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Featured Article

Cannabidiol (CBD) Products for Pain: Ineffective, Expensive, and With Potential Harms

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Abstract: **Cannabidiol (CBD) attracts considerable attention for promoting good health and treating various conditions, predominantly pain, often in breach of advertising rules. Examination of available CBD products in North America and Europe demonstrates that CBD content can vary from none to much more than advertised and that potentially harmful other chemicals are often included. Serious harm is associated with chemicals found in CBD products and reported in children, adults, and the elderly. A 2021 International Association for the Study of Pain task force examined the evidence for cannabinoids and pain but found no trials of CBD. Sixteen CBD randomized trials using pharmaceutical-supplied CBD or making preparations from such a source and with pain as an outcome have been published subsequently. The trials were conducted in 12 different pain states, using 3 oral, topical, and buccal/sublingual administration, with CBD doses between 6 and 1,600 mg, and durations of treatment between a single dose and 12 weeks. Fifteen of the 16 showed no benefit of CBD over placebo. Small clinical trials using verified CBD suggest the drug to be largely benign; while large-scale evidence of safety is lacking, there is growing evidence linking CBD to increased rates of serious adverse events and hepatotoxicity. In January 2023, the Food and Drug Administration (FDA) announced that a new regulatory pathway for CBD was needed. Consumers and health care providers should rely on evidence-based sources of information on CBD, not just advertisements. Current evidence is that CBD for pain is expensive, ineffective, and possibly harmful.**

Perspective: ***There is no good reason for thinking that CBD relieves pain, but there are good reasons for doubting the contents of CBD products in terms of CBD content and purity.***

Key words: *Cannabidiol, pain, efficacy, harm, purity*

Cannabidiol (CBD) is one of many cannabinoid chemicals found in cannabis plants. A 2021 International Association for the Study of Pain position statement concluded that due to a lack of evidence from high-quality research, it did not endorse the general use of cannabinoids to treat pain.[1] The task force concluded that preclinical studies, clinical trials, and systematic reviews were generally of low or very low quality and showed small or nonexistent analgesic effects,[2-4] despite some evidence of a mechanistic effect in animal models of pain.[5] There were no trials of CBD at that time; it came under the heading of absence of evidence of analgesic effect, rather than evidence of absence of analgesic effect.

Yet cannabis-based medicines have been promoted as a source of pain relief, and CBD or hemp extract is sold for "natural" pain management. A survey of advertising claims in Canada showed the most prevalent was the ability to treat or manage pain,[6] as did a survey in North Carolina.[7] CBD is big business; the market worldwide is forecast to be 60 billion U.S. dollars by 2030, with a compounded annual growth rate of nearly 20%.[8] Marketing is leading without the benefits and harms of CBD being known.

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CBD has attracted public and media interest, as demonstrated by trends analysis of internet searches.[9] Reported use was 26% in 16 to 65-year-old residents in the United States, 16% in Canada,[10] 4.3% in Germany,[11] and 2% in the United Kingdom (UK).[12] Most used CBD for a chronic condition, often spending more than $140 a month.[10] A consistent finding is that pain relief is the primary reason for CBD use in over half of users.[10,12] It is openly promoted to sportspeople.[13]

People are often forced to live with pain despite the best efforts of pharmacological, psychological, surgical, physical, and other medical interventions that might work for the few, but not the many.[14,15] Chronic pain is long-lasting, often unrelieved, and typically results in a major reduction in quality of life.[16,17] It is not surprising that people search elsewhere for pain relief: the Pain in Europe survey showed 50% of respondents using nonprescription medicines and 69% nondrug treatments.[16]

Because of legal changes declassifying hemp and CBD as controlled drugs in various countries, CBD is not only prescribed (as Epidiolex) but is also freely available in a range of formulations. Print and online outlets frequently laud the analgesic effects of CBD and provide consumer advice on the best CBD product.[18] These outlets often remain unchecked and unbalanced and appear to be aimed at promoting revenue rather than safe practice. Consumers (people living with pain), their careers, and their professional advisers need more balanced, evidence-informed consumer advice. That can now be provided.

Methods

We searched PubMed and Google Scholar until September 17, 2023 for information relating to the analysis of CBD products, their purity, and presence of contaminants, and for harm reported using CBD products. This was done by using CBD in the tile and/or abstract, with additional terms, such as harm, adverse events, analysis, contaminant, and so on. Articles with relevant information were examined for further references and the "cited by" and "similar articles" functions in these programs. For studies that are not randomized trials, this form of searching has been found to be much more sensitive than electronic searches alone.[19,20]

For completed randomized, double-blind trials comparing CBD with placebo since 2019, from the date of the previous search, we searched PubMed and ClinicalTrials.gov using CBD and pain in the tile and/or abstract, limited to humans, randomized controlled trials, and, separately, clinical trials.

An updated review and data analysis used the methods of the previous systematic review.[2] We analyzed pain outcomes at any time point, for any painful condition, using any CBD product, at any dose, and by any route of administration.

Results

CBD Obtained Without Prescription (Not Pharmaceutical Grade)

Is Nonprescription CBD a Natural Product?

While CBD can be synthesized as a pure chemical and synthetic CBD may be used in some clinical trials, most CBD is derived from the hemp plant.

Is Nonprescription CBD Pure?

The labeling of products containing hemp extract or CBD does not allow for a dependable assessment of purity. It is likely that there will be other substances in any formulation, so it generally will not be just CBD in a tablet, oil, ointment, or spray. Hemp can have over 100 different cannabinoid compounds, many of which could have actions in the body. Depending on the strain of hemp, the amount of the psychoactive delta-9-tetrahydrocannabinol (THC) can vary widely.[21] In an analysis of 105 topical CBD products in the United States, THC was detected in 35%, with a total content of up to 100 mg.[22] Similar disparities were found in Germany and Switzerland.[23,24] Commercial products may also contain untested synthetic chemicals.[25]

Is the Nonprescription CBD Content as Advertised?

Mostly not. The U.S. analysis of 105 products found that only 1 in 4 products were accurately labeled for CBD, 1 in 5 had less than 90% of the advertised CBD, and 1 in 2 had more than 110%.[22] The range indicated that CBD content varied from almost nothing to very large amounts.

Is Nonprescription CBD Safe?

Sporadic cases of serious harm from ingestion of nonprescription CBD products include Stevens-Johnson syndrome, perhaps from CBD, perhaps from some other, unknown, ingredient.[26] Unintentional toxicity can also happen when people believe packaging: an overdose patient "felt the products were healthy and safe based on packaging and therefore did not believe they would have any adverse effects."[27] CBD products containing natural or synthetic cannabinoids can cause harm in children[25] and the elderly.[28] Products labeled as CBD but containing only synthetic chemicals were linked to cases of poisoning in Utah.[29]

Notifications to the America's Poisons Centres and the UK Medicines and Healthcare products Regulatory Agency (MHRA) both show large increases in CBD notifications in recent years from a very low baseline.[30-32] The growth of poison center notifications in the U.S. mirrors the increase in internet searches.[9]

Taking CBD is, of course, not the same as ingesting cannabis plants or inhaling burnt cannabis, but 2 strands of evidence would suggest that caution is needed even with products that claim to contain "only" CBD. A "CBD

Table 1. Details of 16 RCTs Evaluating Cannabidiol for Relief of Pain

REFERENCE, COUNTRY, AND FUNDING	DESIGN	CONDITION	PATIENT DETAILS AND NUMBER ANALYZED	CBD DRUG AND ROUTE AND DURATION	PAIN OUTCOME
Parallel group studies					
Alaia[36] United States Orcosa pharma and links to cannabis companies	Randomized, double-blind, multicentre, placebo-controlled	Patients after arthroscopic rotator cuff repair	Mean age 58 years (Standard deviation (SD) 9 years) 20% women Ethnicity not given Total = 101 CBD = 52 Placebo (Pbo) = 47	Buccal CBD 25 mg or 50 mg 3 times daily 14 days	Day 1 CBD Visual analogue scale (VAS) 4.4 ± 3.1 Pbo 5.7 ± 3.2 (P = .04) Day 2 CBD VAS 4.7 ± 2.8 Pbo 5.3 ± 2.6 (P = .32) Pain 0 to 10 scale On other days no significant difference
Atieh et al[38]United States NIH Grants	Randomized, double-blind, single-center, placebo-controlled	Functional dyspepsia with normal gastric emptying	Mean age 35 years Age range 23 to 48 75% women 92% White Total = 48 CBD = 25 Pbo = 23	Oral CBD 20 mg/kg/day Placebo 4 wks	Mean daily epigastric pain CBD .7 (Interquartile range (IQR) .1–1.3) Pbo .8 (IQR .3–1.1) Pain 0 to 4 scale
Bebee et al[39]Australia and New Zealand Clinical Trial Registry Number 12618000487213 Australia Academic and charitable funding	Randomized, double-blind, single-center, placebo-controlled	Low back pain in emergency center	Mean age 47 years Age IQR 31 to 60 44% women Ethnicity not given Total = 100 CBD = 50 Pbo = 50	Oral CBD 400 mg Placebo Single dose	Mean 2 h pain scores CBD 6.2 (95% confidence interval (CI) 5.5–6.9) Pbo 5.8 (95% CI 5.1–6.6) Mean difference −.3 (95% CI −1.3 to .6) Pain 0 to 10 scale
Haffar et al[42]United States Not stated	Randomized, double-blind, single-center, placebo-controlled	Patients following knee replacement surgery	Mean age 65 years (SD 8 years) 47% women 93% White Total = 80 CBD = 19 Essential oil = 21 Combined = 21 Pbo = 19	Topical CBD 120 mg/oz Essential oil Combination Placebo Daily application for 14 days after surgery	Pain score at day 14 Topical CBD 47 ± 19 Essential oil 33 ± 24 Combination 41 ± 15 Placebo 41 ± 19 Pain 0 to 100 scale
Hansen et al[43]Denmark Danish Ministry of Health and other nonindustry funding sources	Randomized, double-blind, single-center, placebo-controlled	Patients with neuropathic pain and multiple sclerosis or spinal cord injury	Mean age 52 years Age range 21 to 73 74% women Ethnicity not given Total = 114 CBD = 27 THC = 24 Combination = 28 Pbo = 35	Maximum daily oral doses CBD 45 mg THC 22.5 mg Combination 45/22.5 mg Placebo 6 wks	Change in pain using baseline observation carried forward CBD −1.4 ± 1.6 THC −1.4 ± 2.0 Combined −1.6 ± 1.8 Pbo −1.8 ± 1.8 30% pain reduction CBD 4/27 THC 7/24 Combined 14/28 Pbo 16/35

Table 1 (*Continued*)

REFERENCE, COUNTRY, AND FUNDING	*DESIGN*	*CONDITION*	*PATIENT DETAILS AND NUMBER ANALYZED*	*CBD DRUG AND ROUTE AND DURATION*	*PAIN OUTCOME*
Hardy et al[44]Australia Academic with some Pharma funding	Randomized, double-blind, 5 center, placebo-controlled	Patients with advanced cancer	Mean age 65 years (SD 12 years) 47% women Ethnicity not given Total = 142 CBD = 70 Pbo = 72	End of escalation median daily oral CBD 400 mg Up to 28 days	Pain 0 to 10 scale Mean change from baseline Day 14 CBD −.96 ± .30 Pbo −.48 ± .29 Day 28 CBD −1.16 ± .36 Pbo −.84 ± .36
Narang et al[46]NCT04387617 United States/Canada Academic	Randomized, double-blind, 5 center, placebo-controlled	Post uretoscopy pain for urinary calculi	Mean age 59 years (SD 13 years) 60% women Ethnicity not given Total = 90 CBD = 45 Pbo = 45	Oral 20 mg cannabidiol oil (Epidiolex) for 3 postoperative days	Pain 0 to 10 scale Maximum recorded pain day 3 CBD 3.6 ± 2.4 Pbo 3.2 ± 2.8 Pain 0 to 10 scale
Vela et al[49]NTC03693833 Denmark Academic and charitable funding	Randomized, double-blind, single-center, placebo-controlled	Add-on therapy for hand or psoriatic arthritis	Mean age 62 years Age IQR 53 to 71 65% women Ethnicity not given Total = 129 CBD = 68 Pbo = 61	CBD 20 to 30 mg oral daily Placebo 12 wks	Mean change in pain after 12 wks CBD 11.7 (5.3–18) Pbo 11.5 (5.0–18) Mean difference .23 mm (95% CI −9.4 to 9.9) Pain 0 to 100 scale
Xu et al[50]United States Donated materials Theramu	Randomized, double-blind, placebo-controlled,	Peripheral neuropathy of lower extremities	Mean age 68 years (SD 8.9) 38% women Ethnicity not given Total = 29 CBD = 15 Pbo = 14	Topical CBD 250/3 oz daily used up to 4 times daily Placebo 4 wks	Mean surface pain at 4 wks CBD 4.2 (SD 2.3) Pbo 5.9 (SD 2.7) Pain 0 to 10 scale Note that many different pain descriptors measured and unbalanced at baseline
Zubcevic et al[51]Denmark Academic	Randomized, double-blind, placebo-controlled,	Peripheral neuropathic pain	Mean age 65 years Age range 22 to 95 56% women Ethnicity not given Total = 115 CBD = 27 Pbo = 30	Flexible dosing with oral CBD 5 to 50 mg, THC 2.5 to 25 mg, CBD/THC 5/2.5 to 50/25 mg, or placebo 8 wks	Change in weekly average of daily pain (difference from placebo) CBD .76 (.02–1.49) THC .31 (−.42 to 1.03) CBD/THC −.19 (−.90 to .52)
Crossover studies					
Arout et al[37]NCT02751359 United States Insys Therapeutics	Randomized, double-blind, placebo-controlled, within patient Randomized, double-blind,	Experimental pain Noncannabis using volunteers Cold pressor test Healthy adults Experimental pain	Mean age 32 years (SD 8 years) 53% women 8 Black, 2 White, 4 Asian, 3 mixed race N = 17 Mean age 21 years (SD 2.6 years)	0, 200, 400, and 800 mg orally Single dose	No significant acute effects of CBD

Table 1 (*Continued*)

REFERENCE, COUNTRY, AND FUNDING	*DESIGN*	*CONDITION*	*PATIENT DETAILS AND NUMBER ANALYZED*	*CBD DRUG AND ROUTE AND DURATION*	*PAIN OUTCOME*
De Vita et al[40]United States Not stated	placebo-controlled, within patient		67% women Ethnicity not given N = 15	Sublingual 50 mg Single dose	No significant differences in any outcome measures
Dieterle et al[41]NCT04059978 Switzerland Academic and charitable funding	Randomized, double-blind, placebo-controlled, within patient	Opioid-induced hyperalgesia in healthy adults	Median age 25 years (SD 7 years) 54% women 92% White N = 21	1,600 mg oral CBD Placebo Single dose	No significant differences in any outcome measures
Heineman et al[45]NCT0461137 United States Academic	Randomized, double-blind, single-center, placebo within the patient	Patients with symptomatic thumb basal joint arthritis	Mean age 64 years (SD 11 years) 72% women 83% White N = 18	Topical CBD of 6.2 mg/mL in shea butter Placebo butter Twice daily application for 2 wks	Pain at end of 2 wks CBD 2 ± .3 Pbo 5 ± .4 Pain 0 to 10 scale
Schneider et al[47]Switzerland Academic and charitable funding	Randomized, double-blind, placebo-controlled, within patient	Opioid-induced hyperalgesia in healthy adults	Mean age 24 years (SD 3 years) 55% women 90% White N = 20	800 mg oral CBD Placebo Single dose	Average pain scores were: CBD 5.2 ± .7 Pbo 5.3 ± .7 Pain 0 to 10 scale
van Orten-Luiten et al[48]Netherlands APIRx Pharmaceuticals	Randomized, double-blind, placebo-controlled, within patient	Female patients with irritable bowel syndrome	Mean age 31 years Age range 22 to 50 100% women Ethnicity not given N = 32	50 mg CBD chewing gum or placebo chewing gum up to 6 per day depending on symptoms (when pain is 4/10 or higher) 4 wks	Difference between CBD and placebo was .1 (SD 1.1), (95% CI −.3 to .5) Pain 0 to 10 scale

only" label may be inaccurate. Several products claiming not to contain the undoubtedly psychoactive THC did so, and content labeling of cannabis products that are not regulated drugs is likely to be unreliable.[22,33-35]

Pharmaceutical Grade CBD Used in Trials

Current Evidence for Efficacy of CBD in Different Types of Pain

Sixteen clinical trials of CBD for various types of pain have been conducted, and results reported[36–51] (Table 1). Fifteen trials stated using pharmaceutical-supplied CBD or making preparations from such a source; one did not specify though it was sponsored by a pharmaceutical company.[37] The 16 trials were conducted in 12 different pain states, using 3 routes of administration (10 oral, 3 topical, and 3 buccal/sublingual), with CBD doses between 6 and 1,600 mg, and very different durations of treatment (5 single dose, 3 others less than 7 days, 6 between 2 and 6 weeks, and 2 of 8 and 12 weeks).

In total, 917 patients were involved in direct comparisons between CBD and placebo. Two trials (32 patients) examined single CBD doses in experimental pain conditions,[37,40] 4 trials (327 patients) used CBD for up to 14 days for patients with postoperative pain or acute low back pain,[36,39,42,46] 6 trials (437 patients) used CBD for up to 12 weeks for patients with cancer or chronic pain conditions,[43–45,49,50,51] and 4 trials (121 patients) used CBD for 4 weeks in other conditions where the pain was a symptom.[38,41,47,48] ClinicalTrials.gov showed 3 trials completed but not reporting results and few ongoing testing analgesic efficacy.

Trials used various CBD formulations (topical, oral, sublingual, and buccal) at various doses. All were randomized, double-blind, had participants with sufficient pain to be sensitive, were of reasonable quality (Supplementary File 1 shows the risk of bias), made comparisons with placebo, and had a parallel group (794 patients) or crossover designs (123 patients).

Nine parallel-group trials and 2 of 6 crossover trials provided pain results used for a pooled analysis (Fig 1). Ten of these 11 trials showed that CBD produced little or no pain relief, with no statistical or clinically significant difference between CBD and placebo for either trial design. Moreover, 1 parallel-group trial and 4 crossover trials not providing results included in the pooled analysis showed no difference between CBD and placebo. A single trial in 18 patients with symptomatic thumb basal joint arthritis showed a large difference after 2 weeks of treatment with topical CBD, reporting no worse than mild pain in all with CBD but with moderate/severe pain in all with placebo, with an implied number needed to treat (NNT) of 1.[45]

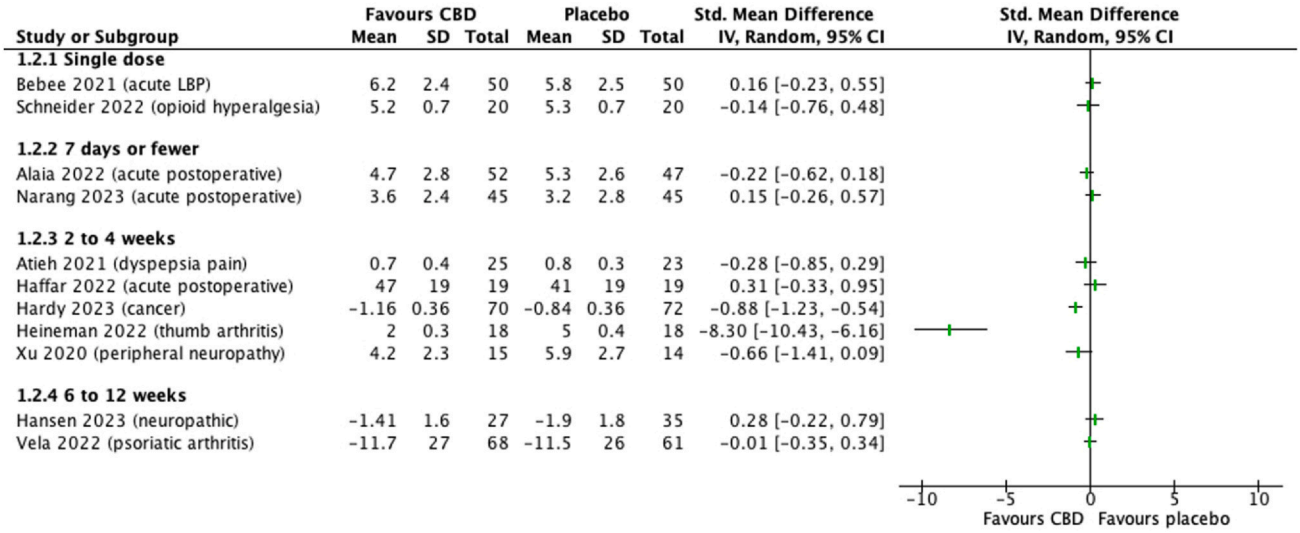

Figure 1. Pooled analysis of CBD versus placebo for pain outcomes according to duration of treatment.

Is Pharmaceutical Grade CBD Safe?

This is at best uncertain, but a 2019 systematic review of CBD adverse events and toxicity in animals and humans concluded that it was not risk-free.[52] Uncertainty also arises because of the relatively small numbers of patients in these trials and partly because of inadequacies in reporting adverse events.[53,54] A meta-analysis of CBD used for epilepsy found that 10% of patients treated with CBD had at least 1 adverse event, twice the rate for placebo and that the risk ratio for serious adverse events was 3.4.[55] There appears to be CBD-related hepatotoxicity, with elevated liver enzymes in about 7% of patients using CBD, much higher than the rate with placebo.[56] Veterans using cannabinoids for chronic pain have an increased risk of cannabis use disorder.[57]

Cannabis and cannabis-based medicines have come under scrutiny regarding road and workplace safety. In 2018 the Occupational and Environmental Medical Association of Canada endorsed a position statement on the implications of cannabis use for safety-sensitive work which recommended that, until definitive evidence is available, it is not advisable to operate motor vehicles or perform safety-sensitive tasks for at least 24 hours following cannabis consumption.[58,59] Cannabis consumption is associated with a more than doubling of the risk for motor vehicle collisions and is also associated with a range of other serious harms.[47,60] A recent cross-sectional study in Canada has reported an almost 500% increase in emergency department visits involving road traffic injuries associated with cannabis following legalization.[61]

Moreover, even for pharmaceutical-grade CBD, there is concern about impairment; the prescribing information for Epidiolex (a CBD product approved in the United States in 2018 for the treatment of certain epilepsy disorders) contains the warning that "[p]rescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX to gauge whether it adversely affects their ability to drive or operate machinery."[62]

Conclusions

Is the Public Protected Against False Claims of Analgesic Efficacy?

In January 2023, the FDA announced that a new regulatory pathway for CBD was needed.[63] In the meantime, the FDA monitors claims made for CBD products, regularly issuing warning letters.[64,65] Canadian advertising standards have advice on restrictions on promoting cannabis products.[66] The UK uses a regulatory advertising framework set out by the Advertising Standards Authority and Committee of Advertising Practice with generic information and specific advice on CBD emphasizing the regulatory complexity. The advice on pain is clear: "Claims to treat or alleviate pain are likely to be considered medicinal and marketers would need to ensure that any necessary licenses and marking authorisations are held and, where relevant, objective claims are supported by documentary evidence."[67] Issues around controlled substances, medicine, novel food, or food supplements all potentially impact the care that the industry should use, and advice is detailed and clear.[66-69] There is even a succinct guide for budding entrepreneurs.[70]

There should be no excuses for misleading the public, and yet it is likely that the public is being misled and possibly placed in harm's way.[6,7,64,65,71] Other than being told to desist using incorrect advertising, it is unclear whether there are any penalties.

It is also unclear why there is tolerance for the marketing and use of a product without proven benefit but with risk of harm to a large population of people suffering from debilitating pain. This may be due to a misplaced perception of safety, a desire of governments to create markets in what is perceived as

a new area for national gross domestic product (GDP) growth, the Western dominance of libertarian societies reluctant to legislate over individual behavior, or simply an expression of desperation in needing any response, even an ineffective one, to a public health disaster hiding in plain sight. The prevalence of chronic pain in the UK, already the commonest chronic condition, is set to increase by over 30% by 2040.[72] What we do know is that if we collude in pretending that we have treatments, we are not facing up to the need for investment in analgesic discovery and innovation. It is sobering to reflect that changes to state medical cannabis laws in the United States to allow greater use have had no important impact on the rate of opioid or nonopioid prescribing or procedures.[73]

It might be argued that, given the disparity of pain conditions tested, the varying dose and route of administration of CBD, as well as differences in duration of treatment, this updated review should not be the last word on CBD for pain. That might be so, but initially, positive results have tended to become less positive with more research,[74] and larger meta-analyses have much smaller effect sizes than meta-analysis of small data sets.[75] Given that well over 50 clinical trials of cannabinoids have failed to show any large analgesic effects since the first RCT almost 50 years ago,[76] there can be no reasonable expectation of much difference from what we have now.

Summing Up

For people living with pain, the evidence for CBD or hemp extract shows it is expensive, does not work, and is possibly harmful.

Health care professionals should use this evaluation to help people living with pain to inform their decisions about unconventional unproven substances being sold as therapeutic. They will increasingly see patients using CBD or similar products, often for pain, and at present, may have a neutral view of CBD.[77] That should probably change.

Regulatory authorities should also take note of the considerable deficiencies existing in the products sold, especially the incorrect labeling of many products, and possible contamination with psychoactive compounds. Based on the evidence, there is a long way for the regulatory authorities to go to achieve this, and regulatory systems should be in place for this. Ultimately it may be down to individuals to complain.

Data availability

All data are from published articles.

Disclosures

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Author Contributions

The authors have collaborated on methodological issues in pain over several decades. Three authors were part of an International Association for the Study of Pain (IASP) task force on cannabinoids, and the other has published on cannabis and motor vehicle collisions. The idea for this article came following discussions between AM, EF, SS, and CE after the publication of several CBD trials because no CBD trials were available for the IASP task force review. RAM drafted the manuscript, and all authors made substantial contributions of intellectual content and edits and approved the final draft. RAM is the guarantor.

Patient involvement

No input from patients with pain was specifically sought for this article, though RAM reports suffering from chronic pain.

Appendix A. Supplementary Data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2023.10.009.

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