Pain Ther
https://doi.org/10.1007/s40122-019-0114-4

REVIEW

An Update of Current Cannabis-Based Pharmaceuticals in Pain Medicine

Ivan Urits · Matthew Borchart · Morgan Hasegawa · Justin Kochanski · Vwaire Orhurhu · Omar Viswanath

Received: November 16, 2018
© The Author(s) 2019

ABSTRACT

Cannabis users have long reported therapeutic properties of the plant for a variety of conditions, some of which include nausea, emesis, seizures, cancer, neurogenic diseases and pain control. Research has elucidated many cannabinoid pharmacodynamic and pharmacokinetic properties, expanding the potential use of cannabinoids as a medical therapy. Due to the inconsistent delivery and control of the active components involved with smoking, pharmaceutical companies are investigating and prioritizing routes other than smoke inhalation for therapeutic use of cannabinoids. In this relatively new field of pharmaceutical development, ongoing drug development promises great benefit from targeted endocannabinoid receptor agonism. Available in Canada and Europe, nabiximols, a specific extract from the *Cannabis* plant, has demonstrated great benefit in the treatment of pain related to spasticity in multiple sclerosis, cancer and otherwise chronic pain conditions. The cannabidiol oral solution Epidiolex®, which is available in the USA, is indicated for management of refractory epilepsy but may offer therapeutic relief to chronic pain conditions as well. Current investigative drugs, such as those developed by Cara Therapeutics and Zynerba Pharmaceuticals, are synthetic cannabinoids which show promise to specifically target neuropsychiatric conditions and chronic pain symptoms such as neuropathy and allodynia. The objective of this review is to provide clinicians with an update of currently available and promising developmental cannabis pharmaceutical derivatives which may stand to greatly benefit patients with otherwise difficult-to-treat chronic conditions.

Keywords: Cannabidiol; Cannabinoids; Epidiolex; Nabiximols; Tetrahydrocannabinol

Enhanced Digital Features To view enhanced digital features for this article go to: https://doi.org/10.6084/m9.figshare.7619327.

I. Urits (✉) · V. Orhurhu
Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
e-mail: iurits@bidmc.harvard.edu

M. Borchart · M. Hasegawa · J. Kochanski
Creighton University School of Medicine, Phoenix Regional Campus, Phoenix, AZ, USA

O. Viswanath
Valley Anesthesiology and Pain Consultants, Phoenix, AZ, USA

O. Viswanath
Department of Anesthesiology, University of Arizona College of Medicine–Phoenix, Phoenix, AZ, USA

O. Viswanath
Department of Anesthesiology, Creighton University School of Medicine, Omaha, NE, USA

Published online: 05 February 2019

INTRODUCTION

With the progressive worldwide liberalization of cannabis and its pharmaceutical derivatives for medicinal use, healthcare providers' understanding of cannabis efficacy continues to evolve concomitantly. The effects of cannabis and its synthetic variants are due to the presence of cannabinoids, the biologically active components, in the plants and their interaction with cannabinoid receptors. Cannabis is most commonly obtained, both for recreational and medical purposes, from the *Cannabis indica* and *C. sativa* plants (family: Cannabaceae). Both of these plants contain the two most prominent ligands at cannabinoid receptors, namely, tetrahydrocannabinol (THC) and cannabidiol (CBD), but it is believed the proportion of cannabinoid composition differs between these plants [1, 2]. THC and CBD are also the most prominent ligands for the therapeutic use of cannabis [1]. There are two isotypes of cannabinoid (CB) receptors, CB1 and CB2. These isoforms of cannabinoid receptors can be found throughout the human body in various organs and tissues [3]. THC is most often associated with the psychotropic effects of cannabis, and CBD, which lacks these psychotropic effects, is associated more with anti-inflammatory, anti-epileptic and anti-emetic effects, as well as other effects [4–7]. In general, it is believed that *C. indica* tends to carry a higher proportion of CBD and that *C. indica* has a higher proportion of THC, although the proportions of THC to CBD have been noted to vary markedly [2].

Consumption of cannabis can be achieved through a variety of modalities, but the most traditional and common route of consumption is via smoke inhalation. When inhaled as a smoke, the components of cannabis are absorbed in the endothelial lining of the alveoli of the lungs and delivered to the central nervous system [8]. However, the amount of active compounds absorbed through smoke inhalation is highly dependent on the smoking dynamics of the individual user. Consequently, the ability to control or dose cannabinoid delivery via smoke inhalation is problematic [8]. As a result of the variable distribution and control of active components involved with smoking, pharmaceutical companies are investigating and prioritizing routes other than smoke inhalation for the therapeutic use of cannabinoids.

Cannabis users have long reported therapeutic properties of the plant for a variety of conditions, some of which include the treatment of nausea, emesis, seizures, cancer, neurogenic diseases and pain control [9]. Research has elucidated many cannabinoid pharmacodynamic and pharmacokinetic properties, expanding its potential use as a medical therapy [10]. To date, three cannabinoid drugs have been approved by the US Food and Drug Administration. One of these is Epidiolex® (GW Pharmaceuticals, Cambridge, UK), which is also the only plant-derived cannabinoid currently approved in the USA. Epidiolex® is a CBD extract that is used to treat epileptic disorders. GW pharmaceuticals also produces the drug nabiximols (Sativex®), which is a marijuana extract currently approved in the UK to treat neuropathic pain, pain due to spasticity, overactive bladder and other symptoms associated with multiple sclerosis (MS). GW Pharmaceuticals is currently planning to conduct phase three trials for nabiximols in the USA. However, the intersection of cannabis safety, efficacy and therapeutic use with changing public attitudes means that the medical community is entering an unknown era of medical cannabis use. And while there are concerns over the relatively unknown long-term consequences of cannabis use, its use in medical management is surely to continue.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

NABIXIMOLS (SATIVEX®)

Use in Multiple Sclerosis

Nabiximols (Sativex®) is an oromucosal cannabinoid spray approved in Canada and many European countries for use as add-on

therapy to reduce spasticity in patients with MS [11]. It contains a 1:1 ratio of THC:CBD; the THC component acts as a partial agonist of the CB1 and CB2 receptors, while the CBD component acts as an antagonist of these receptors [12]. This addition of CBD to THC has been shown to potentiate the beneficial effects of THC while attenuating some of its adverse effects, and may even reduce the risk of dependence [13–15]. Each spray delivers a dose of 2.7 mg of THC and 2.5 mg of CBD and is to be administered to the buccal mucosa. Patients with MS use a median of eight sprays per day, and it is recommended that the daily dose not exceed 12 sprays [11]. It has been shown that nabiximols is effective at reducing patient-reported MS-related spasticity (MSS) and that it can provide other beneficial effects, such as sleep improvement and reduced urinary incontinence [11, 16, 17]. A 2014 study by Yadav et al. reported nabiximols to be effective as a complementary and alternative medicine (CAM) for controlling the symptoms of MSS [18]. Because of its efficacy on MSS, nabiximols is further under investigation for use in treating other sources of spasticity, such as that in post stroke syndrome [19].

In addition to controlling the spasticity associated with MS, nabiximols has also been shown to reduce MS-related pain. In a monocentric study by Ferre et al., MS patients taking nabiximols reported a significantly lower pain level on the pain numeric rating scale (NRS) at 4 weeks of treatment, which continued to drop after 14 weeks of treatment [20]. Two-thirds of the patients in this study achieved $\geq$ 20% reduction on the Scripps Neurologic Rating Scale after 4 weeks of therapy, although the investigators did note that they could not exclude the possibility that this reduction in pain was due to a reduction in spasticity. A double-blind randomized study by Langford et al. on this subject showed mixed results [21]. One phase of the study showed no significant difference between patients receiving the THC/CBD oromucosal spray and those on placebo, while the other phase found a better response rate on those using the active drug, with a significant change in the pain NRS score favoring the THC/CBD arm. These investigators suggested that because their patient population had long-standing pain (mean > 5 years), they may represent an especially treatment-resistant group, and they also noted that those with a shorter history of neuropathic pain (< 4 years) appeared to respond better [21].

Use in Cancer-Related Pain

Given the apparent efficacy of nabiximols in treating MSS and MS-related pain, nabiximols has also been studied to determine its effects on other etiologies of chronic pain, such as cancer-related chronic pain, which occurs in up to 90% of those with advanced disease [22]. Opioids are a mainstay of treatment for pain in these patients, and alternative therapies are widely sought after to avoid drug-related adverse effects associated with long-term opioid use or pain refractory to opioid therapy. Animal models have shown that cannabinoid receptor agonists can act synergistically with opioids in chronic pain models, leading to THC becoming a subject of interest in the management of these patients [23]. A double-blind, randomized, placebo-controlled study of nabiximols by Lichtman et al. sought to determine whether nabiximols could serve as effective add-on therapy for the management of chronic pain in cancer patients, with their primary endpoint being improvement in daily pain. These investigators found a nonsignificant improvement in daily pain NRS scores in patients receiving nabiximols compared to those on placebo [24]. Despite this, the study did find improvement in some of their secondary endpoints, including improvement in sleep disruption and higher scores on the Patient Satisfaction, Subject Global Impression of Change and Physician Global Impression of Change questionnaires. Interestingly, the study also found that its US participants demonstrated greater improvement on nabiximols than did participants from outside the USA. It was postulated that this difference may have been due to the US participants being on an average of a > 25% lower opioid dose than non-US participants, resulting in a reduced downregulation of opioid receptors in the US participants and, subsequently, in a greater

synergism between opioid and cannabinoid receptors [25]. Other studies of nabiximols for the treatment of cancer-related pain have also failed to find significant improvement in baseline pain scores [25, 26]. However, in the study by Portenoy et al., the secondary endpoint (comparing proportion of responders in the active drug arm vs. placebo arm) did demonstrate that nabiximols had an improved analgesic effect in patients on low- and medium-dose therapy (defined as 1–4 sprays per day and 6–10 sprays per day, respectively). The low-dose nabiximols group in this study demonstrated the greatest analgesic effect, with a 26% improvement in pain compared to baseline, while the high-dose group (defined as 11–16 sprays per day) did not demonstrate significant analgesic effects and was found to have poor tolerability [26]. A common finding in these aforementioned studies is that nabiximols therapy tends to improve sleep in patients with chronic cancer-related pain, suggesting that even if nabiximols does not greatly improve pain scores, it may still provide benefit to patients with chronic pain who experience sleep disturbances [24, 26, 27]. The authors of a recent review concluded that there is modest evidence for the benefit of nabiximols in the treatment of chronic pain and suggested that the decision to add this therapy be a discussion between patient and provider when first- and second-line therapy has failed [28]. Overall, nabiximols appears to have some benefit for patients experiencing chronic cancer-related pain, including mild pain improvement and improved sleep. Sample sizes in the studies currently available tend to be small, so further investigation is required to determine whether the relatively small improvements on the pain scale ratings are significant on a wider scale.

Use in Non-Cancer Related Pain

The use of THC/CBD oromucosal spray has also been considered as treatment for non-cancer-related chronic pain conditions, such as chronic neuropathic pain due to dysfunction or lesion of nerves or spinal cord, inflammation caused by various arthritic conditions and migraine headaches. A study published in 2007 by Nurmikko et al. showed promising results to this end, reporting effective relief of peripheral neuropathic pain when nabiximols was given as an add-on to existing therapy [29]. This study showed that 26% of patients receiving nabiximols therapy experienced a $> 30\%$ improvement of pain on the NRS scores. Sleep and allodynia were also both significantly improved on nabiximols therapy [29]. Subsequent studies have been less conclusive about the positive effects of nabiximols on the management of chronic non-cancer pain, but still reported improved analgesic effects. A 2016 review by Rapid et al. concluded that there is evidence for improved analgesia in THC:CBD oromucosal spray, but long-term effects still need further investigation [30]. These authors note that the evidence is based on moderate-quality studies and recommend that caution be exercised when making decisions about its use in the clinical setting. Other ongoing subjects of investigation include the efficacy of nabiximols in pain caused by rheumatoid arthritis (RA). In a randomized controlled trial (RCT) by Blake et al., investigators demonstrated statistically significant improvements in pain and quality of sleep with the use of nabiximols in patients with RA compared to placebo [31]. These authors note that the suppression of the Disease Activity Score-28 for Rheumatoid Arthritis (DAS28), a measure of inflammation in RA, demonstrates the known effect of THC/CBD in attenuating inflammation. They also explain that the effect of nabiximols on their primary endpoint, the suppression of pain on movement, shows its usefulness in providing peripheral analgesia [31]. In this way, nabiximols can help control RA through two different mechanisms. In another study by Blake et al. aimed at determining the effects of nabiximols on chemotherapy-induced neuropathic pain, improvements in pain were observed in patients on the active drug versus those on placebo [32]. Although the power of the study was low and the results not statistically significant, many patients in the study did experience clinically significant improvement in their pain which the authors suggest warrants further investigation with a larger sample size. The authors of a

recent review concluded that there is evidence for a potential role of nabiximols in the management of chronic pain and noted that its classification as a Schedule 1 drug has made investigation difficult [33]. Further studies are required to establish the efficacy and safety guidelines, but with its relatively safe side effect profile, nabiximols shows promise as adjunctive therapy for patients refractory to other methods of pain management.

Safety

The safety and long-term efficacy of nabiximols have also been a subject of investigation. In general, nabiximols has demonstrated a mild side effect profile. The most commonly reported drug-related adverse effects include dizziness, confusion, dry mouth, headache and fatigue [11, 20, 34, 35]. Most adverse effects have been considered to be mild/moderate in severity, and they are often transient effects that occur during the titration period. It is important to note, however, that cannabis use has less commonly been associated with an increased risk of psychiatric side effects, especially the development of schizophrenia [16]. To examine the safety and efficacy of Sativex® over a longer period of time, Serpell et al. followed patients who had participated in a 6-week parent RCT and agreed to take part in an extension study [35]. The patients in this study continued Sativex® treatment for a mean duration of 334 days, with 59 patients (40% of the original study population) continuing treatment for $>$ 1 year. The investigators found that treatment with nabiximols during this time frame was not associated with increased incidence of adverse effects and that the therapeutic benefit was maintained without the need for an increased dose [35]. Another study by Johnson et al. that also examined the long-term efficacy of THC/CBD spray had a shorter median duration of treatment (25 days), but it followed several subjects for $>$ 1 year and reported similar results of continued efficacy with a steady or decreasing incidence of adverse effects [27]. Overall, considering that nabiximols may provide therapeutic benefit to patients whose pain is poorly controlled by conventional means, and given its generally favorable side effect profile, it has been suggested that nabiximols be considered for use as a third-line agent following poor responsiveness to other regimens [30]. For patients who achieve suboptimal pain control through first-line agents (antidepressants and anticonvulsants) and second-line agents (opioid products), THC/CBD may be a consideration as an additional therapy to provide relief of chronic pain.

PLANT-DERIVED CANNABIDIOL (EPIDIOLEX®)

Cannabidiol (CBD) is a white to pale-yellow crystalline solid purified from the *C. sativa* plant. It is the second-most abundant cannabinoid found in this species, behind THC, and is non-psychoactive agent. While it is considered to be a Schedule I controlled substance by the US Drug Enforcement Administration, it is available for over-the-counter purchase at cannabis dispensaries throughout the USA. In an anonymous, voluntary survey of self-reported CBD users, 62% of responders indicated that they use it to treat a medical condition rather than general well-being [36]. The top conditions for which CBD was used in this cohort were chronic pain, anxiety and depression, with 36% of these users reporting CBD alone was an efficacious intervention in symptom reduction. Under the brand name Epidiolex®, it is prepared as a liquid solution at a concentration of 100 mg/mL CBD for oral intake. The common adverse reactions (those reported by $\geq$ 10% of users) include somnolence, diarrhea, fatigue, decreased appetite and elevated transaminases. Due to potential hepatotoxicity, it is recommended to monitor transaminase levels and consider reducing doses of Epidiolex® in patients on other agents associated with hepatocellular injury [37]. Babalonis et al. demonstrated that the use of CBD, when compared to smoked marijuana, was associated with virtually no signals of abuse-related effects when administered in therapeutic doses [38].

Analgesic Mechanism of Action

There is significant debate on the specific route by which CBD elicits analgesia. While originally thought to function through indirect agonism of supraspinal CB1 and CB2, CBD has since been demonstrated to have direct agonistic activity on many cell-surface receptors, including the serotonin 1A receptor (5-HT_{1A}), the adenosine $A2_A$ receptor and the peroxisome proliferator-activated gamma (PPAR-γ) receptor, all of which are associated with anti-inflammatory pathways [39]. Recent literature has pointed towards the latter as the analgesic pathway of CBD.

In a study by Ward et al., CBD was shown to reduce pain in rats with chemotherapy-induced neuropathic pain (CIPN) [40]. The administration of 5.0 mg/kg CBD prior to paclitaxel therapy significantly reduced the development of thermal and mechanical sensitivity, an effect that was found to be reversible through the administration of WAY100635, a 5-HT_{1A} receptor antagonist. In contrast, the addition of CB1 or CB2 antagonists resulted in no reduction in this analgesic effect. The authors concluded that CBD's mechanism of producing analgesia is related to serotonergic agonism in the rostroventral medulla and that that this action is most likely extrinsic to the cannabinoid receptor pathway [40]. A separate study by Rodriguez-Munoz et al. suggests that supraspinal analgesia is achieved through indirect antagonism of *N*-methyl-D-aspartate acid receptors (NMDAR), resulting in potentiation of opioid analgesic activity [41]. CBD avidly inhibits sigma 1 receptors (σ1R), which, when antagonized, inhibit G-protein-coupled receptor 55 (GPCR55) activation of NMDAR. In another study, the administration of CBD 10 min prior to treatment with opioids resulted in 83.4% of the maximum analgesic effect, compared to 57.8% in the control group receiving opioids alone. These effects were almost completely reversed with administration of a σ1R agonist, suggesting σ1R to be a significant target for CBD [42].

Multiple studies have analyzed the effects of CBD in rats with osteoarthritis (OA) induced by joint injections of monoiodoacetate (MIA). OA is associated with increased rates of movement-associated depolarization of joint afferent fibers. This phenomenon has been re-created successfully with MIA injection, with the subsequent administration of low-dose CBD found to significantly decrease afferent firing and raise pain thresholds in mice with OA. Phillpott et al. suggested that CBD desensitizes the joint afferent fibers responsible for mechanosensitive nociception [43]. This study also showed that CBD treatment of MIA-injected joints attenuated the future development of tactile pain, suggesting a prophylactic role in the progression of OA [43].

One of the well-documented targets of CBD is the transient receptor potential cation channel (TRP) superfamily, the members of which are receptors found in nociceptive fibers. TRPA1 is a specific member of this family that is found on nociceptors that produce calcitonin gene-related protein (CGRP), a potent vasodilator and pro-inflammatory agent. It has been demonstrated that TRPA1 plays a central role in the development of OA, as TRPA1 knockout mice show no response to the administration of MIA, failing to develop joint pain or cartilage damage. Furthermore, wild-type mice treated with a direct TRPA1 inhibitor do not develop characteristic OA symptoms after MIA exposure [44]. A study by Hammel et al. analyzed the effects of CBD on inflammatory markers associated with OA in mice, including CGRP and OX42 (a marker associated with microglial activation) [42]. Pretreatment with transdermal CBD resulted in reduced immunohistologic staining of both markers in spinal cord tissue. With previous studies illustrating the role of TRPA1 in the pathogenesis of OA, Hamel et al. hypothesized that CBD's agonist role results in activation–desensitization of these receptors, decreasing the peripheral inflammatory response to noxious stimuli [42]. In a separate study, Hongbo et al. simulated traumatic spinal injuries in mice, finding that CBD treatment following such injuries reduced CD4 T-cell counts and associated inflammatory marker concentrations in spinal tissue [45]. These rats had significantly decreased thermal sensitivity

when compared to the control rats, suggesting an additional route through which CBD quells the immune response following noxious insult [45].

While still not completely understood, the central and peripheral analgesic effects of CBD have been documented. Its modulation of various supraspinal pathways is thought to be responsible for both the inhibition of descending pain fibers as well as the attenuation of opioid-induced analgesia. Peripherally, CBD actively inhibits pathways responsible for neurogenic inflammation in response to nociceptor activation.

Efficacy in Human Subjects

While there is a large collection of evidence from animal models, the analgesic effects of CBD have not been studied extensively in humans. One randomized, cross-over pilot study by Lynch et al. showed promising results for the use of an oral spray containing CBD and other cannabinoids in the management of CIPN [32]. Using a 0- to 10-point NRS for pain intensity (NRS-PI), these investigators found that active treatment with this oral spray resulted in a statistically significant 2.6 point drop in mean NRS-PI score, compared to the 0.6 drop in the placebo group ($p = 0.001$). The needed number to treat (NNT) is a metric used to compare analgesic effects in a wide range of medications, with tricyclic antidepressants and opioids having the lowest NNT in treating neuropathic pain (2.1 and 2.6, respectively). The oral spray used in this study was found to have a NNT of 5.0, which is comparable to many routine agents used in treating neuropathic pain, including selective serotonin reuptake inhibitors (NNT 5.0) and gabapentin (NNT 6.4) [32]. Further studies are required to assess the efficacy of CBD in the management of neuropathic pain associated with a variety of conditions. Over 30% of patients with OA have associated neuropathic pain, and CBD appears to have both acute analgesic and prophylactic properties against disease progression [43].

CANNABINOID DERIVATIVES UNDER INVESTIGATION

Cara Therapeutics' Cannabinoid Compound CR701

Cannabinoid compound CR701 is a synthetic cannabinoid receptor agonist being investigated by Cara Therapeutics (Stamford, CT, USA). Research has already established cannabinoid receptors as potential targets to manage various conditions, some of which include chemotherapy-induced neuropathy, inflammation and pain [1, 46]. Specifically, Cara Therapeutics is investigating the potential of CR-701 to treat neuropathic pain and its ability to decrease hyperalgesia, a process by which nerve endings are hypersensitized to stimulation, and allodynia, which is the sensation of pain from innocuous stimulation [1].

By restricting its agonistic effects to peripherally located cannabinoid receptors, namely, the CB2 receptors, and by avoiding interaction at the CB1 receptors located in the central nervous system, CR701 may offer a therapeutic option that utilizes the anti-inflammatory and antinociceptive properties of CB2 without any psychotropic side effects [1, 47]. Preliminary studies of the drug have shown that when administered in oral form, there was a substantial decrease in hyperalgesia and allodynia in a rat model, determined by animal response to thermal and tactile stimuli [1]. Likewise, other studies, such as that of Malan et al., suggest synthetic cannabinoid agonists may act synergistically with both opioids and nonsteroidal anti-inflammatory drugs (NSAIDS) in controlling pain, thus potentiating use of smaller opioid and NSAID doses and avoiding adverse side effects associated with their use [7]. Studies aimed at highlighting the safety profile of cannabinoid receptor agonists found that detrimental side effects, of which the most prominent are catalepsy and hypothermia, were only present at supratherapeutic doses of $>$ 3 mg/kg body weight, a dose which was found to be the therapeutic dose [6]. Additionally, studies by Mingyue Zang et al. found that cannabinoids carry the advantage of no found

risk of dependence or tolerance, similar to that found in opiate use [48].

Treatment for neuropathic pain is plagued by inconsistent efficacy and traditional treatments beset with unfavorable side effect profiles. CR701 may not only offer stand-alone therapeutic benefits in controlling the inflammation, nociception, hyperalgesia and allodynia associated with various conditions, but may also be associated with the added benefit of potential synergistic action with several other pre-existing treatment options [1, 46, 47, 49]. These unique properties of CR701 may decrease the necessary dose of traditionally used neuropathic pain medications and subsequently decrease the likelihood of adverse side effects [47]. Although CR701 is still in the preclinical development stage, progress in the preliminary data will be met with both excitement and hopefulness. If the results of continued studies on the efficacy and safety of CR701 replicate those of preliminary studies, there is reason to believe that CR701 may become a suitable option for therapeutic treatment of neuropathic pain.

Zynerba Pharmaceutical's ZYN002 Product

ZYN002 (Zynerba Pharmaceuticals, Devon, PA, USA), a pharmaceutically-produced CBD, is being promoted as a therapeutic option for various neuropsychiatric disorders. The company highlights ZYN002 as being the first and only permeance-enhanced synthetic CBD gel in use for disorders such as fragile X syndrome, adult refractory focal epilepsy and developmental and epileptic encephalopathies [3]. Oral administration of CBD is associated with several pharmacokinetic and pharmacodynamic issues, including first pass metabolism, varying serum levels, and low levels of bioavailability [3]. When applied by gel, ZYN002 is able to deliver increased consistency in plasma levels of CBD, avoid first pass metabolism and increase the bioavailability of active compounds [3, 4]. Additionally, when in the presence of high acidity, CBD has been shown to degrade into THC, a compound that can impose unwanted psychoactive effects, some of which include anxiety and altered conscious perception [3]. By eliminating contact of CBD with a high acidity environment like that found in the stomach, a gel form of CBD diminishes the potential of having those unwanted psychotropic effects and thus decreases any potential compounding of pre-existing neuropsychiatric disorders, all the while maintaining higher levels of active CBD in the system [3, 4]. Zynerba Pharmaceuticals tested their permeance-enhanced gel over the course of a 12-month trial, named the STAR 2 trial, and reported that there was a clinically relevant reduction in the frequency of focal seizures with use of both the 195 mg and 390 mg transdermal gel [4]. Longer term use of the drug was also found to increase the anti-epileptic effects of the drug, and the drug was found to be well tolerated over the 12-month trial [4].

Cannabinoids have long been anecdotally touted as effective anti-epileptic remedies, although it has only been relatively recent that the mechanisms of their anti-epileptic properties have become somewhat elucidated. Several studies have found that CBD, more so than THC, may act as a neuromodulator at CB1 receptors located at the presynaptic terminal, which controls the influx of G-protein voltage-gated calcium channels and enhances pre-synaptic potassium conduction [4, 50]. Action at these particular receptors may play a pivotal role in the neuromodulation of neuronal activity. Prior studies have shown that upregulation of CB1 receptors, together with agonistic activity at CB1 receptors, may have strong anti-epileptic activity [47, 51]. CBD has also been shown to decrease the breakdown of anandamide, a neurotransmitter, an action which appears also to have protective effects against epilepsy [47, 52] Overall, the totality of the effects of CBD on seizure and epileptic conditions is still unknown. However, as political and social attitudes on cannabis and synthetic cannabis changes, further research is surely to reveal further mechanisms and effects.

With the relatively new wave of cannabis products now available, Zynerba Pharmaceutical's novel transdermal gel may improve upon more traditional methods of cannabis administration. Likewise, by working on a synthetic

cannabinoid, methods of processing, production and quality may be enhanced upon from conventional cannabis plant extracts [3]. It is Zynerba Pharmaceuticals hope to improve on the class of synthetic cannabinoids through their innovative route of administration and their production processes. Further studies investigating the efficacy and safety of ZYN002 will need to be published, but if shown to be as efficacious and safe as the preliminary studies seem to suggest, ZYN002 has the potential to be a breakthrough treatment option for various neuropsychiatric disorders.

CONCLUSION

With the shift in legislature in the USA and other countries towards an acceptance of the medicinal use of cannabis, further research has granted us a better understanding of how cannabis may provide therapeutic benefit to patients. Moreover, delineation of the molecular mechanisms by which these benefits are achieved has led to the ongoing development of pharmaceutical derivatives of cannabis which may offer targeted therapeutic benefit without associated adverse effects. Epidiolex® is one such compound, currently available in the USA, which excludes the psychotropic effects of cannabis use via isolation of CBD from the cannabis plant. In this relatively new field of pharmaceutical development, ongoing drug development promises benefit from an approach of targeted endocannabinoid receptor agonism for the management of chronic pain conditions. Despite this, the overall quality and clinical significance of available evidence are limited; thus it is difficult to offer a strong recommendation in favor of the routine clinical use of cannabinoid-based pharmaceuticals until further clinical trials are performed.

ACKNOWLEDGMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Ivan Urits, Matthew Borchart, Morgan Hasegawa, Justin Kochanski, Vwaire Orhurhu and Omar Viswanath have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any non-commercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Kumar RN, Chambers WA, Pertwee RG. Pharmacological actions and therapeutic uses of cannabis and cannabinoids. Anaesthesia. 2001;56:1059–68.
2. Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). Am J Bot. 2004;91:966–75.
3. Pertwee RG. Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. Philos Trans R Soc B Biol Sci. 2012;367:3353–63.
4. Perucca E. Cannabinoids in the treatment of epilepsy: hard evidence at last? J Epilepsy Res. 2017;7:61–76.
5. Klauke AL, Racz I, Pradier B, et al. The cannabinoid CB2 receptor-selective phytocannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain. Eur Neuropsychopharmacol. 2014;24:608–20.

6. Zhang H, Lund DM, Ciccone HA, et al. Peripherally restricted cannabinoid 1 receptor agonist as a novel analgesic in cancer-induced bone pain. Pain. 2018;159:1.

7. Malan TP, Ibrahim MM, Lai J, Vanderah TW, Makriyannis A, Porreca F. CB2 cannabinoid receptor agonists: pain relief without psychoactive effects? Curr Opin Pharmacol. 2003;3:62–7.

8. Huestis MA. NIH public access. Chem Biodivers. 2009;4:1770–804.

9. Bajic D, Monory K, Conrad A, et al. Cannabinoid receptor type 1 in the brain regulates the affective component of visceral pain in mice. Neuroscience. 2018;384:397–405.

10. Mouhamed Y, Vishnyakov A, Qorri B, et al. Therapeutic potential of medicinal marijuana: an educational primer for health care professionals. Drug Healthc Patient Saf. 2018;10:45–66.

11. Vermersch P, Trojano M. Tetrahydrocannabinol: cannabidiol oromucosal spray for multiple sclerosis-related resistant spasticity in daily practice. Eur Neurol. 2016;76:216–26.

12. Medicines and Healthcare Products Regulatory Agency (MHRA). Sativex oromucosal spray. Public Assess Rep. 2010;1:1–129.

13. Hayakawa K, Mishima K, Hazekawa M, et al. Cannabidiol potentiates pharmacological effects of Δ9-tetrahydrocannabinol via CB1 receptor-dependent mechanism. Brain Res. 2008;1188:157–64.

14. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2005;66:234–46.

15. Todd SM, Arnold JC. Neural correlates of interactions between cannabidiol and Δ9-tetrahydrocannabinol in mice: implications for medical cannabis. Br J Pharmacol. 2016;173:53–65.

16. Rice J, Cameron M. Cannabinoids for treatment of MS symptoms: state of the evidence. Curr Neurol Neurosci Rep. 2018;18:50.

17. Nielsen S, Germanos R, Weier M, et al. The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews. Curr Neurol Neurosci Rep. 2018;18:8.

18. Yadav V, Bever C, Bowen J, et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82:1083–92.

19. Marinelli L, Balestrino M, Mori L, et al. A randomised controlled cross-over double-blind pilot study protocol on THC:CBD oromucosal spray efficacy as an add-on therapy for post-stroke spasticity. BMJ Open. 2017;7:1–6.

20. Ferrè L, Nuara A, Pavan G, et al. Efficacy and safety of nabiximols (Sativex®) on multiple sclerosis spasticity in a real-life Italian monocentric study. Neurol Sci. 2016;37:235–42.

21. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260:984–97.

22. Mercadante S, Portenoy RK. Breakthrough cancer pain. Pain. 2016;157:2657–63.

23. Smith FL, Cichewicz D, Martin ZL, Welch SP. The enhancement of morphine antinociception in mice by Δ9-tetrahydrocannabinol. Pharmacol Biochem Behav. 1998;60:559–66.

24. Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as a adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. J Pain Symptom Manage. 2017;55(2):179–188.e1.

25. Fallon MT, Albert Lux E, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. Br J Pain. 2017;11:119–33.

26. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13:438–49.

27. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manag. 2013;46:207–18.

28. Serafimovska T, Arsova-Sarafinovska Z, Stefanoski S, et al. Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients with malignant diseases. J Pain Res. 2018;11:837–42.

29. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a

randomised, double-blind, placebo-controlled clinical trial. Pain. 2007;133:210–20.

30. Canadian Agency for Drugs and Technologies in Health (CADTH). Cannabinoid buccal spray for chronic non-cancer or neuropathic pain: a review of clinical effectiveness, safety, and guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2016. https://www.ncbi.nlm.nih.gov/pubmed/27831665.

31. 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 (Oxford). 2006;45:50–2.

32. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manag. 2014;47:166–73.

33. Blake A, Wan BA, Malek L, et al. A selective review of medical cannabis in cancer pain management. Ann Palliat Med. 2017;6:215–22.

34. Russo M, Naro A, Leo A, et al. Evaluating Sativex® in neuropathic pain management: a clinical and neurophysiological assessment in multiple sclerosis. Pain Med (United States). 2016;17:1145–54.

35. Serpell MG, Notcutt W, Collin C. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. J Neurol. 2013;260:285–95.

36. Corroon J, Phillips JA. A cross-sectional study of cannabidiol users. Cannabis Cannabinoid Res. 2018;3:152–61.

37. Greenwich Biosciences, Inc. EPIDIOLEX® (cannabidiol) oral solution. Highlights of prescribing information. 2018. Carlsbad: Greenwich Biosciences, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf.

38. Babalonis S, Haney M, Malcolm RJ, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. Drug Alcohol Depend. 2017;172:9–13.

39. Welty TE, Luebke A, Gidal BE. Cannabidiol: promise and pitfalls. Epilepsy Curr. 2014;14:250–2.

40. Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT 1A receptors without diminishing nervous system function or chemotherapy efficacy. Br J Pharmacol. 2014;171:636–45.

41. Rodríguez-Muñoz M, Onetti Y, Cortés-Montero E, Garzón J, Sánchez-Blázquez P. Cannabidiol enhances morphine antinociception, diminishes NMDA-mediated seizures and reduces stroke damage via the sigma 1 receptor. Mol Brain. 2018;11:1–12.

42. Hammell DC, Zhang LP, Ma F, et al. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. Eur J Pain. 2016;20:936–48.

43. Philpott HT, O'Brien M, McDougall JJ. Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. Pain. 2017;158:2442–51.

44. Moilanen LJ, Hämäläinen M, Nummenmaa E, et al. Monosodium iodoacetate-induced inflammation and joint pain are reduced in TRPA1 deficient mice—potential role of TRPA1 in osteoarthritis. Osteoarthr Cartil. 2015;23:2017–26.

45. Li H, Kong W, Chambers CR, et al. The non-psychoactive phytocannabinoid cannabidiol (CBD) attenuates pro-inflammatory mediators, T cell infiltration, and thermal sensitivity following spinal cord injury in mice. Cell Immunol. 2018;329:1–9.

46. Azofeifa A, Mattson ME, Schauer G, McAfee T, Grant A, Lyerla R. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. MMWR Surveill Summ. 2016;65:1–28.

47. Hasin DS. US epidemiology of cannabis use and associated problems. Neuropsychopharmacology. 2017;43:195–212.

48. Zhang M, Dong L, Zou H, et al. Effects of cannabinoid type 2 receptor agonist AM1241 on morphine-induced antinociception, acute and chronic tolerance, and dependence in mice. J Pain. 2018;19(10):1113–29

49. DiNitto DM, Choi NG. Marijuana use among older adults in the USA: user characteristics, patterns of use, and implications for intervention. Int Psychogeriatr. 2011;23:732–41.

50. Friedman D, Devinsky O. Cannabinoids in the treatment of epilepsy. N Engl J Med. 2015;373:1048–58.

51. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085–96.

52. Kloft L. Review: The efficacy of cannabidiol (CBD) as potential antipsychotic medication. Maastricht Student J Psychol Neurosci. 2017;6:1–15.