2019;85(9):1888–900.
48. Millar SA, Stone NL, Yates AS, O'Sullivan SE. A systematic review on the pharmacokinetics of cannabidiol in humans. Front Pharmacol. 2018;9:1365.
49. Government A. Safety of low dose cannabidiol. In: Administration DoHTG, editor. 2020.
50. Stohs SJR, S. D. Is cannabidiol hepatotaxic or hepatoprotective: a review. Toxicol Res Appl. 2020;4.
51. Foster BC, Abramovici H, Harris CS. Cannabis and cannabinoids: kinetics and interactions. Am J Med. 2019;132(11):1266–70.
52. Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology. 2018;90(14):e1204–11.
53. Crippa JAS, Zuardi AW, Guimarães FS, Campos AC, de Lima OF, Loureiro SR, et al. Efficacy and safety of cannabidiol plus standard care vs standard care alone for the treatment of emotional exhaustion and burnout among frontline health care workers during the COVID-19 pandemic: a randomized clinical trial. JAMA Netw Open. 2021;4(8): e2120603.
54. Batalla A, Bos J, Postma A, Bossong MG. The impact of cannabidiol on human brain function: a systematic review. Front Pharmacol. 2020;11: 618184.
55. Boehnke KF, Gagnier JJ, Matallana L, Williams DA. Substituting cannabidiol for opioids and pain medications among individuals with fibromyalgia: a large online survey. J Pain. 2021.
56. Häuser W, Jung E, Erbslöh-Möller B, Gesmann M, Kühn-Becker H, Petermann F, et al. The German fibromyalgia consumer reports - a cross-sectional survey. BMC Musculoskelet Disord. 2012;13:74.
57. Gardiner KM, Singleton JA, Sheridan J, Kyle GJ, Nissen LM. Health professional beliefs, knowledge, and concerns surrounding medicinal cannabis - a systematic review. PLoS ONE. 2019;14(5): e0216556.
58. Merlin JS, Althouse A, Feldman R, Arnsten JH, Bulls HW, Liebschutz JM, et al. Analysis of state cannabis laws and dispensary staff recommendations to adults purchasing medical cannabis. JAMA Netw Open. 2021;4(9): e2124511.
59. Bhaskar A, Bell A, Boivin M, Briques W, Brown M, Clarke H, et al. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. J Cannabis Res. 2021;3(1):22.
60. Boehnke KF, Clauw DJ. Brief commentary: cannabinoid dosing for chronic pain management. Ann Intern Med. 2019;170(2):118.
61. Dahlgren MK, Sagar KA, Lambros AM, Smith RT, Gruber SA. Urinary tetrahydrocannabinol after 4 weeks of a full-spectrum,

high-cannabidiol treatment in an open-label clinical trial. JAMA Psychiat. 2021;78(3):335–7.
62. Gallily R, Yekhtin Z, Hanuš LO. The anti-inflammatory properties of terpenoids from cannabis. Cannabis Cannabinoid Res. 2018;3(1):282–90.
63. GallilyR Y, HanušLO. Overcoming the bell-shaped dose-response of cannabidiol by using cannabis extract enriched in cannabidiol. Pharmacol Pharm. 2015;6(2).
64. Linares IM, Zuardi AW, Pereira LC, Queiroz RH, Mechoulam R, Guimarães FS, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999). 2019;41(1):9–14.