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CBD-oil for pain management: myths and evidence

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Abstract: *Background:* Recently, there has been a growing interest in the analgesic properties of a non-psychoactive phytocannabinoid, cannabidiol (CBD). Although society's expectations are high, the supporting evidence remains questionable. This study aims to explore society-shared beliefs about cannabidiol and compare them to the current scientific literature.
Methods: First, we searched on the internet to collect information about the public claims regarding CBD's analgesic potentials. Second, we conducted a narrative review to gather the current evidence on the same topic.
Results: Worldwide, there are organisations, physicians and patients who propagate CBD as a safe and effective analgesic remedy.
So far, most of the high-quality papers regarding CBD's analgesic effect, are rodent studies. Although CBD is a phytocannabinoid, its analgesic effect may not be mediated through the classic cannabinoid receptors, but rather through other chemical structures, such as 5-HT1a, TRPV1 and Glycine alfa receptors. In contrast to the animal studies, human studies are few with controversial results. Moreover, there are some safety issues to concern as well.
Discussion: Given the low-quality of evidence from human studies, the lack of standardisation of the currently used CBD products, and the possible adverse effects, we cannot support the common use of CBD in pain management.
Conclusion: We conclude that most of the common beliefs about CBD are actually „myths" and not based on robust evidence.

Abbreviations

CBD - Cannabidiol
THC - Tetrahydrocannabinol
CBN - Cannabinol
CB1R - Cannabinoid receptor type 1
CB2R - Cannabinoid receptor type 2
TRPV1 - Transient Receptor Potential Cation Channel Subfamily V Member 1
TRPV2 - Transient Receptor Potential Cation Channel Subfamily V Member 2
TRPA1 - Transient Receptor Potential Ankyrin 1
ENT1 - Equilibrative Nucleoside Transporter 1
GPR55 - G-Protein Coupled Receptor Protein 55
5-HT1aR -5-Hydroxytryptamine 1A Receptor
5-HT2aR -5-Hydroxytryptamine 2A Receptor
CFA - Complete Freund's Adjuvant
TBI - Traumatic Brain Injury
GABA - Gamma-Aminobutyric Acid
FAAH - Fatty Acid Amide Hydrolase
FDA - Food and Drug Administration
TENS - Transcutaneous Electrical Nerve Stimulation
ICU - Intensive Care Unit

Introduction

Cannabis Sativa has been used by humanity for thousands of years for medical, textile, industrial, and religious reasons. In ancient China, its hallucinatory effects were well known. To our knowledge, the Sumerians used it for treating epilepsy, Galen, the well known Greek physician applied it for chronic otalgia, and the Persians used it for migraine. During the American Civil War, the military nurses administered it to palliate injured soldiers (1).

Although the whole plant has more than 500 constituents (1), in this paper, we will focus on only one, the cannabidiol (CBD), and its oil. Given the lack of typical cannabis side-effects ("high") and believed therapeutic possibilities have led to the recent popularity of the CBD products.

Interestingly, CBD's working mechanism is not restricted to the classical cannabinoid receptors, such as CB1 and CB2 receptors. At the molecular level, there is evidence that CBD inhibits voltage-gated Na+ channels and some other membrane channels like TRPV1, TRPV2, TRPA1 (2, 3).

The exact mechanism of this inhibition is not well known, but CBD alters with the properties of the lipid layer in which the channels are situated.

Furthermore, it is proven that cannabidiol interacts with various receptors, including ENT1,

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GPR55, 5-HT1aR, 5-HT2aR, and alfa-3 glycine receptors (3,4).

In addition to its proven beneficial effect for treating some forms of epilepsy (Dravet syndrome and Lennox-Gastaut syndrome), it is thought to have potential benefits in other pathologies such as migraine, depression, addiction and anxiety disorder (5).

To date, most of the reviews regarding the analgesic effects of CBD evaluated the therapeutic potential of the nabiximols. This cannabis-based medicine contains nearly the same concentration of tetrahydrocannabinol (THC) and cannabidiol.

This review aims to compare society-shared beliefs about the only CBD-containing products to current scientific evidence.

Methods

This review consists of two parts. First, we have conducted a non-exhaustive search on the internet to identify the society-shared beliefs of CBD's analgesic potential. We aimed to include popular, diverse sources such as a website, a physician and a patient testimony.

Second, we used study terms like 'CBD AND Pain', 'cannabidiol AND Pain', 'chronic pain AND cannabidiol, acute pain AND cannabidiol', 'analgesic AND cannabidiol', 'cancer pain AND cannabidiol' on Pubmed and Embase. We performed our research to explore weather CBD treatment could attenuate pain. We included both human and animal studies. We included all studies regarding cannabidiol's effect on pain. Only English language publications were included. Studies regarding the adverse effects of cannabidiol were included as well. If we could not reach an article through the library of the KU Leuven, we have contacted the authors for the manuscript. We included only studies where CBD's effect on pain independently was reported. One study was excluded because the pre-treatment had failed to cause hyperalgesia, so the antinociceptive effect of CBD could not be evaluated.

Results

The research was conducted on 5 May 2020.

On Pubmed and Embase, we have found all together 5030 papers. After excluding the duplicates and implicating our inclusion criteria, we have had 20 animal studies, 1 veterinarian survey, 11 human, or human-related studies, and 2 papers on the adverse effects of cannabidiol.

Society-shared beliefs

Public claims can be entirely spread through social media as well. In a social media surveillance study about cannabidiol use, the authors observed that pain and anxiety were the two main medical conditions to find in comments on CBD. From the total number of comments (3968) about CBD, 2052 were mentioning pain, 286 headache, and 222 migraine (6).

Additionally, there are plenty of websites aiming to popularise CBD. CBDOIL.org might be one of the most known and best updated. According to this website, CBD has therapeutic potential in the treatment of chronic arthritis pain and chronic nerve pain. As they explain the reason of CBD's positive effect, it works through the endocannabinoid system and helps to synchronise the homeostasis of our body (7).

In a Youtube video, called "Demons of the diamond", David Wells, a former baseball player, tells his experience about CBD-oil. During his professional baseball carrier, he needed to undergo many surgeries because of game injuries. Due to the repetitive operations and injuries, he started to take painkillers, and finally, he became addicted to them. After a prolonged struggle with legal and illegal painkillers, adding CBD to his therapy, which helped him to entirely quit using his previous pain medications (8).

Furthermore, the usage of CBD-oil is not restricted to self-administration. In the routine of some physicians, it is integrated in their daily medical practice too. Dani Gordon, a Canadian doctor, is only one of the professionals, who treat patients with fibromyalgia and with arthritis pain by CBD.

Regarding the working mechanism of CBD, she gives us a clear explanation on her Youtube channel. In line with the theory of the aforementioned website, she declares, that CBD may be able to rebalance the cannabinoid system (9).

Animal studies

Most data on the analgesic effects of CBD are reported from rodent research.

In an online survey, veterinarians were asked about their clinical experience with cannabis-derivates. Analgesia for chronic pain is one of the most reported positive effects of cannabidiol according to the study (10).

In a placebo-controlled, observer-blinded study, they treated mice with CFA to induce hyper-

sensitivity to thermal pain. The mice who were treated with intrathecal CBD experienced less nociception compared to the placebo group. In animals whose alfa-3 subunit of the glycine receptor was missing CBD had significantly less analgesic effect. The knockout of CB1 or CB2 receptors did not influence the CBDs' protective outcome against thermal pain (4).

In another placebo-controlled study, the researchers induced mild traumatic brain injury (TBI) to mice. On day 14 and day 21, oral CBD-treated TBI mice experienced significantly less tactile allodynia than vehicle-treated mice. In addition to this on day 14, CBD-treated TBI mice showed significantly less aggressive behaviour than vehicle-treated mice. Furthermore, compared to the placebo-treated TBI mice, CBD reduced the depressive-like behaviour of animals on day 60.

At the end of the experiment, the levels of Glutamate, D-aspartate, and GABA were measured. This analysis proved that CBD treatment could significantly reduce the elevated Glutamate and D-Asp levels and increase the decreased GABA levels (11).

In another placebo-controlled, prospective animal study, the authors proved that seven days of subcutaneous CBD treatment did significantly reduce mechanical allodynia and decrease anxiety-like behaviour. Interestingly, the antiallodynic effect was blocked both by TRPV1 antagonist, capsazepine and by 5-HT1a antagonist, WAY100635. Compared to capsazepine, WAY100635 blocked only partially the analgesic effect of CBD (12).

Other researchers showed that in mice exposed to spinal cord injury, intraperitoneal CBD treatment decreased T-cell activation as well as the level of pro-inflammatory cytokines and chemokines. Besides the anti-inflammatory benefits, CBD-treated animals showed less sensitivity to thermal pain than vehicle-treated animals (13).

In another study, the effect of CBD was investigated on incision pain in male rats.

Intraperitoneal CBD treatment (3 and 10 mg/kg) or local CBD application (10 to 40 nmol/0.25 microL) in the anterior cingulate cortex lightened it in a dose-dependent way. Interestingly, low doses (0.3 mg/kg and 1 mg/kg) and high doses (30 mg/kg) of intraperitoneal CBD had no significant antiallodynic weight (14).

In a further placebo-controlled, multi-drug study, sciatic nerve injury was used as a neuropathic pain model. Gelatine (as placebo), CBD, THC (Tetrahydrocannabinol), and morphine were applicated to mice through self-administration. Compared to placebo and morphine, cannabidiol proved to be a sufficient product to relieve neuropathic pain. Besides, CBD failed to produce analgesia in a pain-naive state (15).

Few additional studies were carried out to investigate CBD's effect on chemotherapy-induced neuropathic pain conditions.

In one of these animal studies, neuropathic pain was induced by a commonly used chemotherapy medication, paclitaxel. Compared to the vehicle-treated group, in the cannabidioltreated group, the mice were significantly less sensitive to mechanical allodynia. The positive effect of CBD was reversed by a 5-HT1A antagonist, but not by CB1R or CB2R antagonists, confirming that the analgesic effect of CBD is not mediated through the classic cannabinoid receptors (16).

CBDs' effect on chemotherapy-induced allodynia was investigated by other researchers as well. Cannabidiol was proved to be capable of preventing both mechanical and cold allodynia following paclitaxel treatment (17).

In a further study regarding chemotherapy generated neuropathic pain, both CBD and THC turned to be comparable to gabapentin in mitigating tactile allodynia (18).

In a chemotherapy-induced neuropathic pain model, both CBD and THC attenuated mechanical allodynia caused by paclitaxel or vincristine. Furthermore, CBD turned out to be an efficient analgesic in the oxaliplatin group as well. The combination of these cannabis-derivates provided a synergic antiallodynic effect in animal groups whose neuropathic pain was induced by oxaliplatin or paclitaxel (19).

Many studies confirm CBD's analgesic potential in arthritis pain models as well.

In a placebo-controlled animal study, osteoarthritis was induced in Wistar rats. They were also treated by different concentrations of intra-articular CBD (100 mg, 200 mg, 300 mg) or by vehicle. The conclusion was that CBD application relived osteoarthritis-caused pain both in the behavioural and in the electrophysiological tests. Besides, prophylactic CBD treatment prevented the saphenous nerve demyelination and significantly attenuated the development of secondary allodynia. Parallel with the aforementioned studies, the analgesic effect of CBD was inhibited by TRPV1 antagonist SB266791, but neither by CB1R antagonist AM281 nor by CB2R antagonist AM630 (20).

In an additional experiment, other authors found similar results. The researchers induced knee

joint inflammation in rats and examined whether the different concentrations of transdermal CBD could influence it. They found that the daily application of 6.2 mg CBD reduced the inflammation, the spontaneous pain rating scores, and the hypersensitivity to painful heat stimulation (21).

In a veterinarian placebo-controlled, owner blinded, cross-over study, osteoarthritic dogs were treated by CBD-oil (2 mg/kg or 8 mg/kg) or by placebo. The animals received treatment every 12 hours for four weeks. In the CBD-group, increased activity and decreased pain were observed. Besides the positive effects, there were no significant side-effects reported (22).

In a further randomised, placebo-controlled animal study, a preclinical model of Parkinson's disease was induced in mice. The authors showed that experimental parkinsonism sensitised the animals to thermal and mechanical stimulations. Both acute and chronic application of CBD decreased the hyperalgesia and allodynia in this condition. Ineffective doses of a FAAH inhibitor (URB597) or a TRPV1 antagonist (capsazepine) turned to be able to potentiate the antinociceptive effect of CBD. However, the inverse agonist of the CB1 receptor (AM251) prevented the analgesic effect of cannabidiol (23).

In another experiment, CBD was found to be effective in treating both neuropathic and inflammatory pain conditions. In the inflammatory pain model, CBD reduced lipid peroxidase production, and normalised NO production in glutathione-dependent enzyme activity. Even though CB1 and CB2 receptor antagonists failed to prevent CBD's effect, TRPV1 receptor antagonisation turned out to be effective in decreasing CBDs' antihyperalgesic impact (24).

Ophthalmology is and another field of medicine that could profit from cannabidiol use. In a corneal injury mice model, CBD turned out to be effective in reducing hyperalgesia to capsaicin. This property of cannabidiol is mediated by 5-HT1A receptor (25).

Different authors found similar effects in rats with induced painful diabetic neuropathy.

Thus, CBD showed a significant allodynic impact, which could be reversed by 5-HTa1 receptor antagonist, but not by CB1R or CB2R antagonists. On the other hand, a glycine receptor antagonist could not prevent CBD's analgesic effect. Besides, they observed no considerable side-effects, and CBD did not affect body weight or glycaemic level (26).

Another placebo-controlled study, humanised male and female sickle cell mice were treated by Epidolex - the only FDA approved cannabidiol medication- and then they were evaluated weather Epidolex could improve their pain symptoms. In male mice, Epidolex turned out to be sufficient to relieve acute mechanical hyperalgesia, and it was not effective in decreasing acute cold- or deep-hyperalgesia. It could not treat acute pain in female mice at all. In the treatment of chronic pain of male sickle mice, Epidolex was capable of handling mechanical-, cold- and heat-hyperalgesia. The authors suggest that female mice may need higher doses of cannabidiol than male mice (27).

The combination of CBD and CBN (cannabinol) on myofascial pain was examined in an animal model study. Muscle sensitisation was induced by intramuscular NGF (nerve growth factor).

The authors observed a significant attenuation of mechanical sensitisation in both CBD (5 mg/kg) an CBN (1mg/ kg) groups, and the combination of those products had the same benefits with a longer duration of action. They concluded that the combination of those cannabis-derivates could attenuate each other's effect in treating pain conditions like temporomandibular disorders or fibromyalgia without central side-effects (28).

Despite its known analgesic properties, lower doses (1.5mg/kg) of CBD pre-treatment is proven to be sufficient for abolishing the antinociceptive effect of low- and high-frequency TENS (29).

Human studies

In one of the few, high-quality human studies, single-use of Bedrolite (cannabidiol dominant cannabis with minimal or no THC concentration) was examined in the treatment of fibromyalgia.

Authors found similar levels of pain score in the CBD and placebo-treated group (30).

In a prospective single-arm cohort study, chronic pain patients received additional CBD hemp extract to their initial opioid therapy. Previously, all patients had been taking opioids for at least one year. 94 of the 97 patients who completed the 8-week follow-up period, used cannabidiol hemp extract. Fifty participants (53.2% of the 94 patients) were able to reduce their opioid medications at week 8, and 89 (94% of the 94 patients) patients experienced a significant improvement in the pain-related quality of life. There were no severe side-effects observed. This study suggests that cannabidiol extract has a potential role in the therapy of chronic pain patients (31).

In a placebo-controlled trial, patients with temporomandibular disorder received transdermal

CBD over the masseter muscle for fourteen days. At the end of the experiment, the patients who were taking CBD had significantly lower pain intensity and decreased masseter muscle activity compared to the control group (32).

In a further double-blinded, placebo-controlled experiment, transdermal, synthetic CBD gel (ZYN002) was applied to treat pain caused by osteoarthritis. Although 12 weeks of treatment of ZYN002 led to better pain scores, it was statistically not different from placebo. There were significantly more responders in the ZYN002 group than in the placebo group, and the application of this product was well tolerated. Interestingly men in contrast to women experienced a significant reduction in pain scores (33).

In Uruguay, where cannabis and its derivatives are mostly legal, seven patients with chronic pain after kidney transplant received CBD for three weeks. As a result, two of them experienced total pain improvement, four patients responded partially, and only by one patient was observed no analgesic effect. Unfortunately, this study was neither blinded nor controlled by placebo (34).

There are three case studies regarding paediatric patients with severe epidermolysis bullosa with inadequate pain control. After adding CBD to their therapy, all three children experienced improvements in their dermatological symptoms and all required reduced doses of analgesics with better pain control (35).

In a case report, a female patient with neurofibromatosis was treated by cannabidiol oil.

After three months of treatment, she experienced a significant improvement in her average daily pain score (from 6/10 to 1/10) and a considerable reduction in her migraine episodes (from 15 per month to 5 per month) (36).

In an "anecdotal, spontaneous, compassionate-use, retrospective, open-label "study, women with severe dysautonomic syndrome after HPV vaccination received CBD-rich hemp oil for three months. Most of them experienced significantly reduced body pain with improvement in social role functioning (37).

In a cross-sectional survey, patients of a palliative outpatient clinic were asked about their cannabis use. 24% (14/58) of the patients reported using CBD, and 50% (7/14) of them experienced pain relief (38).

According to another cross-sectional survey, CBD can be moderately capable of treating chronic pain syndrome triggered by endometriosis (39).

Other authors used an application to collect data on different medical cannabis products used as a short-term analgesic. According to the responders, CBD provides neither positive nor negative effects in curing pain. The authors pointed out that CBD" s lack of short-term effects may be due to its long latency (40).

Adverse effects

Although, cannabidiol gained enormous popularity during the last years as a therapeutic remedy, its potential adverse and harmful effects are not widely discussed.

In a study on male mice, CBD application for 34 days led to a 30% reduction in fertility rate and a 23% reduction in the number of litters (41).

Chronic CBD usage in animals may cause attenuation in the number of germ and Sertoli cells, reduction in mammalian testis size, and decreased concentration of hypothalamic, pituitary, and gonadal hormones (42).

In a placebo-controlled human study, the authors evaluated whether the discontinuation of CBD administration would lead to withdrawal symptoms. Thirty healthy individuals received cannabidiol for four weeks, and then they were separated into two groups. The Group 1 volunteers took CBD further for another two weeks, and the Group 2 volunteers switched to placebo instead of cannabidiol. Although there was a relatively high incidence of mild adverse effects, the volunteers experienced no withdrawal symptoms after the discontinuation of CBD (43).

Potential adverse effects are not the only potential dangers of "cannabidiol products". In 2016, 84 not- FDA- approved cannabidiol products were controlled in the United States. Only 31% of them were labelled correctly, and 21% of them contained delta-9- THC at the mean concentration of 0.45 mg/ml. In the Czech Republic (Czechia) 29 CBD products were controlled, and the examiners found a high level of carcinogen polycyclic aromatic hydrocarbons in 69% of the controlled products (44).

A 56-year-old female patient was admitted to the ICU because of severe Steven-Johnson Syndrome and Toxic Epidermal Necrolysis after initiation of cannabidiol therapy – mentioned in a case report. Finally, she passed away from septic shock (45).

Table 1

Table of all rodent studies with a summary of main trial points: Type of study, Limit of significance, Number of animals, Pain model, Used molecules and Results.

Study	Type of study	Limit of significance	Number of animals	Pain model	Used molecules	Results
Abraham AD and others, Neuro-psycho-pharmacology.12/2019 (15)	placebo-controlled study	$p<0.05$	total 143 mice	Neuro-pathic pain	THC, CBD, morphine, gelatine	1.CBD significantly relived allodynia. ($p<0.0012$.) 2.CBD failed to reduce hyperalgesia. (Control vs CBD ($p=0.0093$ 3. CBD did not produce analgesia in the pain-naive state.
Varun and others, Blood 2019 134 Supplement 1.(27)	placebo-controlled study	$p<0.05$	not given	acute and chronic pain in sickle mice	Epidolex	Acute pain:1. Treatment with Epidolex lead to a decrease in mechanical hyperalgesia ($p<0.05$) in male sickle mice. Acute pain:2. treatment with Epidolex lead to decrease in cold hyperalgesia in male mice without statistical significance. Acute pain:3. No changes after Epidolex treatment in male sickle mice for deep hyperalgesia. Acute pain:4. No changes after Epidolex treatment in female sickle mice for cold-, deep, mechanical -hyperalgesia. Chronic pain: 1.In male sickle mice Epidolex significantly reduced mechanical hyperalgesia. ($p<0.01$) Chronic pain: 2.In male sickle mice Epidolex significantly reduced cold hyperalgesiaChronic pain: 3.In male sickle mice Epidolex significantly reduced heat-hyperalgesia. ($p<0.05$). ($p<0.01$)
Crivelaro do Nasciemento and others, Neuropharmacology 2020.(23)	placebo-controlled study	$p<0.05$	total 49 mice	pain in induced Parkinson's desease	CBD, morphine, celecoxib, URB597, AM251, Capsazepine, SCH336	1. Acute administration of CBD 60 min previously to nociceptive test could significantly decrease the hyperalgesic response compared to placebo. ($p<0.05$). 2. Acute doses of 10 mg/kg and 100 mg/ kg of CBD (30 mg/kg not) could significantly decrease the allodynic response ($p<0.05$), this effect of CBD was comparable to the antinociceptive effect of morphine. ($p>0.05$) 3. Both acute and chronic administration of CBD (10 mg/kg) decreased the hyperalgesic response compared to placebo. ($p<0.01$) 4. Both acute and chronic administration of CBD (10 mg/kg) increased the withdrawal latency for cold stimulus. ($p<0.01$) 5. URB597, AM251, Capsazepine, SCH336 lead neither to antiallodynic nor to antihyperalgesic response. ($p>0.05$) 6. Pre-treatment with the FAAH inhibitor (URB597) potentiated the effect of CBD ($p<0.05$)in hyperalgesic and in allodynic models. 7. Pre-treatment with the TRPV1 antagonist (capsazapine) potentiated the effect of CBD in hyperalgesic and in allodynic models. ($p<0.05$) 8. Pre-treatment with the CB1 receptor antagonist (AM251) inhibited the analgesic effects induced by CBD in hyperalgesic and in allodynic models. ($p<0.05$) 9. Pre-treatment with the CB2 receptor inverse agonist (SCH336) did not influence CBD's antinociceptive effect in hyperalgesic models ($p>0.05$) but inhibited it in one allodynic model. ($p<0.05$)
Kogan and others Front Vet Sci. 2019 Jan 10;(10)	online survey	/	2130 participants, veterinarians	Use of cannabis derivatives	different cannabis derivatives	1.Pain management is one of the most important topics in discussions with clients on CBD. 2. Antiallodynic effect was blocked by both TRPV1 and 5-HT1a antagonists. ($p<0.001$)
Li and others.Cell Immunol. 2018 Jul;329:1-9.(13)	placebo-controlled study	$p<0.05$	total 61 mice	spinal cord injury	CBD	1. CBD decreased T-cell activation as well as the level of pro-inflammatory cyto-kines and chemokines.($p<0.05$) 2. CBD-treated animals showed less sensitivity to thermal pain than vehicle-trea-ted animals. ($p<0.05$)
Xiong ant others. J Exp Med. 2012 Jun 4;209(6):1121-34. (4)	placebo-controlled, observer-blinded study	$p<0.05$	mice (number not determined)	thermal hypersensitivity	CBD	1.CBD administration led to less hypersensitivity. ($p<0.05$) 2. In animals whose alfa-3 subunit of the glycine receptor was missing CBD had significantly less analgesic effect. ($p<0.05$)

Study	Type of study	Limit of significance	Number of animals	Pain model	Used molecules	Results
Belardo and others. Front Pharmacol. 2019 Apr 16;10:352 (11)	placebo-controlled study	p<0.05	total 80 mice	model of traumatic brain injury	CBD	1.CBD-treated TBI mice showed less aggressive behaviour, and had less tactile allodynia than vehicle-treated mice. (p<0.05) 2. CBD treatment reduced the elevated Glutamate and D-Asp levels and increase the decreased GABA levels. (p<0.05)
De Gregorio and others. . Pain. 2019 Jan;160(1):136-150 (12)	placebo-controlled study	p<0.05	total 229 mice	mechanical allodynia	CBD	1. CBD treatment reduced mechanical allodynia (p<0.001) and decreased anxiety-like behaviour.(p<0.001).
Karina and others Front Pharmacol. 2017; 8: 391. (14)	placebo-controlled study	p<0.05	total 275 rats	incision pain	CBD	1. Intraperitoneal CBD treatment (3 and 10 mg/kg) (p<0.05) or local CBD application (10 to 40 nmol/0.25 microL) in the anterior cingulate cortex (p<0.05) decreased mechanical allodynia. 2. Low doses (0.3 mg/kg and 1 mg/kg) and high doses (30 mg/kg) of intraperitoneal CBD had no significant effect on pain. (p>0.05
Ward and others, Br J Pharmacol. 2014 Feb;171 (16)	placebo-controlled study	p<0.05	total 40 mice	chemotherapy-induced neuropathic pain	CBD, WAY100635	1.CBD administration lead to less mechanical allodynia (p<0.0001) 2. The effect of CBD was reversed by 5-HT1A antagonist (WAY100635) (p<0.0001), but not by CB1R or CB2R (SR144528) antagonists. (SR141716) (SR144528) (p>0.05).
Harris and others, Planta Medica 2016 82 :13 (18)	placebo-controlled study	p<0.05	mice (total number not determinded)	chemotherapy-induced neuropathic pain	CBD, THC, gabapentine	1. CBD , THC and gabapentin could decrease the mechanical allodynia following oaclitaxel treatment. (p=0.035 for CBD, p=0.007 for THC, and p=0.002 for gabapentin)
King and others, Br J Pharmacol. 2017 Sep;174 (19)	placebo-controlled study	p<0.05	total 344 mice	chemotherapy-induced neuropathic pain	CBD, THC	1. CBD decreased allodynia caused by paclitaxel (p<0.05), vincristine (p<0.05), and oxaliplatin (p<0.05). 2. THC decreased allodynia caused by paclitaxel (p<0.05) and vincristine (p<0.05). 3. The combination of CBD and THC could synergically decreasse allodynia caused by oxaliplatin (p<0.05) and paclitaxel (p<0.05).
Gamble and others, Front Vet Sci. 2018 Jul 23;5:165 (22)	placebo-controlled study	p<0.05	total 16 dogs	osteoarthritic dogs	CBD	1. CBD decreased osteoarthritis-caused pain. (p<0.02)
Ward and others, Anesthesia and Analgesia 10/2014 Volume 113 (17)	placebo-controlled study	p<0.05	total 146 mice	chemotherapy-induced neuropathic pain	CBD	1. CBD prevented the development of chemotherapy-induced cold (p<0.0001) and mechanical (p<0.0.0001) allodynia
Philpott and others, Pain 2017 Dec; 158 (20)	placebo-controlled study	p<0.05	rats (total number not determinded)	ostheoartihtis pain model	CBD	1.CBD decreased osteoarthritis -caused pain both in the behavioural (p<0.0001) and in the electrophysiological tests (p<0.0001) . 2. CBD treatment could prevent the saphenous nerve demyelination (p<0.05) and significantly attenuated the development of secondary allodynia (p<0.0001). 3. The analgesic effect of CBD was inhibited by TRPV1 antagonist SB266791 (p<0.05), but neither by CB1 R antagonist AM281 (p>0.05) nor by CB2R antagonist AM630 (p>0.05)
Hammell and others, Eur J Pain. 2016 Jul;20 (21)	placebo -controlled study	p<0.05	total 54 rats	ostheoartihtis pain model	CBD	1. CBD reduced inflammation (p<0.05), spontaneous pain rating scores (p<0.05), and hypersensitivity to painful heat stimulation. (p<0.05)
Jesus and others, Brain research.2019 Jul 15 (26)	placebo -controlled study	p<0.05	rats (total number not determinded)	diabethic neuropathic pain model	CBD WAY100135, AM251, AM630, strychine hydrochloride	1. CBD decreased mechanical allodynia. (p<0.0001) 2. CBD's analgesic effect was reversed by 5-HTA1 (WAY100135) receptor antagonist. (p<0.0001) 3. CBD's analgesic effect was influenced neither by CB1R antagonsit (AM251) (p>0.9999), nor by CB2R antagonist (AM630) (p>0.9999). 4. CBD's analgesic effect was not influenced by the glycine receptor antagonist (strychnine hydrochloride). (p=0.6784)

Study	Type of the study	Limit of significance	Number of animals	Pain model	Used molecules	Results
Costa and others, European Journal of Pharmacology 2007 556 (24)	placebo-controlled study	p<0.05	rats (total number not determinded)	inflammatory and neuropathic pain model	CBD, capsazepine, rimonabant, SR144528	1.CBD decreased mechanical thermal (p=0.0141) and mechanical (p=0.0074) hyperalgesia. 2. CBD's analgesic effect was influenced neither by (rimonabant) (p<0.001) , nor by CB2R antagonist (SR144528) (p>0.001). 3. The analgesic effect of CBD was inhibited by TRPV1 antagonist (capsazepine). (p<0.001) 4. CBD reduced lipid peroxidase production (p<0.05), and in normalizedNO production in glutathione-dependent enzyme activity (p<0.05)
Hayes and others, Archives of Oral Biology, 8/2019, volume 104 (28)	placebo -controlled study	p<0.05	total 54 rats	myofascial pain model	CBD, CBN	1. CBD decreased mechanical sensitisation. (p<0.05) 2. CBN decreased mechanical sensitisation. (p<0.05) 3. The combination of CBD and CBN could decrease mechanical sensitisation with longer lasting effect than the products alone. (p<0.05)
Thapa and others, Cannabis Cannabinoid Res. 2018 Feb 1 (25)	placebo-controlled study	p<0.05	mice (total number not determinded	corneal injury model	CBD, capsaicin, AM251, WAY100635	1. CBD decreased hyperalgesia to capsaicin. (p<0.001) 2. CBD's analgesic effect was reversed by 5-HTA1 (WAY100635) receptor antagonist. (p>0.05) 3. CBD's analgesic effect was not reversed by CB1R antagonist (AM251). (p<0.01)
Gonclaves and others, Neurol Sci. 2014 Dec 15; (29)	placebo-controlled study	p<0.05	rats (total number not determinded)	analgesic effect of TENS	CBD	1.Low doses of CBD (1.5 mg/kg) decreased the analgesic effect of 10 Hz and 150 HzTENS. (p<0.001)

Discussion

The purpose of the present review was to challenge the society-shared beliefs about the painkilling effects of CBD by evidence-based studies.

In contrast to the "beliefs", the analgesic effect of CBD might be mediated by receptors like glycine receptor, TRPV1 receptor, and 5-HT1a receptor and not by the classic cannabinoid receptors (like CB1 and CB2). Furthermore, it is unclear how CBD might mitigate pain by maintaining the homeostasis of the body.

Despite the growing interest in the CBD as a remedy for headaches, to date, there is no single study supporting it.

Concerning fibromyalgia, although it is treated by CBD by "medical experts" (9), the only study on this topic could not prove any benefit of cannabidiol compared to placebo (30).

Nevertheless, animal studies about arthritis pain showed more promising results (20, 21, 22). In other rodent models concerning pain caused by central or peripheral nervous system damage, CBD likes to be an effective antiallodynic remedy (4, 11, 12, 13, 15, 16, 17, 18, 19, 26).

Even though plenty of preclinical studies supports CBD's analgesic potential, the clinical evidence on this issue remains scarce.

None of "recommendations" on CBD use as a painkiller could mention any high-quality human paper as a reference.

In 2018 The Task Force of The European Pain Federation provided a summary of clinical recommendations of cannabinoid use in pain management (46). Neither their paper nor the aforementioned studies can support the safe and effective use of CBD products as an analgesic remedy.

Besides, our findings on CBD agree with the current position statement of the "*INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN"*. In which it is recommended to avoid using all kinds of cannabinoids for pain management as long as sufficient evidence is lacking (47).

Importantly, most trials are underpowered to formulate firm conclusions to guide clinical practice. Nearly 500 patients would be needed to be included in each arm of future clinical trials (48).

To date, all human studies on CBD together do not cover so many patients.

Table 2

Table of all human studies with a summary of main trial points: Type of study, Number of patients Limit of significance, Pain syndrome, Used molecules and Results

Study	Type of the study	Number of patients	Limit of significance	Pain syndrome, circumstence	Result(s)
Highet BH and others, Am J Hosp Palliat Care 1/2020 (38)	Cross-sectional survey	total 58 patients (14 using CBD)	not determined	palliative outpatient clinic	1. Improvement in pain in 50% (7/14). 2. Improvement in appetite in 29% (4/14). 3. Improvement in insomnia in 29% (4/14). 4. 29% (4/14) were using CBD with marijuana. 5. 21% (3/14) were reporting side-effects
Capano A and others, Postgrad Med. 1/2020 (31)	Prospective, single-arm cohort study	131 patients, 97 completed the follow up, 94 used CBD-extract	$p<0.05$	pain management centre, chronic pain patients using opioids at least for a year	1. 50 patients (53%) were able to reduce their opioid medication. 2. 89 patients (94%) reported improved pain-related quality of life. 2/a: PDI (Pain Disability Index) showed no improvement. (P=0.7) 2/b:PSQI (Pittsburgh Sleep Quality Index) showed significant improve-ment. (p=0.03) 2/c: PEG (Pain Intensity and Interference) showed significant improve-ment. (p=0.006) 2/d: willingness to reduce opioid did not change significantly. (p=0.8)
Hegazy O and Platnick H2. Cureus. 2019 Dec 6;(36)	Case study	1 female patient	not determined	Clinic, neurofibromatosis type-1	1. Her pain was significantly reduced (from 6/10 to 1/10) after 3 months of treatment. 2. She experienced significantly fewer migraine episodes (5 per month instead of 14 per month)
Nitecka-Buchta A and others, J Clin Med. 2019 Nov 6; (32)	Placebo-controlled study	total 60 patients (30 used transdermal CBD)	$p<0.05$	Temporomandibular disorder, Medical University of Silesia	1. EMG masseter muscle activity was significantly decreased in the CBD-group compared to the placebo- group. 2. The pain intensity was significantly decreased in the CBD- group compared to the placebo group.
van den Donk and others, Pain. 2019 Apr;160, (30)	Placebo-controlled study	total 20 patients	$p<0.05$	fibromyalgia	1. CBD did not lead to any improvements in pain score compared to placebo. ($p>0.05$)
Hunter and others,Osteoarthritis and Cartilage Volume 26, Supplement 1, April 2018 (33)	Placebo-controlled study	total 120 patients	$p<0.05$	osteoarthritis	1. The application of CBD gel (ZYN002) did not lead to significant improvement in pain scores compared to placebo.
Cunetti and others,Transplant Proc. 2018 Mar (34)	Clinical survey	total 7 patients	not determined	chronic pain following kidney transplantation	1. 2 patients experienced total pain improvement, 4 patients responded partially, 1 patient had no analgesic benefit
Malcom and others, Pediatric Dermatology 2018 35 :4 (35)	Case study	total 3 patients	not determined	pediatric patients with epidermolysis bullosa	1. All patients experienced a reduction in their pain scores.
Armour and others, BMC Complement Altern Med. 2019 Jan 15 (39)	Anecdotal, retrospective, open-label study	total 484 complet answers	$p<0.05$	pain due to endometriosis	1. The third of the CBD users couldreduce their endometriosis-related medication with more than 50%. ($p<0.05$)
Palmieri and others, Isr Med Assoc J. 2017 Feb;19 (37)	Anecdotal, retrospective, open-label study	12 patients	$p<0.05$	dysautonomic syndrome after HPV vaccination	1. CBD decreased the pain and improved the social role functioning. ($p<0.02$)
Li and others, Complementary Therapies in Medicine October 2019, (40)	Internet survey through Releaf App	1014 users	$p<0.05$	different pain categories	1. 1. CBD provides neither positive nor negative effects in curing pain. ($p>0.05$)

Conclusion

This review aimed to compare the "myths" about the analgesic potential of CBD to the "facts" based on scientific evidence. Interestingly cannabidiol expresses its analgesic potential mostly through working on Glycine alfa, TRPV1, and 5HT1a receptors and less through the classical cannabinoid receptors. Additional phytocannabinoids - like CBN- may potentiate the pain-relieving effect of CBD. Although many animal studies are correlating with the "myths", human studies are less conclusive.

Based on the preclinical experiments, cannabidiol has the potential ever to be considered as a painkilling remedy. However, there are still many questions to answer regarding the correct dosing, patient population, route of administration, interaction with other medications, etc. In most of the studies, there were no severe side-effects reported, even though cannabidiol has some possible serious adverse effects concerning the reproductive system.

To date, the evidence supporting the analgesic usage of CBD remains scarce. Based on the currently available literature, we cannot support the use of CBD for pain management. Better communication is warranted to correct the current "myths" about CBD.

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