

The Pharmacology of Cannabinoids in Chronic Pain

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Keywords

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Abstract

Background: Our objective was to provide an overview of the currently available scientific and clinical data supporting the use of *Cannabis* and *Cannabis*-derived products for the treatment of chronic pain disorders. We also provide information for researchers, clinicians, and patients to be better informed and understand the approach behind the recommendation of *Cannabis* as a potential adjuvant in the treatment/control of chronic pain. Cannabis and its bioactive compounds have sparked interest in the field of pain treatment in spite of its controversial history and status as a controlled substance in many countries. With the increase in chronic pain, physicians and patients have started to look at alternative ways to treat pain aside from traditional treatments. One alternative is the use of cannabis to reduce/treat chronic pain disorders based on anecdotal accounts and the function of its phytocannabinoids. The two main cannabinoids in cannabis, tetrahydrocannabinol (THC) and cannabidiol, act on CB1 and CB2 receptors (in addition to several additional receptors). It is through these pleiotropic receptor interactions that

these compounds elicit their biological function including the reduction of chronic pain. In this narrative review, we included the most recent evidence supporting the use of cannabis in the treatment of chronic pain disorders including chronic neuropathic pain, cancer-induced neuropathic pain, chronic musculoskeletal pain, and chronic headaches and migraines.

Summary: Evidence suggests that cannabis and cannabinoids have an analgesic effect that arises from a combination of compounds and various receptor systems. These effects may be maximized with the use of a combination of cannabinoids. At the same time, the combination of cannabinoids helps minimize the undesirable side effects of some cannabinoids such as the psychoactivity of THC. With these findings, further research is necessary to assess the analgesic properties of other cannabinoids like cannabichromene and cannabigerol and their contributions to the reduction of pain.
Key Messages: Cannabis and its bioactive compounds show potential in the reduction of chronic pain.

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Introduction

Chronic pain is one of the most common reasons adults seek medical care and is linked to poor health, reduced quality of life, and increased rates of depression [1, 2]. The 2019 National Health Interview Survey (NHIS) defined chronic pain as pain that lasts more than 3 months and further reported that 20.8% of US adults suffer from chronic pain [3]. The use of *Cannabis sativa* L. as a medicinal remedy dates back thousands of years. In ancient China, cannabis was used to treat gout, malaria, digestive disorders, and menstrual pain [4]. Recent scientific research suggests that cannabis and cannabinoids have antinociceptive properties resulting in numerous ongoing clinical investigations related to cannabinoid effects on pain [1, 5–10]. Moreover, given the complex pharmacodynamics of the cannabinoids, there is a wealth of targets that could contribute to potential analgesia. This narrative review will discuss the pharmacological properties of cannabis and its constituents focusing on the mechanisms by which they may attenuate chronic pain, focusing primarily on literature published within the prior 15 years (following a PubMed search using “cannabis”/“cannabinoids” AND “chronic pain,” “headaches,” “neuropathic pain,” “musculoskeletal pain”).

Chronic pain affects more than 100 million Americans, and it is the most common patient-reported medical reason for seeking medical cannabis, accounting for 62.2% of the total patient-reported qualifying conditions [11]. Pain is considered a warning sign of damage to the body, and it is classified into different types based on the origin of the pain [12]. Nevertheless, pain should not be confused with nociception which is the detection (through specialized receptors) of injurious stimuli followed by a reflex withdrawal or a behavioral response (nocifensive withdrawal) [13]. Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [12]. The IASP expanded the definition of chronic pain as “pain which has persisted beyond normal tissue healing time” which, in the absence of other factors, is generally taken to be 3 months [14–16]. Chronic pain is a complex problem that frequently presents as a result of a disease or an injury; however, according to some clinicians, it is not merely an accompanying symptom, but rather a separate condition [14, 15]. More recently, clinicians have started to divide chronic pain into two divisions: (1) chronic primary pain where pain may be considered a disease in its own right (e.g., fibromyalgia or nonspecific lower back

pain), and (2) chronic secondary pain where pain may be considered a symptom of a separate problem such as in chronic cancer-related pain (both primary cancer pain and pain following treatment), neuropathic pain, visceral pain, posttraumatic pain, postsurgical pain, headache and orofacial pain, and musculoskeletal pain [14, 15]. This distinction was put in place to improve health policy, research, classification, diagnosis, and patient care, thereby advancing the recognition of chronic pain as a health condition [15].

Cannabis and Cannabinoids

Cannabis contains several bioactive compounds that are of pharmaceutical interest for the study of pain and other disorders [5]. These compounds normally fall into 3 classes: terpenes, flavonoids, and cannabinoids (generally unique to the genus *Cannabis* and the focus of this review) [1, 4, 5, 17]. Over 180 different cannabinoids have been isolated from *Cannabis sativa*, the two most abundant and well-studied cannabinoids are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) [5, 17]. THC has been shown to have appetite stimulating and anti-nausea effects, and it is the main cannabinoid responsible for the psychoactive effects of cannabis [17–19]. CBD has been shown to have anti-inflammatory, antioxidant, antiepileptic, anxiolytic, antidepressant, and analgesic properties [17–20]. CBD and THC have a wide potential for therapeutic effects based on their multiple molecular targets including ion channels, receptors, transporters, and enzymes [17–20] (shown in Fig. 1).

Cannabinoids and Their Mechanisms

For much of the five millennia of the documented use of cannabis, the mechanisms of action of cannabinoids were largely unknown. More recently, it was discovered that their effects in the human body are mediated, in part, by the endocannabinoid system (ECS) and its components [17]. The ECS encompasses endocannabinoid molecules (the two best known are N-arachidonylethanolamine [anandamide] and 2-arachidonoylglycerol), their synthesizing enzymes (diacylglycerol lipase and N-acyl-phosphatidylethanolamine-specific phospholipase D) and degrading enzymes (fatty acid amide hydrolase and monoacylglycerol lipase), and the two major cannabinoid receptors (CB1R and CB2R) [17, 18]. Cannabinoid receptor type 1 (CB1R) and cannabinoid receptor type 2 (CB2R) are primary G-protein-coupled receptors that inhibit adenylate cyclase activity and decrease

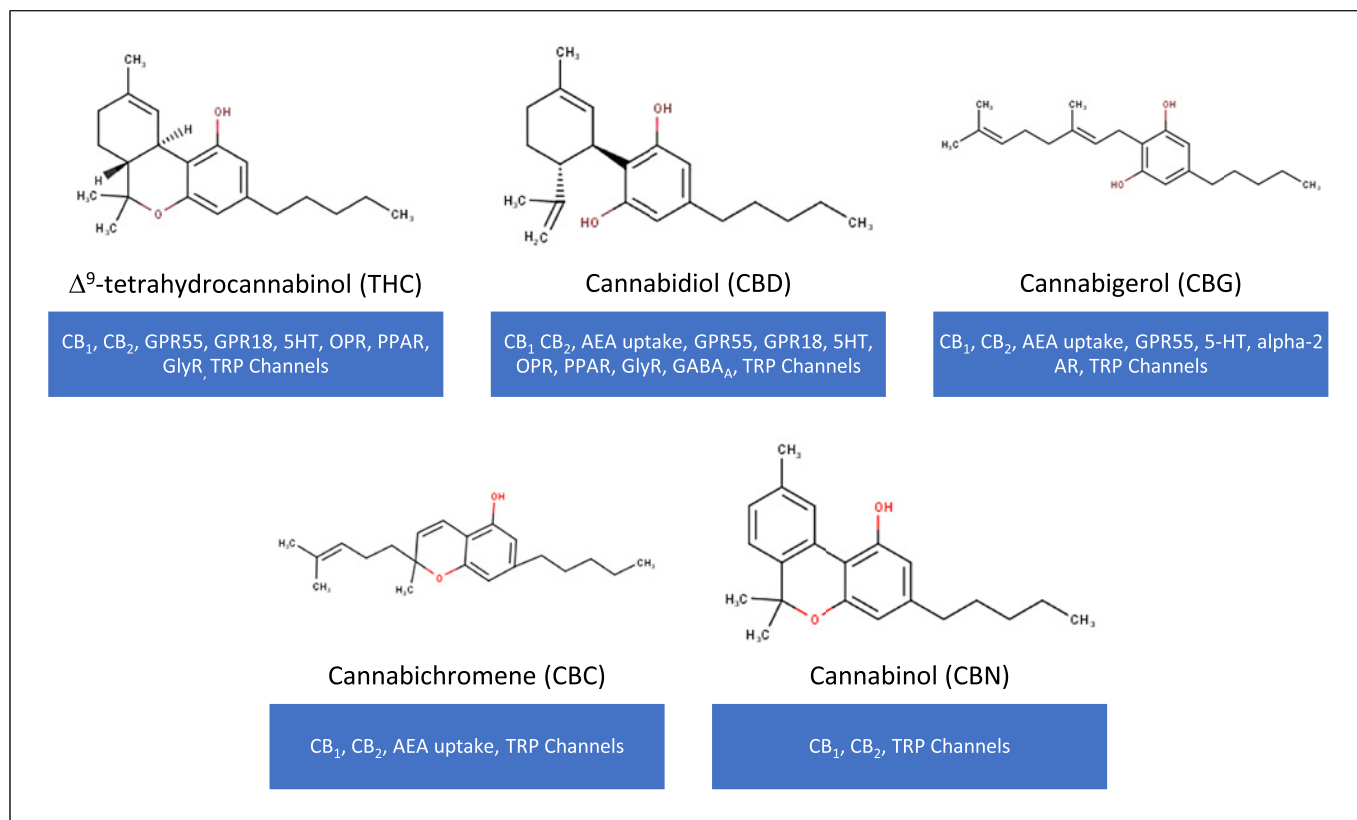


Fig. 1. Phytocannabinoids and their molecular targets. Chemical structures of THC, CBD, CBG, CBC, and CBN. Most cannabinoids interact with CB1 and CB2 receptors, GPR55 and TRP channels but have activities at a variety of other molecular targets [21, 22].

intracellular calcium concentrations, leading to their downstream effects [18, 19, 23]. The CB1 receptor is primarily found in the central nervous system including areas involved in pain modulation, but it is also found, to a lesser extent, in peripheral tissues including the heart, liver, pancreas, muscle, adipose tissue, and the reproductive system [18, 23, 24]. Meanwhile, the CB2 receptor is mainly expressed in the periphery and in immune cells playing a role in inflammation and immunomodulation within the human body [18, 21, 24]. Apart from the cannabinoid receptors, phytocannabinoids interact with a variety of other receptors that might contribute to analgesia. Studies in mouse and rat models suggest that CBD produces an antinociceptive and anti-inflammatory effect via agonistic interactions with spinal cord serotonin (5-HT) type 1A receptors (5-HT_{1A}) [6, 21, 23–25]. This subtype of serotonin receptor acts through G-protein coupling and inhibits adenylyl cyclase. CBD serves as an agonist at α 1-adrenergic receptors, activates peroxisome proliferator-activated receptor gamma (PPAR γ) and transient receptor potential (TRP) channels V1–V3 and A1; however, it inhibits G-protein-coupled receptor 55 (GPR55) and TRPM8

channel [4, 22, 26–28]. In contrast, THC is a full agonist at GPR55/GPR18, PPAR γ , and TRPV2-4/TRPA1 channels while being an antagonist for 5-HT_{3A} and TRPM8 channel and A1 (see Table 1) [4, 18, 22, 24, 26–29]. Anatomical and functional co-localization studies have shown that these receptors are expressed in the same regions as CB1 and CB2 receptors in both the central and peripheral nervous systems [18].

Not all cannabinoids have the same affinity or potency for CB1 and CB2 receptors. The affinity of CB1 and CB2 receptors for THC generally exceeds that of other cannabinoids including CBD [30]. THC is also known to act as a partial agonist of both CB1 and CB2 receptors, presenting a mixed agonist-antagonist profile depending on the cell type, concentration, receptor expression, and presence of other endo- and exocannabinoids [18, 30]. As a result, the high abundance of CB1 receptors in the brain leads to the psychoactive and antinociceptive effects of this exogenous cannabinoid [18, 30]. In contrast, CBD has a lower affinity for CB1 and CB2 receptors and modulates their

Table 1. Pharmacodynamics of phytocannabinoids

Receptor	Δ^9 -THC		CBD	
	affinity, nM	function	affinity, nM	function
CB1	K_i : 5.1–80.3 [4, 17, 30]	Partial agonist [4, 18, 22, 26, 29]	K_i : 1,458.5–4,900 [4, 17, 24, 30]	Negative allosteric modulator [19, 22, 26] Weak antagonist [4, 18, 19, 22, 24]
CB2	K_i : 3.1–75.3 [4, 17, 30]	Partial agonist [4, 18, 22, 26, 29]	K_i : 372.4–4,200 [4, 17, 30]	Inverse agonist [4, 26, 29] Agonist [26] Weak antagonist [18, 19, 22, 30]
GPR55	EC_{50} : 8 [4]	Agonist [4, 22, 26, 29]	IC_{50} : 445 [4, 24]	Inhibitor [26] Antagonist [4, 22, 24]
TRPV	EC_{50}/IC_{50} : V1 – not detected [4, 17] EC_{50} : V2 – 650 [4] EC_{50} : V3 – 9,500 [4] EC_{50} : V4 – 850 [4]	V1 – unknown [4, 18, 22, 29] V2–4 – agonist [18, 22, 26, 29]	EC_{50} : V1 – 1,000 [4, 24] EC_{50} : V2 – 1,250 [4, 24] EC_{50} : V3 – 3,700 [4, 24] EC_{50} : V4 – 800 [4, 24]	V1–4 – agonist [4, 22, 24, 26, 29]
5-HT	EC_{50}/IC_{50} : not tested [4]	1A – unknown [4] 3A – antagonist [22, 26]	EC_{50}/IC_{50} : not detected [4, 24]	1A – agonist [22, 26, 29] 3A – antagonist [22, 26, 27, 29]
PPAR γ	EC_{50} : 21,200 [4, 28]	Agonist [22, 26, 29]	EC_{50} : 2,010 [4, 24, 30]	Agonist [22, 24, 29] Activator [26]

Phytocannabinoids and their affinity for receptors including their function.

activity in an indirect and unexpected manner by acting as an antagonist of both receptors [18, 19, 30, 31]. These studies suggest that CBD can act as a noncompetitive antagonist or even an inverse agonist and this behavior is heavily influenced by the concentration of CBD [18, 19, 30–32]. Recently, it has been proposed that CBD may act as a negative allosteric modulator of CB1 receptors [26]. When used in conjunction with THC, CBD reduces THC's psychoactivity and simultaneously increases clinical efficacy through its own properties [18, 19, 32–34]. Furthermore, CBD also exhibits agonist activity for TRPV1 and GPR55 but acts as an antagonist of GPR19 and Cav2.2 channels, which participate in pain signaling and have an antinociceptive effect [18, 20, 32]. Through the interaction of these receptors, cannabinoids have the potential to provide analgesia through mechanisms including the inhibition of the release of neurotransmitters from presynaptic nerve endings (e.g., glutamate, GABA, and acetylcholine) and the reduction of inflammation (e.g., inhibition of prostaglandin E-2 synthesis) [19, 26, 35, 36]. Considering the many different receptor interactions (the promiscuous nature of cannabinoid receptor binding), there may not be a single dominant signaling pathway at play.

Medical Marijuana and Its History

Marijuana (THC-dominant *Cannabis*) is designated a schedule I substance by the federal government in the USA [37] meaning that there is no accepted medical use. However, this is not the case in numerous other countries and selected sub-jurisdictions (states) in the USA where the medicinal properties of cannabis, especially for pain relief, have been widely recognized [38]. Some examples of Schedule I drugs according to the DEA are heroin, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote. Throughout the 20th century, a series of obstacles restricted the use of cannabis in the USA starting with the Pure Food and Drug Act of 1906 which, for the first time, regulated the labeling of medical preparations containing cannabis [7, 39, 40]. These obstacles also coincided with the decline in use of cannabis due to its variability in effects depending on patients and preparation, an unknown pharmacological profile, the introduction of the first analgesics and anti-inflammatory drugs, including aspirin, and the worry surrounding the uncontrolled use of cannabis for recreational purposes [7, 39, 40]. The first major obstacle was a prohibitionist policy requested by Harry Anslinger (the supervisor of the Federal Bureau of Narcotics) that in 1937 introduced the

Marihuana Tax Act that prescribed the payment of a 1-dollar tax for each business deal regarding cannabis for medical or industrial use and a 100-dollar tax for all other purposes [7, 39, 40]. Cannabis itself was not banned, but its purchase was rendered expensive due to the penalties, and violations were extremely punitive [39, 40]. As a result, experimentation on the medical use of cannabis was discontinued [39]. Dr. William Woodward, from the Medical American Association, opposed the policy and continued to support the pharmacological potential of cannabis in multiple pathological conditions, despite its adverse psychoactive effects [39, 40]. In addition, Fiorello La Guardia, the Mayor of New York, commissioned the New York Academy of Medicine to provide a report later known as “La Guardia Committee” which repudiated the risk of marijuana addiction and its detrimental effects [40]. Nonetheless, in 1941, *Cannabis* was removed from the National Formulary by the US Pharmacopeia and, in 1945, Anslinger forced the American Medical Association to reject the La Guardia report and recommend prohibition of studies on cannabis’ medical use [7, 39, 40]. Due to the popularization and large consumption of cannabis as a recreational drug, the 1961 United Nations Single Convention on Narcotic Drugs placed cannabis under the strictest control regime along with heroin and other substances of abuse [7]. In 1970, as part of the Controlled Substance Act, cannabis and its products were listed under schedule I due to their psychoactive effects, including addictive and abusive potential, making the possession of cannabis illegal in many countries [7, 41].

Despite its status as a controlled substance, scientific research on cannabis did not completely stop but continued in the form of basic research around the world [39, 41]. In 1964, Israeli scientists, Yehiel Gaoni and Raphael Mechoulam, identified for the first time the chemical structure of the most abundant cannabinoid, THC, responsible for the psychoactivity of cannabis [7, 39, 40]. Then, in the 1990s, the discovery of the cannabinoid receptors and the characterization of the ECS renewed the scientific interest in cannabis research and publications focused on the pharmacological properties of phytocannabinoids and the therapeutic value of this plant [39, 40]. In the last 2 decades, scientific efforts by numerous pharmaceutical companies have pursued the development of synthetic drugs able to target the ECS [39, 40] (shown in Table 2). For example, in 1986, dronabinol (synthetic THC) was approved for the management of chemotherapy-induced emesis; later, it received approval for combatting weight loss in HIV/AIDS patients. Epidiolex® (CBD purified from *Cannabis*) has also been approved for intractable pediatric seizure conditions

(Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex). In 2010, nabiximols was approved for various conditions including neuropathic pain, spasticity in multiple sclerosis (MS) (Canada), and cancer-related pain (Canada and Europe) (see Table 2) [17, 41]. Approval of these compounds, and their use in patients, falls under the responsibility of the Food and Drug Administration (FDA) and are available only with a prescription from a licensed medical provider [29, 41]. Even though cannabis is not approved by the FDA, THC-containing medications like Marinol® and Syndros® have been approved for appetite stimulation and treatment of nausea and vomiting in cancer patients [29]. Meanwhile, countries are reviewing and changing their policy on cannabis – allowing its medical use, decriminalization, and even legalization for recreational purposes [39, 40]. Lastly, the 2017 report from the US National Academy of Medicine on the health effects of cannabis and cannabinoids confirmed the limitation of scientific knowledge and recognized three therapeutic uses with substantial evidence of the effectiveness of cannabis and its products: (1) alleviation of chronic pain in adults (cannabis); (2) as antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids); and (3) the improvement in patient-reported MS spasticity symptoms (oral cannabinoids) [7, 9]. In addition, the Agriculture Improvement Act of 2018 (Farm Bill) removed hemp and its derivatives (including CBD derived from hemp) from the Controlled Substance Act as long as the source plant contained no more than 0.3% Δ^9 -THC by dry weight [42]. This change in policy has led to an extensive increase in cannabinoid research specifically in the treatment of pain disorders while also increasing the development of cannabis-derived synthetic products such as Δ^8 - and Δ^{10} -THC with little to no oversight [42].

Cannabis in Chronic Pain

While *Cannabis* has been used medically for thousands of years, interest in cannabis and phytocannabinoids has greatly increased in preceding decades for the management and treatment of medical conditions [17]. The number of disorders for which *Cannabis* has shown therapeutic benefits keeps growing, and with this growth, its medical use has also increased. As of February 2024, 47 states, the District of Columbia, and three territories have legalized cannabis for medical purposes [45]. In order to utilize cannabis for medical purposes, patients must possess a license or certification card from a medical provider which certifies that they have a qualifying

Table 2. List of cannabis-derived products

Name	Regulatory status	Number of clinical trials	Comments	References
Dronabinol (Marinol® and Syndros®) (synthetic THC)	Approved for chemotherapy-induced emesis and weight loss in HIV/AIDS patients	88 [43]	FDA and EMA approved Schedule III substance Side effects include heart palpitations, asthenia, abdominal pain, and amnesia. Rare depersonalization	[8, 17, 41, 43]
Nabilone (Cesamet™) (Synthetic cannabinoid similar to THC)	Approved for chemotherapy-induced emesis and neuropathic pain	8 [43]	FDA and EMA approved Schedule II substance Side effects include orthostatic hypotension, dry mouth, drowsiness/vertigo, euphoria, dyspnea, and headache. Rare psychosis	[1, 17, 41, 43, 44]
Cannabidiol (Epidiolex®) (purified CBD from cannabis)	Approved for severe pediatric seizure conditions (Lennox-Gastaut syndrome or Dravet syndrome)	205 [43]	FDA and EMA approved Side effects include hepatocellular toxicity, decreased appetite, diarrhea, drowsiness, and fatigue	[17, 24, 41, 43]
Nabiximols (Sativex®) (plant extract with equal amounts of THC and CBD)	Approved for neuropathic pain, spasticity in multiple sclerosis (MS) (Canada), and cancer-related pain (Canada and Europe)	8 [43]	EMA approved Side effects include dizziness, fatigue, blurred vision, vertigo, constipation, appetite decrease or increase, and depression Rare palpitations, changes in blood pressure, and hallucinations	[1, 17, 19, 20, 31, 40, 41, 43]
Synthetic products and natural extracts approved by the FDA and/or EMA and the number of clinical trials [43].				

condition (a medical condition recognized by individual states to benefit from cannabis use) [11]. Currently, the most common patient-reported qualifying condition, and the one with the greatest potential for therapeutic use, is the relief of chronic pain [11, 17].

Chronic pain accounts for more than 67% of the total patient-reported qualifying conditions for the use of medical cannabis [11, 46]. It is a common and complex problem that significantly impacts the lifestyle of individuals and our society [14]. Chronic pain is also the leading source of human suffering and disability worldwide and commonly presents as a result of injury or a disease [14, 15]. However, it is its own separate condition and not merely an accompanying symptom of other illnesses. Therefore, chronic pain has both its own classification and medical definition [14]. Chronic pain can be divided into different types or conditions based on its origin, but it can generally be divided into chronic neuropathic pain, cancer-related chronic pain, and chronic musculoskeletal pain.

Chronic Neuropathic Pain

Currently, due to the lack of high-quality clinical evidence, IASP does not endorse the general use of cannabis and cannabinoids for the relief of pain [47]. Yet, current scientific research supports the use of medical cannabis in the treatment of chronic neuropathic pain [1, 5, 8, 19]. Chronic neuropathic pain arises as a direct consequence of a lesion or disease of the somatosensory nervous system [8, 15, 48]. It can result from physical trauma (herniated disc, compression by a tumor), toxin exposure (chemotherapy-induced, alcohol, heavy metals), infection (HIV, herpes zoster), metabolic disease (diabetes, vitamin deficiencies), cancer and cancer treatment (chemotherapy-induced neuropathy), or autoimmune disorders (MS) [1, 49–51] (shown in Fig. 2). This pain is perceived in the innervation area that is somatotopically represented within the damaged nervous system structure and can be spontaneous or induced by sensory stimuli [15]. The symptoms associated with

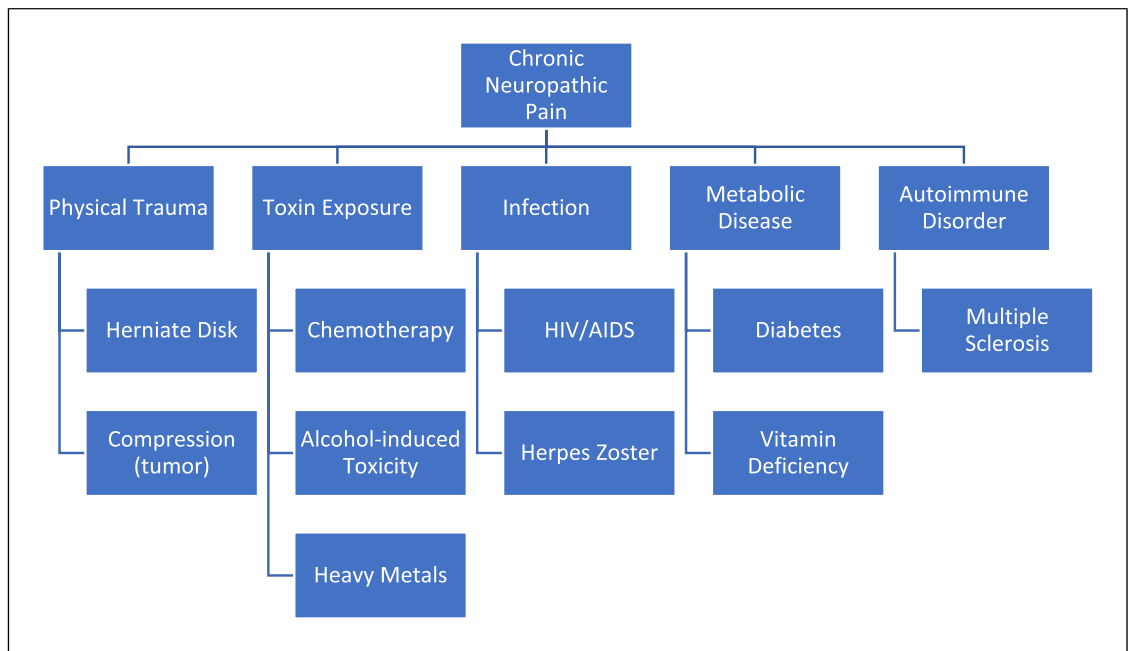


Fig. 2. Causes of chronic neuropathic pain. Neuropathic pain arises from a direct lesion or disease of the somatosensory nervous system. Chronic neuropathic pain can result from physical trauma, toxin exposure, infection, metabolic disease, and/or autoimmune disorders. Adapted from text in [1, 49, 50].

neuropathies (e.g., allodynia, burning pain, electrical-like sensations) can persist and become chronic. At the same time, patients experience sleep disturbances, anxiety and depression, and low quality of life [8, 15]. In the USA, it is estimated that 6–10% of the population suffers from this chronic pain condition, but the actual numbers might be higher as only patients with severe pain seek medical attention [8, 15, 48, 49].

The most common approach to treating chronic neuropathic pain is conservative pharmacological management followed by interventional strategies such as nerve blocks. Pharmaceutical treatment with analgesics (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]), tricyclic antidepressants (amitriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine), calcium channel α_2 - δ ligands (gabapentin and pregabalin), or opioids (tramadol) are often inadequate because they have limited effectiveness, intolerability, or contraindications to other medications (see Table 3) [8, 15, 49, 52–55]. The lack of efficacy of pharmacological treatments can lead to, increasing use, abuse, and dependence, and increased medical provider costs [8]. As a result, new approaches to treat chronic neuropathic pain in patients are needed [8, 15].

The treatment of chronic neuropathic pain remains a challenge for specialists and primary care physicians; as a

result, the study of cannabinoids for the relief of chronic pain has intensified [49]. The two most abundant and studied cannabinoids, THC and CBD, along with an understudied cannabinoid, cannabigerol (CBG), have been shown, in our laboratories, to reduce neuropathic pain in animal models [1, 4, 8, 49]. Cannabinoids suppress neuropathic pain through mainly CB1 and CB2 receptor mechanisms [49, 56]. As mentioned previously, THC is a partial agonist of CB1 and CB2 receptors, and its psychoactive effects are the result of supraspinal activity. On the other hand, CBD has low affinity for CB1, CB2, and TRPV1 receptors, leading to minimal to no psychoactive effects [19, 49]. Compared to THC and CBD, CBG has a distinctive structure and a pharmacological profile resulting in a unique combination of receptor activation. It is a weak agonist of CB1 receptors, a partial agonist of CB2 receptors, an agonist of TRPA1 and TRPV1-4 channels, an antagonist of TRPM8 channels, and an agonist of α_2 adrenergic receptors. Finally, CBG reduces inflammation by inhibiting the enzymes involved in the production of prostaglandins [8]. In recent studies, our own laboratories have also shown the structurally-unique cannabinoid, cannabichromene, also possesses analgesic properties across multiple pain domains in animal models – including chemotherapy-induced neuropathy [57, 58].

Table 3. Neuropathic pain treatment recommendations

Treatment	Recommendations	References
First-line	SNRI – duloxetine, venlafaxine Tricyclic antidepressants Gabapentin, pregabalin Lidocaine plasters	[52–55]
Second-line	Capsaicin 8% patches Lidocaine (lignocaine) patches Tramadol	[52–55]
Third-line	Strong opioids Cannabinoids	[52–55]
Fourth-line	Other strong opioids Cannabinoids	[52–55]

First- through fourth-line treatments recommended for neuropathic pain [52–55]. SNRI, serotonin-norepinephrine re-uptake inhibitor.

Multiple studies and researchers have investigated the recommended cannabinoid dosage required to attenuate pain, but one principle remains: start low and go slow. Basically, guidance suggests starting at a minimal dosing level and increasing that dose in small increments as the benefits depend on the individual, the type of pain, and the cannabis presentation [59]. As a result, the dose of THC required to relieve pain is not completely agreed upon as THC is normally not used by itself for the management of chronic pain and recent data suggest that cannabinoids can work better in combination with each other [1, 17, 19]. For example, Bhaskar et al. [60] developed three treatment protocols denominated as (1) routine protocol, (2) conservative protocol and (3) rapid protocol. The detailed examination of each protocol is beyond the scope of this review, but it is important to point out that the first 2 protocols started patients with increasing doses of CBD until a max dose of 40 mg/day was achieved. After this dose, THC could be added and increased until a max dose of 40 mg/day was reached. The third protocol starts with patients receiving equal and increasing doses of both CBD and THC the 40 mg/day dose of THC is reached. In these protocols, CBD is the primary compound later followed by THC which is never used at its maximum dose recommended without the addition of CBD [59, 60]. Preclinical animal studies have also shown that high doses of THC, in combination with other cannabinoids, can exacerbate pain-like symptoms, whereas low doses are ineffective, suggesting that

THC dose has a small therapeutic window [49]. Nevertheless, dronabinol, an orally administered and synthetically produced THC preparation, has been approved for the treatment of anorexia and weight loss in patients with either HIV/AIDS or chemotherapy-induced nausea and vomiting [17]. CBD has shown pain reduction capabilities alone and in combination with other cannabinoids with low abuse potential [8, 61–65]. In clinical applications, CBD has shown to reduce inflammation, muscle spasms, and seizures. In combination with THC, CBD also helps reduce psychoactive effects by decreasing the levels of 11-OH-THC (a more psychoactive metabolite of THC), serving as a receptor antagonist (or inverse agonist), and attenuating short-term memory loss, anxiety, and appetite [49]. Due to this synergistic effect, THC and CBD can benefit from being administered together. As an example, Sativex® (nabiximols), an oromucosal spray of *Cannabis* plant extract containing THC and CBD at equal amounts (along with other plant constituents), effectively reduced neuropathic pain to nearly the same level as nabilone, an orally administered synthetic cannabinoid similar in structure to THC [1, 17, 44]. In contrast, other studies suggest that while phytocannabinoids may be effective in reducing neuropathic pain, THC only intervention appeared to provide the most relief; in the form of nabilone or a vaporized whole plant (in which non-THC cannabinoid concentrations were less than 1%) [66–68]. Nonetheless, the use of medical cannabis has been associated with about a 20% reduction in pain regardless of the type of pain (including neuropathic pain, non-neuropathic pain, tumor pain, or non-tumor pain) and patients prefer oral preparation with balanced ratios of THC to CBD or with high CBD content [59, 69–71].

Cannabis contains other cannabinoids, like CBG, with distinct analgesic mechanisms apart from cannabinoid receptor activity [49]. In animal studies and in vitro experiments, CBG is a potent agonist at the adrenergic receptor (α_2 AR) reducing pain through neuronal hyperpolarization and decreased norepinephrine release [4, 8, 21, 72]. In addition to this pharmacology, recent studies (in our laboratories) suggest that CBG elicits a portion of its analgesic effects through CB1 and CB2 agonism [4, 8]. It has been found that SR144528, a CB2 selective receptor antagonist, can block CBG-induced antinociception raising the question of whether CBG acts directly as an α_2 ARs agonist to reduce pain or in combination with the blockade of the constitutive activity of CB2 receptors in neuropathy

[8]. Synergistic effects have also been seen with CBG as a recent study showed that the combination of CBG and CBD was more effective than pure CBG at attenuating neuropathic pain in a mouse model [8]. The same study raised a couple of concerns: (1) a small therapeutic window as low doses of CBG can stimulate an inflammatory cascade, while higher doses do not, and (2) the antinociception effect of CBG was not as effective as a CBG-dominant hemp extract (suggesting that there may be other contributing factors) [8, 73]. Future research into cannabinoids like THC, CBD and CBG should focus on the optimal therapeutic doses and the effects these cannabinoids can have on the management of chronic neuropathic pain in humans. A further confound in considering the use of THC-dominant *Cannabis* products (in its many forms) is its euphorogenic psychoactive nature. Is the complex cannabis product actually alleviating, or is it providing anti-anxiety and sedating effects? Future studies will be required to address this important aspect of cannabis use in the neuromodulation of pain.

Cancer-Induced Chronic Neuropathic Pain

Cancer and its life-saving treatments can lead to a multitude of secondary side effects that diminish the quality of life of patients. Chronic cancer-related pain is pain caused by the cancer itself (by the primary tumor or by metastases) or by its treatment (surgery, chemotherapy, and radiotherapy) [15]. One factor that has increased in frequency, in cancer patients and survivors, is chronic neuropathic pain also known as chemotherapy-induced peripheral neuropathy [1, 17]. Cancer-related neuropathic pain can manifest along with additional nociceptive and inflammatory components making it harder to treat with one or a few medications [19]. Reports suggest that cannabinoids can be used as adjuvants to attenuate these complications [19, 74]. When using cannabinoids for cancer-related pain, patients do not typically take cannabinoids in the forms of pure THC or CBD but rather use botanical-derived products that may contain varying ratios of cannabinoids and include other compounds found in *Cannabis*, like terpenes and flavonoids [1]. Human studies have focused on the two primary cannabinoids in the form of nabiximols (Sativex®: equal parts THC and CBD in a complex plant extract) which is approved in Canada and some European countries for the treatment of cancer-related chronic pain (see Table 2) [75–78]. A randomized, placebo-controlled, graded-dose nabiximols trial with advanced cancer pa-

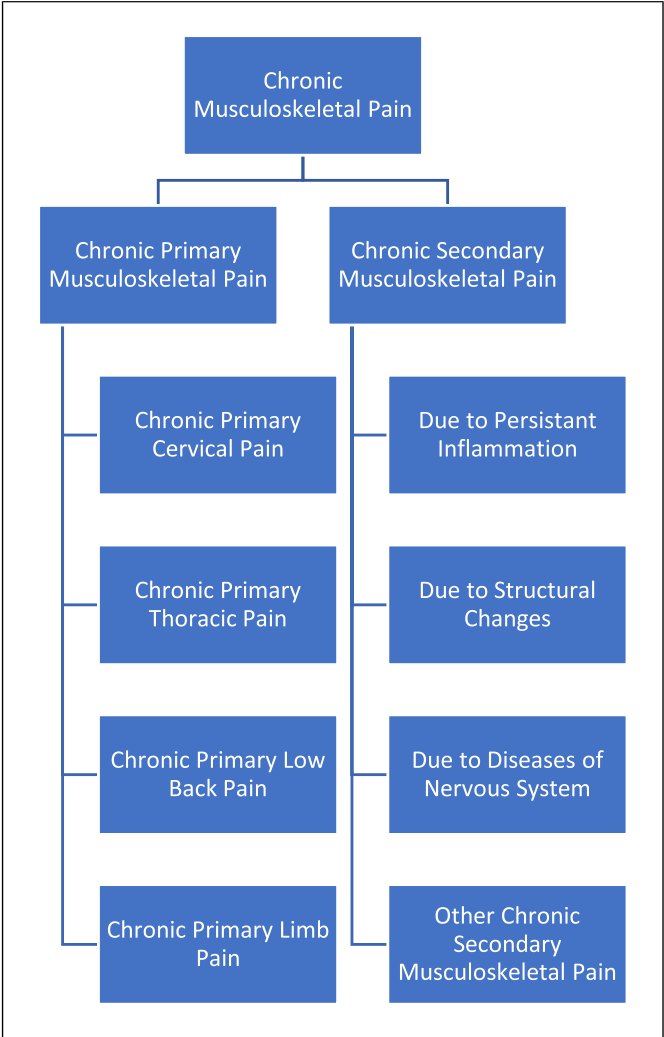


Fig. 3. Classification of chronic musculoskeletal pain. The IASP (International Association for the Study of Pain) divided chronic musculoskeletal pain into two categories: chronic primary musculoskeletal pain and chronic secondary musculoskeletal pain. Primary musculoskeletal pain is considered its own condition (e.g., chronic low back pain). Secondary musculoskeletal pain arises from an underlying condition (e.g., pain associated with Parkinson’s disease or MS). Modified from [15, 81].

tients whose pain was not fully relieved by strong opioids, demonstrated significantly better pain relief and sleep with a THC:CBD oromucosal spray following 35 days of treatment with lower doses (1–4 and 6–10 sprays per day) (each spray delivered 100 µL of solution containing 2.7 mg THC and 2.5 mg CBD) [19, 75]. Our recent studies into the minor cannabinoid CBG have shown that it can attenuate mechanical hypersensitivity, leading to the decrease in chronic neuropathic pain in a neuropathic mouse model of cisplatin-induced peripheral neuropathy

[8, 79]. It also suggested that CBG attenuated chemotherapy-induced mechanical hypersensitivity through α_2 ARs and CB1Rs. Along with these results, a 1:1 mixture of CBG and CBD in a hemp extract was tested resulting in a significantly more effective reduction in mechanical hypersensitivity in neuropathic mice compared to pure CBG [8]. This reduction in mechanical hypersensitivity and chronic treatment with CBG reduced pain sensitivity up to 60–70% of baseline levels and produced significant analgesia 24 h after the last of seven and fourteen daily injections [79]. The design of this experiment used a more translatable approach of pain relief from mice to human conditions; nevertheless, much of the research into CBG is still coming from experiments utilizing murine models and further testing is needed [79].

Chronic Musculoskeletal Pain

Chronic musculoskeletal pain represents the most prevalent set of chronic pain conditions [80]. Chronic musculoskeletal pain is defined as pain arising from musculoskeletal structures such as bones, joints, muscles, or related soft tissues [15, 16, 81]. In the 11th edition of the International Classification of Diseases (ICD-11), the IASP divided chronic musculoskeletal pain into two domains: chronic primary musculoskeletal pain and chronic secondary musculoskeletal pain [16, 81] (shown in Fig. 3). Chronic primary musculoskeletal pain is pain that cannot be attributed directly to a known disease and must be considered as its own condition. It is characterized by significant emotional distress (anxiety, anger, frustration, or depressed mood) and functional disability (interfering in daily life activities). Examples of chronic primary musculoskeletal pain include chronic low back pain, recurrent tension headaches, and migraines [81]. Chronic secondary musculoskeletal pain is characterized as persistent or recurrent pain that arises as part of an underlying disease or condition. It is caused by (1) inflammatory illnesses due to infection, deposits, or autoimmune processes, leading to (2) structural musculoskeletal changes and by (3) diseases of the motor nervous system. Examples include chronic pain associated with Parkinson's disease and MS [15, 81]. The separation of chronic musculoskeletal pain allows for a better understanding of the pathophysiology of the syndrome and can lead to more effective medical treatments and pain management [81].

Chronic back pain is one of the leading causes of disease burden causing moderate to severe interference

with daily activities [82, 83]. The current treatment approaches for chronic back pain are (1) non-pharmacological options (including exercise, rehabilitation, and acupuncture) and, for patients with inadequate responses, (2) pharmacological treatment [83, 84]. The first line of pharmacological treatment is NSAIDs followed closely by opioid analgesics. The limited evidence supporting opioids' long-term effectiveness, along with their various well-documented and undesirable side effects, has increased the interest in alternative treatments for patients with chronic musculoskeletal pain. Medical cannabis can offer a third treatment approach as its mechanisms of action, through the ECS, is independent of the opiate pathway making it more attractive as an adjunct therapy for pain management with the goal of decreasing reliance on opioids [85, 86]. Opioid use for chronic pain including chronic low back pain demonstrated modest improvements in pain perception, physical functioning, and sleep quality; however, these benefits come at a high risk of developing substance use disorders, overdose, and death [87, 88]. Because of this, recent studies investigated the impact of cannabis as an adjunct/alternative treatment to opioid prescription finding that patients diminished their use of opioids and, in some instances, eliminating their use altogether [87, 88]. Patients were guided in their choice of cannabis administration by trained physicians based on medical conditions while one study recommended an oral route of delivery over vaporization. Greis et al. [88] found that the number of filled opioid prescription decreased, there was improvement in pain scores, and that the use of multiple routes of cannabis administration was more effective in replacing opioids. In this study, dosing information was not provided. However, patients did attend a certification visit with an approved practitioner during which the optimal dosing parameters were reviewed and a recommendation of starting with low dosages of THC combined with CBD was made to limit psychoactive side effects. Finally, Takakuwa and coworkers reported that 51% of patients (using a median of 1.4 g of cannabis per day) were able to stop opioid use, while 48% of patients (using 0.64 g of cannabis per day) that did not stop opioids were able to reduce opioid use. These findings clearly support the use of cannabis as an adjunct therapy for the treatment of chronic back pain.

Even with limited evidence, medicinal cannabis is more likely than placebo to produce between a 30% and 50% reduction in pain scores and reduce pain intensity ratings in patients with chronic non-cancer pain and fibromyalgia [82, 89]. In a recent clinical study, Cybis® 10:25, an oromucosal-administered THC and CBD

combination, was first assessed in patients with chronic back or neck pain [82]. It contains 10 mg/mL Δ^9 -THC and 25 mg/mL CBD in medium-chain triglyceride oil. CBD was added to counteract the psychoactive effects of THC and contribute to the analgesic effect [82]. The study found a dose-dependent improvement in pain levels with a 28.8% reduction in pain with the 1.0 mL dose and a 34.1% reduction with the 1.5 mL dose. Researchers also noted a reduction in the levels of depressive symptoms and anxiety with an increase in sleep disturbances but improvement in sleep adequacy with increasing doses. Overall, the study showed Cybis[®] was well tolerated, with reduction in pain and mild to moderate adverse effects [82].

A recent systematic review investigated the efficacy of cannabis to treat non-surgical and surgical back pain. The reviewed reports showed that cannabis is effective in treating back pain with acceptable side effects. The main types of cannabis being used were THC, dronabinol, and nabilone. It also suggested that cannabis could become an alternative over other types of medication or as an adjunct for back pain management; however, long-term follow-up is needed before healthcare providers can confidently recommend cannabis for back pain [85]. The use of cannabis to lessen chronic musculoskeletal pain, like back pain, will increase as the legalization of medicinal and recreational cannabis expands across the country and worldwide.

Chronic Headaches and Migraines

As other alternatives are being explored for the treatment of chronic musculoskeletal pain, medical cannabis demonstrates promising evidence for the treatment of recurrent tension headaches and migraines [90]. A migraine is both a primary disorder and a clinical syndrome that is characterized by nausea and vomiting, photophobia, and phonophobia [90, 91]. In 2016, migraines were the second largest cause of disability in both males and females younger than 50 years with a prevalence of 20.7% in women and 9.7% in men, and the primary cause of years lived with disability [90, 92–94]. It is estimated that migraines affect 1 billion people worldwide and 37 million people in the USA [90, 92, 94]. Headaches associated with a migraine are unilateral and pulsatile and described as a migraine without aura (sensory disturbances that may precede a migraine) [91–93]. A headache associated with aura is a migraine headache with cerebral dysfunction and symptoms including visual, sensory, speech, motor, brainstem, and

retinal manifestations [91]. The first line of treatment for migraines includes acetaminophen (Tylenol[®]), NSAIDs, antiemetics, and serotonin receptor agonists [91, 92, 95]. The effectiveness of these treatment therapies varies from one individual to another leading physicians and patients to pursue alternative remedies including the use of medical cannabis [96–98]. A recent systematic review, published in 2022, synthesized the results from 12 publications including studies of the acute effects of medical cannabis on migraine attacks, as well as studies examining the effects of cannabis as migraine prophylaxis involving almost 2,000 patients and found that medical cannabis significantly reduced nausea and vomiting associated with migraine attacks after 6 months [90]. The review included multiple formulations of cannabinoid products, including oral preparations, inhalational medicinal cannabis, an oral drop formulation, vaporized cannabis flower, as well as edible, topical, and smoked marijuana in varying doses and frequency. In addition, medical cannabis also reduced the number of days of migraines after 30 days, and the frequency of migraine headaches per month. This evidence suggests a potential for cannabis as both prophylactic and abortive treatment for migraines reducing the headache frequency, pain intensity, and the burden of chronic headaches on the population [90]. Even with these benefits, it is necessary to investigate the best route of administration to achieve the optimal dosage to treat adults as low doses can be ineffective and high doses can lead to a reduced analgesic effect [96]. In addition, there is a need for future studies to enroll larger numbers of participants and evaluate the safety and potential to develop tolerance after prolonged use [90].

Potential Entourage Effects of Cannabis

Above, we address the potential interactions of the various cannabinoids (CBG, CBD, THC) and their ability to work together. In addition, *Cannabis sativa* L. produces other compounds like terpenes and flavonoids that could increase the effects of natural extracts over synthetic products, manage side effects of more abundant cannabinoids, and even reduce chronic pain on their own. In a recent study, terpenes including α -terpineol, β -caryophyllene, and γ -terpinene produced a dose-related reversal of mechanical allodynia and thermal analgesia in a mouse model of neuropathic pain adding to the complexity of natural extracts from cannabis [99]. In addition, Schwarz et al. [100] found that terpenes such as geraniol, linalool, β -pinene, α -humulene, and β -

caryophyllene produced antinociception compared to morphine in a murine chemotherapy-induced peripheral neuropathy model of chronic pain and identified the adenosine A2A receptor as the mechanism by which terpenes produce this antinociception. With the identification of up to 40 terpenes in some cannabis strains, their number and concentration may increase the overall therapeutic effect, including analgesia and antinociception, and could be the answer to why people attribute relief from certain symptoms to specific cannabis strains [99, 101]. The interaction between cannabinoids, terpenes, and flavonoids is outside of the scope of this review but requires further exploration.

Risks of Cannabis and Cannabinoids

The use of cannabis and cannabinoids for the treatment of chronic pain disorders and recreational use does not come without risks, as chronic use of high THC products can lead to dependence and cannabis use disorder [102–107] and precipitate drug-drug interactions [108]. Acute intoxication can also lead to anxiety, distorted perceptions (paranoia, hallucinations, delusions), and physical health risks (including cannabis hyperemesis syndrome) [59, 105]. As a result, clinicians and patients are recommended to review/share relevant medical history and consult cannabis interaction resources like Drugs.com and the CANNabinoid Drug Interaction Review (CANN-DIR.psu.edu) [109]. Future research will focus on the mechanisms of cannabis-induced disorders specifically looking at the genetic variability in patients including potential polymorphisms, leading to extreme side effects. Understanding the interactions between multiple cannabinoids in the relief of pain and the side effects mechanisms will enable clinicians to provide confident recommendations for the use of *Cannabis* and cannabis-based products for the treatment of chronic pain.

Conclusions

Cannabis sativa L. has been used as a medicinal remedy for thousands of years. It has gone through multiple periods of acceptance, dismissal/rejection, re-acceptance, illegality and, most recently, rediscovery of its potential to address chronic medical conditions. In the last few decades, its recreational use has received growing acceptance, while its medical use has been encouraged in multiple jurisdictions. Most modern research has focused

on the phytocannabinoids produced by the plant which have been found to help minimize chronic neuropathic pain and mitigate other disorders including seizure conditions (e.g., Lennox-Gastaut and Dravet syndromes) and spasticity in MS. This review has provided scientific evidence supporting the use of cannabis as an adjuvant in the treatment of chronic pain which could also lead pain reduction to the point of minimizing other pharmacological treatments.

Chronic neuropathic pain, chronic musculoskeletal pain (back pain), and neurogenic syndromes (migraines) can be debilitating and resistant to treatment. Current treatment approaches are inadequate producing minimal to no relief from pain in many cases or are accompanied by limiting side effects. Cannabinoids can help suppress chronic pain by interacting with cannabinoid receptors in the central nervous system, PNS, and the generalized ECS. Cannabinoids can be used in combination to lessen the undesirable side effects or increase the analgesic effects of prescription medications. An example of this is the use of CBD to attenuate the psychoactive effects produced by THC. This was seen in the development of both Cybis® and Sativex®. In contrast, other studies have shown that the combination of CBG and CBD is more effective at reducing mechanical hypersensitivity, thus potentially increasing analgesia [8]. Further research is needed with long-term studies and studies including minor cannabinoids like cannabichromene and CBG to investigate their role in the reduction of pain and mitigation of undesirable side effects.

Conflict of Interest Statement

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