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NEUROPATHIC PAIN (E EISENBERG, SECTION EDITOR)

Medical Cannabis for Neuropathic Pain

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Abstract

Purpose of Review Many cultures throughout history have used cannabis to treat a variety of painful ailments. Neuropathic pain is a complicated condition that is challenging to treat with our current medications. Recent scientific discovery has elucidated the intricate role of the endocannabinoid system in the pathophysiology of neuropathic pain. As societal perceptions change, and legislation on medical cannabis relaxes, there is growing interest in the use of medical cannabis for neuropathic pain.

Recent Findings We examined current basic scientific research and data from recent randomized controlled trials (RCTs) evaluating medical cannabis for the treatment of neuropathic pain. These studies involved patients with diverse etiologies of neuropathic pain and included medical cannabis with different THC concentrations and routes of administration. Multiple RCTs demonstrated efficacy of medical cannabis for treating neuropathic pain, with number needed to treat (NNT) values similar to current pharmacotherapies.

Summary Although limited by small sample sizes and short duration of study, the evidence appears to support the safety and efficacy of short-term, low-dose cannabis vaporization and oral mucosal delivery for the treatment of neuropathic pain. The results suggest medical cannabis may be as tolerable and effective as current neuropathic agents; however, more studies are needed to determine the long-term effects of medical cannabis use. Furthermore, continued research to optimize dosing, cannabinoid ratios, and alternate routes of administration may help to refine the therapeutic role of medical cannabis for neuropathic pain.

Keywords Medical marijuana · Neuropathic pain · Cannabis · THC · CBD · Cannabinoid

Introduction

Despite a significant amount of research, the treatment of neuropathic pain remains a major challenge for pain specialists and primary care physicians. In the USA, it has been estimated that 6–10% of the population suffers from pain with neuropathic signs and symptoms [1]. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system [2]. In our experience, many patients continue to experience neuropathic pain symptoms despite adequate trials of analgesics from multiple classes of neuropathic agents. These treatment failures with anti-neuropathic pain agents may be due to lack of analgesic efficacy, intolerance, or contraindications to various classes of medications. Patients with poorly controlled neuropathic pain have significantly poorer health status and increased symptoms of anxiety and depression [3–5]. On a societal level, neuropathic pain is associated with significant societal costs resulting from higher healthcare utilization, disability, and lost productivity [3–5].

Clinically, we have noticed a broad spectrum of symptoms described in patients with neuropathic pain, and similarly varied patient response to the available treatments. There have been many efforts to subtype neuropathic pain in order to predict treatment response based on clinical characteristics of the pain symptoms; however, developing effective, reproducible treatment plans for various neuropathic pain subtypes has proven difficult [6, 7••]. We believe that a highly individualized treatment plan is the cornerstone of neuropathic pain treatment. Thus, we feel it is imperative that physicians treating neuropathic pain have an understanding of pain mechanisms, the efficacy of our standard therapies, and the data behind non-standard therapies on the horizon, including medical cannabis.

This article is part of the Topical Collection on *Neuropathic Pain*

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Mechanisms of Neuropathic Pain

In neuropathic pain states, maladaptive changes occur in response to injury and result in the afferent pain pathways deviating from their normal function of alerting the brain to actual or potential tissue damage [8]. The neuropathic pain syndrome is characterized by (1) an increase in afferent nerve spontaneous activity and (2) an exaggerated or abnormal response of the central or peripheral nervous system to afferent input or stimuli [8]. The initial injury to the central or peripheral nervous system that leads to neuropathic pain can be caused by various insults including physical trauma (herniated disc, compression by a tumor), toxin exposure (chemotherapy, alcohol, heavy metals), infection (HIV, herpes zoster), metabolic abnormalities (diabetes, vitamin deficiencies), and abnormal immune system activation (multiple sclerosis) [8]. Although neuropathic pain is a complex disorder seen in various disease states, there are likely common mechanisms occurring in response to nerve injury may underlie the classic symptoms experienced in patients with neuropathic pain [8].

Increased Ectopic Activity

Patients with neuropathic pain often express sensations of spontaneous pain that indicate activity of nociceptive afferent fibers in the absence of a known stimulus. These ectopic discharges may originate from various points on the injured nerve, including the dorsal root ganglion (DRG), axon, nerve terminals, or neuroma formed after injury [9]. In addition, apparently uninjured nerves in close proximity to the site of injury can generate ectopic discharges as a result of abnormal nerve "cross talk" or ephaptic transmission [10].

In animal models of neuropathic pain, changes in ion channel activity and expression have been reported following afferent pathway nerve injury [11–16]. Increased Na^+ channel and Ca^{++} channel expression and conductance seen at the level of the neuroma and DRG in injured nervous tissue is well documented [11, 14, 16, 17]. An increase of inward Na^+ current, coupled with a hypopolarization due to decreased K^+ ion channel expression, lowers the firing threshold and may be responsible for the ectopic discharges seen following nerve injury [15, 17]. Altered TRPV-1 expression has been demonstrated in injured nerve fibers and surrounding C fibers, which theoretically could lead to depolarization and spontaneous activity triggered by fluctuations within normal ranges of body temperatures [12, 18]. Sympathetic stimulation may induce ectopic signal generation via upregulation of alpha receptors on the injured nerve and post-ganglionic sympathetic nerve sprouting towards the injured axon and DRG [19].

Neuronal Sensitization

Neuropathic pain is further characterized by central and peripheral neuronal sensitization [8]. Symptoms of neuronal sensitization include allodynia, a painful response to a typically non-noxious stimulus, and hyperalgesia, an exaggerated pain response to a normally painful stimulus. Sensitization likely shares similar mechanisms theorized to produce ectopic activity, but additional stimuli and maladaptive changes may occur.

Following nerve injury, inflammatory mediators, including calcitonin-gene related peptide (CGRP) and Substance P lead to increased vascular permeability [8]. This results in localized edema and increased exposure of the nerve environment to prostaglandins, bradykinin, cytokines, and growth factors that are released from the injured nerve terminals and the surrounding cells [8]. Exposure to this inflammatory milieu increases neuronal mechanical and chemical sensitivity to stimuli at the location of injury and in the DRG [8]. In addition, it is hypothesized that exposure to growth factors leads to neuronal sprouting and neuroma formation, which themselves demonstrate decreased stimulation thresholds as described above [20]. Peripheral nerve injury and inflammation also causes activation of glial cells within the spinal cord, which promotes central sensitization and contributes to the maintenance of the neuropathic pain state [8, 20].

Descending Inhibitory Pathways

The role mood, emotional state, and memory associations play in pain perception is well documented. Serotonergic, dopaminergic, noradrenergic, glycinergic, and GABAergic pathways originate in various supra-spinal centers and project to the medullary and spinal dorsal horns where they modulate nociceptive signaling [21, 22]. In chronic pain, dysfunction of these modulatory pathways leads to decreased inhibition, and in some cases, potentiation of nociceptive signaling [13, 21]. Dysfunction of descending pathways is not unique to neuropathic pain; however, the efficacy of antidepressant medications (tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors) in the treatment of neuropathic pain suggests that modulation of these pathways is an important consideration when treating patients experiencing neuropathic pain symptoms.

Treatment of Neuropathic Pain

There is a variety of pharmaceutical options for patients suffering from neuropathic pain symptoms, including, but not limited to anti-depressants, anti-epileptics, and opioids. A meta-analysis of the more commonly used neuropathic pain agents demonstrated a number needed to treat ranging from 3.6 (TCAs) to 7.7 (pregabalin) [23••]. However, as with all medications, both efficacy and side effect profiles must be

taken into consideration when choosing a therapy. The same meta-analysis demonstrated a number needed to harm ranging from 11.7 (strong opioids—oxycodone, morphine) to 25.6 (gabapentin) [23••]. Many of the medications conventionally used to target neuropathic pain symptoms have significant side effect profiles and may be contraindicated in certain subsets of patients with co-existing diseases [22, 23••]. Phytocannabinoids, derived from the flower of the Cannabis plant, as well as their synthetic derivatives have demonstrated exogenous activity within the neuropathic pain pathways previously described [24••]. Historical use of cannabis suggests it may offer a similar efficacy (NNT = 5.6) and comparable or improved side effect profile when compared to our currently accepted therapeutic options [25••].

History of Medicinal Cannabis

The use of cannabis for medicinal purposes dates back over 5000 years. Its use as an analgesic has been documented in the world's oldest pharmacopeia, the Chinese *pen-ts'ao ching,* and cannabis was widely used in Indian Ayurvedic medicine for neuralgia, headache, toothache, and other maladies as early as 1000 B.C [26]. Cannabis was introduced to Western medicine following the 1839 publication of a book titled *On The Preparation of the Indian Hemp, or Gunjah* by William O'Shaughnessy, an Irish physician who had served the British forces in India and experimented with the use of medical cannabis [26]. Following this introduction, cannabis use as medicine became widespread throughout Europe and America in the mid-ninetieth and early twentieth centuries. Pharmaceutical companies marketed various forms of cannabis tinctures and extracts [26]. In the United States Dispensatory as early as 1845, cannabis was noted to be "capable of producing most of the therapeutic effects of opium, and may be employed as a substitute for that narcotic, when found to disagree with a patient from some peculiarity of constitution" [27]. In the early twentieth century, the development of synthetic pharmaceuticals such as opioids, nonsteroidal anti-inflammatory agents, and barbiturates, coupled with increased federal restrictions and taxation of cannabis, led to a significant decrease in cannabis use for most of the rest of the century [26, 28]. The later half of the twentieth century saw the discovery of the endocannabinoid system, subsequent research on the pharmacology of cannabinoids, and growing scientific evidence supporting the efficacy of cannabis for pain. These findings, along with changing social perceptions and the spread of medical marijuana laws, have led to a resurgence of interest in its therapeutic properties.

The Endocannabinoid System

The endocannabinoid system (ECS) has been shown to play an integral role in the regulation of neuropathic pain and operates via multiple mechanisms involving neuromodulation and immunomodulation at peripheral, spinal, and supraspinal levels [24••, 29, 30]. The ECS consists of endogenous cannabinoids, their receptors, and the enzymes responsible for their synthesis, regulation, transport, and metabolism [24••, 29–31]. Three types of cannabinoids are recognized in the literature: phytocannabinoids derived from the cannabis plant, synthetic cannabinoids which are synthetically generated compounds targeting various components of the ECS, and endogenous or *endocannabinoids*, such as anandamide (arachidonoyl ethanolamide, AEA) and 2-arachidonoyl glycerol (2-AG) that are produced by the body [24••, 29–31].

Cannabinoid Receptors

Cannabinoids act on cannabinoid receptors located on neurons in the central and peripheral nervous systems and also act on immune and other nonneural cells located in the brain, spinal cord, and periphery [24••, 30]. The CB1 receptor was discovered in 1988 and is expressed mostly in the brain and is also found on presynaptic terminals of peripheral nociceptors, and neurons in the dorsal root ganglion and spinal cord [24••, 30, 32–34]. It is classified as an inhibitory G-protein coupled receptor and functions via the regulation of adenylate cyclase and mitogen-active protein kinase (MAPK) signaling pathways [24••, 30, 33, 34]. Presynaptic CB1 receptor activation results in the inhibition of calcium influx and the decreased release of the primary neurotransmitter, thereby reducing and/or modulating nociceptive transmission [24••, 30, 33, 34]. The typical neurotransmitters affected are GABA and glutamate; however, acetylcholine, norepinephrine, dopamine, 5-HT and others have been implicated [24••, 30, 33, 34]. CB1 receptor activity at the spinal level is postulated to modulate ascending pathways of the spinal thalamic tract, and to suppress nociception, windup, and central sensitization in the spinal cord dorsal horn [24••, 30, 33, 34]. At the supra-spinal level, CB1 receptor activity regulates pain through the activation of descending inhibitory pathways in the periaqueductal gray and raphe nucleus, and by acting on the limbic system to modulate the integration of the affective component of pain [24••, 35, 36].

The CB2 receptor was discovered in 1992 and is also classified as an inhibitory G-coupled protein receptor [24••, 30, 37, 38]. CB2 receptors are generally found on immune and nonneural cells (macrophages, microglia, and astrocytes), and in tissues with immune function (spleen, tonsils, lung, testes, and brain) [24••, 29, 30, 39, 40]. CB2 receptors function in close conjunction with CB1 receptors to modulate nociceptive transmission at peripheral, spinal, and supraspinal levels [24••, 30, 40]. CB2 receptor activation decreases the release of pro-inflammatory cytokines (interleukins, interferon gamma and tumor necrosis factor alpha), resulting in reduced inflammation, nociception, and hyperalgesia [24••, 30, 33, 40]. Through

a variety of cannabinoid receptor mechanisms and complex interactions, the ECS plays an important role in the physiologic transmission, emotional perception, neuromodulation, and immunomodulation of neuropathic and chronic pain [24••, 29, 30, 33, 34, 37–40].

Animal models have illustrated the intricate roles CB1 and CB2 receptors have in the development of neuropathic pain states. Studies in mice have shown that the selective deletion of peripheral CB1 receptors enhanced neuropathic pain and reduced the analgesic effects of systemic cannabinoids [24••, 41]. Interestingly, the global deletion of CB1 receptor enhanced anxiety-like and depression-like behavior, implicating a role of the CB1 receptor in modulating the affective component of pain [24••, 35, 42]. Global CB2 receptor suppression enhanced the manifestations of neuropathic pain in animal models, while the overexpression of CB2 receptor in the CNS reduced the manifestations of neuropathic pain [24••, 39]. Furthermore, increased CB2 receptor expression has been demonstrated in response to immune cell activation and peripheral nerve injury [24••, 39, 43].

Endocannabinoids

Endocannabinoids are naturally occurring lipid transmitters produced by the body that bind to central and peripherally located cannabinoid receptors [30, 31]. They are generated from the cleavage of post-synaptic membrane phospholipid precursors in an "on demand" and "activity dependent" manner and act on presynaptic CB1 receptors via a retrograde signaling mechanism [24••, 30, 31]. Anandamide (AEA), mean *bliss* in Sanskrit, is a human endocannabinoid that acts on CB1, CB2, and TRPV1 receptors [24••, 30, 31, 44]. It is found in greatest amounts in the brain and purported to play a role in the regulation of sleep, relaxation, feeding, memory, neuroprotection, and immunomodulation [24••, 30, 31, 33, 34, 44]. 2-arachidonoyl glycerol (2-AG) is synthesized from diacylglycerol and acts via retrograde signaling on presynaptic CB1 receptors to reduce calcium influx and inhibit neurotransmitter release [24••, 30, 31, 34]. AEA is degraded rapidly by fatty acid amide hydrolase (FAAH) located in post-synaptic neurons, and 2-AG is degraded by presynaptic monoacylglycerol lipase (MAGL) [24••, 30, 31, 34]. Both FAAH and MAGL have generated interest as potential targets for pharmaceutical therapies [29].

Phytocannabinoids

Over 100 phytocannabinoids have been found in the cannabis plant, many of which contain analgesic properties including delta-9 tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol, cannabigerol, and others [24••, 30, 33, 34]. THC and CBD are the most abundant phytocannabinoids and the most studied [24••, 30, 33, 34]. THC is the main psychoactive component of cannabis, and CBD is minimally psychoactive [24••, 30, 33, 34]. THC is a partial agonist of CB1 and CB2 receptor, and its psychoactive effects are likely the result of supraspinal activity [24••, 30, 33, 34]. CBD has low affinity for CB1, CB2, and TRPV1 receptors and also regulates AEA reuptake and metabolism [24••, 30, 33, 34]. Clinical reports suggest CBD may reduce inflammation, muscle spasm, and seizures, as well as reduce the psychoactive effects of THC and attenuate the effects of THC on short-term memory, anxiety, and appetite [24••, 30, 33, 45]. CBD reduces levels of 11-OH-THC (a more potent psychoactive metabolite of THC) which may account for this attenuation effect of CBD on THC [46]. These properties suggest CBD is an important modulator of the clinical and pharmacologic effects of THC and the ECS and have generated significant interest in the medical community [29, 33, 34, 46].

The plasma level of THC required to relieve pain is unknown. Animal studies show that high dose THC produces aversion behavior whereas lower doses produce preference behavior. Human cannabis smokers also report opposing effects suggesting a therapeutic window [47, 48]. Human studies also suggest this therapeutic window as a healthy volunteer study using experimental pain showed that a medium dose of inhaled cannabis reduced pain whereas a high dose increased pain [49]. These same observations were made in clinical studies using a sublingual spray consisting of a THC:CBD extract in cancer pain. The primary efficacy endpoint was met with the low and medium dose but not the high dose [50]. Overall, these studies show that THC should be carefully dosed as higher doses can lead to worsening of pain.

In addition to THC and CBD, Cannabis contains other phytocannabinoids such as cannabinol and cannabigerol, and compounds like terpenes that have demonstrated analgesic properties [29, 30, 33, 34, 51]. To make matters more complex, cannabinoids have been described to have analgesic mechanisms beyond cannabinoid receptor activity, such as cross reactivity with opioid receptors and NMDA modulation [29, 33, 52]. A great deal of our understanding of the ECS and its role in pain modulation has developed from the study of synthetic cannabinoids, a field that is of growing interest and may result in significant clinical applications in the near future. However, this article will focus on the role of plant-derived medical cannabis and cannabis-based medicinal extracts in the treatment of neuropathic pain.

Clinical Data

Inhaled Cannabis

A small number of randomized controlled trials (RCTs) performed in the mid to late 2000s evaluated the effectiveness of inhaled cannabis for treating neuropathic pain and generally

yielded favorable results (Table 1). In 2007, a prospective, randomized placebo controlled trial in 50 patients demonstrated efficacy of smoked cannabis cigarettes for reducing chronic neuropathic pain from HIV-associated peripheral neuropathy [53]. Cannabis cigarettes containing 3.56% THC were smoked three times daily for 5 days, and patients reported a 34% reduction in daily pain, with 52% of patients reporting > 30% reduction in pain, which is the generally accepted minimum pain reduction to be considered clinically significant in studies [53]. These results were substantiated in 2009 in a phase II, double-blinded, placebo-controlled, crossover trial of analgesia with smoked cannabis in patients with HIV-associated distal sensory predominant polyneuropathy [54]. Twenty-eight patients completed the trial and reported significant reduction of pain intensity with cannabis of various potency (1–8% THC), with 46% of patients reporting > 30% reduction in pain vs 18% for placebo [54]. In a study evaluating the efficacy of cannabis for central and peripheral neuropathic pain, 38 patients smoked placebo, 3.5% or 7% THC in 3, 6-h sessions [55]. Both doses of cannabis demonstrated equianalgesia and superiority over placebo [55]. Ware et al. studied the efficacy of cannabis smoked short-term in a randomized placebo controlled trial involving 21 Canadian patients with greater than 3 months of post-traumatic or post-surgical neuropathic pain [56]. They demonstrated significantly lower mean daily pain intensity scores and improved sleep in the high dose (9.4%) cannabis treatment group over placebo [56]. Although these studies primarily evaluated the short-term use of the medical cannabis, the investigators generally concluded that inhaled cannabis was well tolerated with mild to moderate adverse effects [53–56].

Over the last 5 years there has been a growing popularity of cannabis vaporization devices which heat the plant material to a temperature that releases the active cannabinoids without producing many of the harmful compounds associated with carbon combustion. In 2010, Abrams et al. demonstrated reduced carbon monoxide levels with vaporized cannabis compared to a standard cannabis cigarette in 18 patients and concluded that vaporization was a safe and effective mode of THC delivery [60••]. Three years later, vaporized cannabis (1.29 and 3.53% THC) was used in a double-blinded, randomized placebo controlled, crossover trial in 39 patients with central and peripheral etiologies of neuropathic pain [57••]. Greater than 30% reduction was achieved in 57% of the low-dose group and 61% of the high-dose group, both results being statistically significant, and a NNT of 3.2 and 2.9 was generated for the low- and high-dose groups, respectively [57••]. The same researchers followed this investigation in 2016 with a randomized, placebo-controlled crossover study evaluating short-term use of vaporized cannabis in 42 patients with neuropathic pain from spinal cord injury [58]. They demonstrated analgesic benefit and reported NNT of 4 for the low dose vs placebo and 3 for the high dose vs placebo [58]. In a study of vaporized cannabis for diabetic peripheral neuropathy, Wallace et al. demonstrated efficacy at low, medium, and high doses (1%, 4%, 7% THC) compared to placebo in a randomized, double-blinded, placebo controlled crossover trial of 16 patients [59••]. They reported a significant dose-dependent reduction in spontaneous pain scores after a single dosing session of vaporized cannabis [59••].

Similar to the data from RCTs evaluating smoked cannabis, the authors of these studies of vaporized cannabis reported that it was generally well tolerated with minimal adverse reactions [57••, 58, 59••, 60••]. These studies also concluded that vaporized cannabis delivery is safe, effective, and can be easily titrated to target effect [57••, 58, 59••, 60••]. However, all of these studies evaluated daily-inhaled cannabis only for a short duration (weeks), and clinical trials examining the risks associated with long-term medical use are currently lacking. Interestingly, many of the studies demonstrated analgesic efficacy of low dose of THC that was comparable to higher doses. Given this information, if one were to recommend medical cannabis to a patient, it may be prudent to start with lower concentrations of THC to avoid potential adverse psychoactive effects. For comparison, the concentrations of THC found in cannabis available at many medical marijuana dispensaries can be up to 2.5 times higher than the concentrations evaluated in these RCTs. Lastly, these RCTs primarily evaluated THC-dominant cannabis strains and did not evaluate strains with significant concentrations of CBD. Some hybrid and CBD-dominant strains have been reported to have analgesic benefit with fewer adverse psychoactive effects compared to THC-dominant strains and are becoming more available to consumers and patients.

Cannabis-Based Medicinal Extracts

As research and clinical experience continue to support the analgesic properties of cannabis, concurrent interest in identifying and isolating the major components responsible for its observed effects has increased. The two major components of cannabis, THC and CBD, are available as extracts in their isolated forms, or in a combination form with varying ratios of THC:CBD. In our experience, these extracts are typically administered as an oromucosal solution, as favorable pharmacokinetics for this route of administration provide a short time to onset and may thus offer ease of titration to medication effect.

Initial efficacy studies performed in Europe comparing THC, CBD, and THC:CBD (1:1) extracts to placebo demonstrated significant reductions in mean pain severity scores and improvement in sleep measures in patients with neuropathic pain due to various etiologies including MS, spinal cord injury, brachial plexus injury, unilateral peripheral nerve injury, post-herpetic neuralgia, and complex regional pain syndrome (CRPS) type II [61, 62•, 63•, 64•]. These randomized, double-

Table 1 Summary of randomized, double-blinded, controlled trials evaluating the efficacy and side effect profile of short-term medical cannabis for neuropathic pain

Study	Number of subjects Etiology of neuropathic pain	Control	Intervention	Duration of treatment	Results	Authors' conclusions
Abrams et al. [53]	50 Painful HIV associated sensory polyneuropathy	Smoked placebo cannabis with cannabinoids extracted	Smoked cannabis, 3.56% THC TID	5 days	Active groups when compared to placebo • Reduction in daily pain score* • Greater percentage of subjects with ≥30% reduction in pain intensity compared to baseline* • Reduction in experimentally induced hyperalgesia to brush and von Frey hair stimulation* • No difference in evoked pain using heat pain thresholds	Smoked cannabis was well tolerated and effective. The findings are comparable to oral drugs used for chronic pain [53].
Ellis et al. [54]	28 Painful HIV associated sensory polyneuropathy	Smoked placebo cannabis with cannabinoids extracted	Smoked cannabis, 1–8% THC 4 times daily for 5 day intervals. Dose self-titrated on day 1 of cycle to target dose of greatest analgesic effect without significant adverse effects (crossover)	One 5 day active period (1 week wash in, 5 days active dose or placebo, 2 weeks wash out, 5 days active dose or placebo, 2 weeks wash out)	Active group when compared to placebo: • Reduction in daily pain score* • Greater percentage of subjects with ≥30% reduction in pain intensity compared to baseline* • No difference in mood and daily functioning	Smoked cannabis was generally well tolerated and effective when added to concomitant analgesic therapy.
Wilsey et al. [55]	38 Central and peripheral neuropathic pain (CRPS type I, spinal cord injury, peripheral neuropathy, nerve injury)	Smoked placebo cannabis with cannabinoids extracted	Smoked cannabis, (9 cued puffs) low dose (3.5%) or high dose (7%) THC (crossover)	Three, 6 h experimental sessions	Active groups when compared to placebo: • Reduction in daily pain score* • Reduction in pain unpleasantness* • Increase in global impression of change* • Reduction in neuropathic pain scale score* • Decreased neuropsychological performance* • Increased psychoactive effect* • No difference in evoked pain using heat pain thresholds	Cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs. The use of marijuana as medicine may be limited by its method of administration (smoking) and modest acute cognitive effects, particularly at higher doses [55].
Ware et al. [56]	21 Post-traumatic or post-surgical neuropathic pain	Smoked placebo cannabis with cannabinoids extracted	Smoked cannabis, 25 mg of 2.5%, 6%, or 9.4% THC TID (crossover)	Three 5 day active periods (5 days active dose #1 or placebo, 9 day washout period, 5 days active dose #2 or placebo, 9 day washout period, 5 days active dose #3 or placebo, 9 day washout)	9.4% THC group when compared to placebo: • Reduction in pain score* • Improved ability to fall asleep* • Increased drowsiness*	A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated [56].
Wilsey et al. [57••]	39 Central and peripheral neuropathic pain (CRPS 1, CRPS 2, diabetic	Inhalation of vaporized placebo cannabis	Vaporized cannabis, low dose (1.29%) or medium dose (3.53%) THC. 4	Three 6 h sessions	Active groups when compared to placebo:	The analgesia obtained from a low dose of delta-9-tetrahydrocannabinol

Table 1 (continued)

Study	Number of subjects Etiology of neuropathic pain	Control	Intervention	Duration of treatment	Results	Authors' conclusions
	neuropathy, idiopathic peripheral neuropathy, post-herpetic neuralgia, brachial plexopathy, lumbosacral radiculopathy, central neuropathic pain, spinal cord injury, MS, thalamic pain)	with cannabinoids extracted	cued puffs, followed by 4–8 cued puffs 2 h later, titrated by subject (crossover)		• Reduction in daily pain score* • Reduction in pain unpleasantness* • Increase in global impression of change* • Reduction in neuropathic pain scale score* • Decreased neuropsychological performance* • Increased psychoactive effect* • No difference in evoked pain using heat pain thresholds when compared to placebo.	(1.29%) in patients is a clinically significant outcome. In general, the effect sizes on cognitive testing were consistent with this minimal dose. As a result, one might not anticipate a significant impact on daily functioning [57••].
Wilsey et al. [58]	42 Spinal cord injury	Inhalation of vaporized placebo cannabis with cannabinoids extracted	Vaporized cannabis, 2.9% or 6.7% THC. 4 cued puffs, followed by 4–8 cued puffs 3 h later, titrated by subject (crossover)	Three 8 h sessions	Active groups when compared to placebo: • Reduction in pain intensity* • Increased psychoactive effect*	This study supports consideration of future research that would include longer duration studies over weeks to months to evaluate the efficacy of medical cannabis in patients with central neuropathic pain [58].
Wallace et al. [59••]	16 Painful diabetic peripheral neuropathy	Inhalation of vaporized placebo cannabis with cannabinoids extracted	Vaporized cannabis, 400 mg plant material of low (1%), medium (4%), and high (7%) THC	Four 4 h sessions	Active groups when compared to placebo: • Dose dependent reduction in spontaneous pain intensity* and subjective psychoactive effects* middle dose and high dose groups when compared to placebo: • Dose dependent reduction in evoked von Frey filament and foam brush pain thresholds* • Dose dependent increase in euphoria* High dose when compared to placebo: • Increased % reduction in spontaneous pain scores* • Increased somnolence*	Inhaled cannabis demonstrated a dose-dependent reduction in diabetic peripheral neuropathy pain in patients with treatment-refractory pain. This adds preliminary evidence to support further research on the efficacy of the cannabinoids in neuropathic pain [59••].

*p value ≤ 0.05

blinded, placebo-controlled trials suggest the efficacy of cannabis-based extracts for the treatment of neuropathic pain symptoms, while demonstrating tolerability in patients whose pain symptoms had been refractory to conventional therapy. The side effect profiles were consistent across the studies and were reported as mild to moderate, with the most common adverse effects (AEs) being gastrointestinal issues, dizziness, and intoxication. The AEs were self-limited and completely resolved upon discontinuation of the medication.

A combination of THC (2.7 mg/spray) and CBD (2.5 mg/spray) oromucosal spray (Nabiximols) has received regulatory approval for multiple sclerosis (MS) induced spasticity in Europe, New Zealand, and Canada [65]. Nabiximols also has regulatory approval in Israel for both MS spasticity and MS neuropathic pain and a Notice of Compliance with Conditions (NOC/c) policy in Canada for MS neuropathic pain and refractory cancer pain [65]. A few studies conducted in the last 5 years evaluated the efficacy of Nabiximols in patients with central pain due to MS and in patients with peripheral neuropathic pain [66•, 67••, 68, 69, 70•, 71]. One study published results of 339 patients with MS and central neuropathic pain who had significant pain symptoms despite conventional therapy who received the THC:CBD extract in conjunction with their previous analgesic regimen. Although there was no significant difference in number of patients achieving a 30% reduction in pain scores between the active and control groups at the end of the initial 14 week trial period, a significant difference in change from baseline pain score and sleep quality in favor of the active group was noted during the randomized withdrawal phase [66•]. Another study evaluated the effect of Nabiximols on 303 patients with peripheral neuropathic pain and allodynia over a 15 week time period and reported a significant difference in sleep quality measures, global impression of change, and number of patients achieving a 30% reduction in pain scores between the active and control groups. However, no significant change in mean pain scores was demonstrated [67••].

Extension studies have been performed to investigate the long-term efficacy of 1:1 THC:CBD oromucousal spray [64•, 68, 69]. An open label 2 year extension trial of patients with MS and refractory central pain (dysesthesias and painful spasticity) and an open label 52 week follow-up of patients with neuropathic pain did not demonstrate evidence of medication tolerance or worsening of adverse effects over the extended study period [64•, 68]. Another study demonstrated similar findings, but in addition, noted that the proportion of patients who reported at least 30% benefit from THC:CBD use increased over the 38 week open-label extension study [69]. This finding may suggest that, like many other medications used for neuropathic pain, a few weeks of consistent use may be needed to achieve maximum benefit.

Of note, the above studies excluded patients with diabetic neuropathy from participation. The few studies of cannabis extract on neuropathic pain due to diabetes mellitus did not find significant benefit over placebo, although one study cited that depression was a major confounding factor in their results [70•, 71].

Data suggests that cannabis-based medical extracts may be a useful adjuvant for some patients with neuropathic pain symptoms. However, the data seems to suggest that cannabis extracts may not be as efficacious as other methods of administration such as inhalation, as discussed above. It is unclear what accounts for this difference, but it may be related to the presence of various other compounds found in inhaled cannabis, including terpenes and phytocannabinoids other than THC and CBD that may be absent from the extract formulations.

Discussion

Nearly 20 years of clinical data supports the short-term use of cannabis for the treatment of neuropathic pain. Over that time about a dozen randomized double-blinded, placebo-controlled trials have demonstrated significant pain relief over placebo with results and tolerability profiles comparable to current pharmacologic therapies (Table 1) [25••, 53–56, 57••, 58, 59••, 60••, 72]. The data includes multiple routes of cannabis administration, different cannabinoid ratios, and patients with diverse etiologies of neuropathic pain, and suggests potential for a wide range of applications of medical cannabis.

We must also remain cautious as most studies only evaluated short-term use and few studies met IMMPACT criteria of greater than 12 weeks administration. As a result, there is currently a lack of evidence on the potential adverse effects of the chronic medical use of cannabis. There is also limited and conflicting data regarding the risks associated with chronic recreational cannabis use in adults [73–75]. It is important that a distinction is made between medical use and recreational use of cannabis, as the latter typically seeks intoxication, and the former involves professional guidance and may result in lower THC consumption. Anecdotally, physician-guided medical cannabis use has generally been well tolerated.

Many cannabis products are commercially available with multiple routes of administration; however, vaporization and oral mucosal delivery have the most clinical evidence supporting their safety and tolerability when used medically. Presumably, many of the extracts available in medical marijuana dispensaries for sublingual and oral mucosal delivery may have pharmacologic profiles similar to trial results; however, none of them are FDA approved and they may not be subject to stringent quality assurance. Furthermore, insufficient regulation of medical cannabis, in general, may predispose consumers to risks not adequately appreciated in RCTs. In addition, current laws force many patients to obtain cannabis from dispensaries, with significant variability in their

medical expertise, and their recommendations to patients of cannabis products and use may or may not be supported by medical evidence. With many states relaxing restrictions on cannabis for medical and recreational use, serious efforts are needed by local, state, and federal government officials to develop adequate quality assurance initiatives to ensure patient safety. Finally, for those physicians who choose to recommend cannabis, we have a responsibility to educate ourselves in order to properly advise patients should they choose to pursue cannabis therapies [76].

Conclusion

Humans have utilized the analgesic benefits of cannabis for millennia, while more recently scientific evidence has implicated the ECS as having an integral role in the pathophysiology of neuropathic pain. Neuropathic pain is challenging to treat, and adverse effects often limit many pharmaceutical options. RCTs conducted over the last two decades have demonstrated efficacy of medical cannabis comparable to current therapies for the treatment of neuropathic pain. This data is limited by small sample sizes and studies of short duration but appears to support the safety and tolerability of cannabis vaporization and oral mucosal delivery. Continued research is needed to assess functional outcomes in addition to reduced pain scores, evaluate long-term tolerability, optimal dosing and alternate routes of administration, and provide education and guidance for physicians.

Compliance with Ethical Standards

Conflict of Interest Gemayel Lee, Brittany Grovey, Tim Furnish, and Mark Wallace declare no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014;155(4):654–62. https://doi.org/10.1016/j.pain2013.11.013. Epub 2013 Nov 26.
2. International Association for the Study of Pain (IASP) reference: IASP. Diagnosis and classification of neuropathic pain. Pain Clin Update. 2010;18(7):1–6.
3. McDermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM. The burden of neuropathic pain: results from a cross-sectional survey. Eur J Pain. 2006;10(2):127–35. https://doi.org/10.1016/j.ejpain.2005.01.014.
4. Schaefer C, Mann R, Sadosky A, Daniel S, Parsons B, Nieshoff E, et al. Burden of illness associated with peripheral and central neuropathic pain among adults seeking treatment in the United States: a patient-centered evaluation. Pain Med. 2014;15(12):2105–19. https://doi.org/10.1111/pme.12502.
5. Schaefer C, Sadosky A, Mann R, Daniel S, Parsons B, Tuchman M, et al. Pain severity and the economic burden of neuropathic pain in the United States: BEAT Neuropathic Pain Observational Study. Clinicoecon Outcomes Res. 2014;6:483–96. https://doi.org/10.2147/CEOR.S63323. eCollection 2014.
6. Attal N, Fermanian C, Fermanian J, Lanteri-Minet M, Alchaar H, Bouhassira D. Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion? Pain. 2008;138(2):343–53. https://doi.org/10.1016/j.pain.2008.01.006.
7. •• Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G, et al. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. Pain. 2017;158(2):261–72. https://doi.org/10.1097/j.pain.0000000000000753. **This study used database analysis of patients with neuropathic pain to identify subgroups of neuropathic pain based on characteristic sensory profiles. The authors hypothesize that these subgroup profiles may be related to pathophysiological mechanisms and maybe useful for subgroup analysis of responders versus non-responders of neuropathic pain therapies in clinical trials.**
8. Yaksh TL, Wiese AJA. Survey of systems involved in nociceptive processing. In: Deer TR, Leong MS, Buvanendran A, Gordin V, Kim PS, Panchal SJ, Ray A, editors. Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches. Berlin: Springer. The American Academy of Pain Medicine Textbook on Pain Management; 2014.
9. Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as the periphery in normal and nerve injured rats. Pain. 1983;17(4):321–39. https://doi.org/10.1016/0304-3959(83)90164-1.
10. Seltzer Z, Devor M. Ephaptic transmission in chronically damaged peripheral nerves. Neurology. 1979;29(7):1061–4. https://doi.org/10.1212/WNL.29.7.1061.
11. Hong S, Morrow TJ, Paulso PE, Isom LL, Wiley JW. Early painful diabetic neuropathy is associated with differential changes in tetrodotoxin-sensitive and –resistant sodium channels in dorsal root ganglion neurons in the rat. J Biol Chem. 2004;279(28):29341–50. https://doi.org/10.1074/jbc.M404167200.
12. Ma W, Zhang Y, Bantel C, Eisenach JC. Medium and large injured dorsal root ganglion cells increase TRPV-1, accompanied by increased alpha2c-adrenoceptor co-expression and functional inhibition by clonidine. Pain. 2005;113(3):386–94. https://doi.org/10.1016/j.pain.2004.11.018.
13. Price TJ, Cervero F, de Koninck Y. Role of cation-chloride-cotransporters (CCC) in pain and hyperalgesia. Curr Top Med Chem. 2005;5(6):547–55. https://doi.org/10.2174/1568026054367629.
14. Thakor DK, Lin A, Matsuka Y, Meyer EM, Ruangsri S, Nishimura I, et al. Increased peripheral nerve excitability and local NaV1.8 mRNA up-regulation in painful neuropathy. Mol Pain. 2009;5:14. https://doi.org/10.1186/1744-8069-5-14.
15. Takeda M, Tsuboi Y, Kitagawa J, Nakagawa K, Iwata K, Matsumoto S. Potassium channels as a potential therapeutic target

for trigeminal neuropathic and inflammatory pain. Mol Pain. 2011;7:5. https://doi.org/10.1186/1744-8069-7-5.

16. Zhou C, Luo ZD. Nerve injury – induced calcium channel alpha-2-delta-1 protein dysregulation leads to increased pre-synaptic excitatory input into deep dorsal horn neurons and neuropathic allodynia. Eur J Pain. 2015;19(9):1267–76. https://doi.org/10.1002/ejp.656.
17. Misawa S, Sakurai K, Shibuya K, Isose S, Kanai K, Ogino J, et al. Neuropathic pain is associated with increased nodal persistent Na(+) currents in human diabetic neuropathy. J Peripher Nerv Syst. 2009;14(4):279–84. https://doi.org/10.1111/j.1529-8027.2009.00239.x.
18. Fischer MJ, Reeh PW. Sensitization to heat through G-protein-coupled receptor pathways in the isolated sciatic mouse nerve. Eur J Neurosci. 2007;25(12):3570–5. https://doi.org/10.1111/j.1460-9568.2007.05582.x.
19. Shinder V, Govrin-Lippmann R, Cohen S, Belenky M, Ilin P, Fried K. Structural basis of sympathetic-sensory coupling in rat and human dorsal root ganglia following peripheral nerve injury. J Neurocytol. 1999;28(9):743–61. https://doi.org/10.1023/A:1007090105840.
20. Vallejo R, Tilley DM, Vogel L, Benyamin R. The role of glia and the immune system in the development and maintenance of neuropathic pain. Pain Pract. 2010;10(3):167–84. https://doi.org/10.1111/j.1533-2500.2010.000367.x.
21. Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. J Clin Invest. 2010;120(11):3779–87. https://doi.org/10.1172/JCI43766.
22. Wakaizumi K, Kondo T, Hamada Y, Narita M, Kawabe R, Narita H. Involvement of mesolimbic dopaminergic network in neuropathic pain relief by treadmill exercise: a study for specific neural control with Gi-DREADD in mice. Mol Pain. 2016;12. Print 2016.
23.•• Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162–73. https://doi.org/10.1016/S1474-4422(14)70251-0. **A meta-analysis of 229 RCTs evaluated the efficacy of many of the accepted treatments for neuropathic pain calculating NNT, NNH and GRADE recommendation for each therapy.**
24.•• Maldonado R, Baños JE, Cabañero D. The endocannabinoid system and neuropathic pain. Pain. 2016;157(Suppl 1):S23–32. https://doi.org/10.1097/j.pain.0000000000000428. **An informative article on the endocannabinoid system and its role in the pathophysiology of neuropathic pain. Discusses current basic science research and examines data from preclinical animal studies and clinical trials.**
25.•• Andraea MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. J Pain. 2015;16(12):1221–32. https://doi.org/10.1016/j.jpain.2015.07.009. **A novel Bayesian meta-analysis that included data from 5 RCTs studying the efficacy of inhaled cannabis for chronic neuropathic pain. Results a suggested inhaled cannabis has a NNT of 5.6 for neuropathic pain.**
26. Zuardi AW. History of cannabis as a medicine: a review. Rev Bras Psiquiatr. 2006;28(2):153–7. https://doi.org/10.1590/S1516-44462006000200015.
27. Wood GW, Bache F. The dispensatory of the United States of America, vol. 1238. 6th ed. Philadelphia: Grigg and Elliot; 1845.
28. Furnish TJ, Wallace MS. Marijuana and cannabinoids for pain. In: Staat PS, Silverman SM, editors. Controlled substance management in chronic pain: a balanced approach. Switzerland: Springer International; 2016.
29. Scotter EL, Abood ME, Glass M. The endocannabinoid system as a target for the treatment of neurodegenerative disease. Br J Pharmacol. 2010;160(3):480–98. https://doi.org/10.1111/j.1476-5381.2010.00735.x.
30. Russo EB, Hohmann AG. Role of cannabinoids in pain management. In: Deer TR, Leong MS, Buvanendran A, Gordin V, Kim PS, Panchal SJ, Ray AL, editors. Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches. Berlin: Springer. The American Academy of Pain Medicine Textbook on Pain Management; 2014.
31. Wang J, Ueda N. Biology of endocannabinoid synthesis system. Prostaglandins Other Lipid Mediat. 2009;89(3–4):112–9. https://doi.org/10.1016/j.prostaglandins.2008.12.002.
32. Devane WA, Dysarz FA 3rd, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol. 1988;34(5):605–13.
33. Jensen B, Chen J, Furnish T, Wallace M. Medical marijuana and chronic pain: a review of basic science and clinical evidence. Curr Pain Headache Rep. 2015;19(10):50. https://doi.org/10.1007/s11916-015-0524-x.
34. Fine PG, Rosenfeld MJ. Cannabinoids for neuropathic pain. Curr Pain Headache Rep. 2014;18(10):451. https://doi.org/10.1007/s11916-014-0451-2.
35. Rácz I, Nent E, Erxlebe E, Zimmer A. CB1 receptors modulate affective behaviour induced by neuropathic pain. Brain Res Bull. 2015;114:42–8. https://doi.org/10.1016/j.brainresbull.2015.03.005.
36. Gaetani S, Dipasquale P, Romano A, Righetti L, Cassano T, Piomelli D, et al. The endocannabinoid system as a target for novel anxiolytic and antidepressant drugs. Int Rev Neurobiol. 2009;85:57–72. https://doi.org/10.1016/S0074-7742(09)85005-8.
37. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;258(5090):1946–9. https://doi.org/10.1126/science.1470919.
38. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365(6441):61–5. https://doi.org/10.1038/365061a0.
39. Racz I, Nadal X, Alferink J, Baños JE, Rehnelt J, Martín M, et al. Crucial role of CB(2) cannabinoid receptor in the regulation of central immune responses during neuropathic pain. J Neurosci. 2008;28(46):12125–35. https://doi.org/10.1523/Jneurosc.3400-08.2008.
40. Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharmacol. 2008;153(2):319–34. https://doi.org/10.1038/sj.bjp.0707531.
41. Agarwal N, Pacher P, Tegeder I, Amaya F, Constantin CE, Brenner GJ, et al. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci. 2007;10(7):870–9. https://doi.org/10.1038/nn1916.
42. Nadal X, La Porta C, Andreea Bura S, Maldonado R. Involvement of the opioid and cannabinoid systems in pain control: new insights from knockout studies. Eur J Pharmacol. 2013;716(1–3):142–57. https://doi.org/10.1016/j.ejphar.2013.01.077.
43. Wotherspoon G, Fox A, McIntyre P, Colley S, Bevan S, Winter J. Peripheral nerve injury induces cannabinoid receptor 2 protein expression in rat sensory neurons. Neuroscience. 2005;135(1):235–45. https://doi.org/10.1016/j.neuroscience.2005.06.009.
44. Clapper JR, Moreno-Sanz G, Russo R, Guijarro A, Vacondio F, Duranti A, et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. Nat Neurosci. 2010;13(10):1265–70. https://doi.org/10.1038/nn.2632.
45. Babayeva M, Assefa H, Basu P, Chumki S, Loewy Z. Marijuana compounds: a nonconventional approach to Parkinson's disease therapy. Parkinson's Dis. 2016;2016:1279042–19. https://doi.org/10.1155/2016/1279042.
46. Nadulski T, Pragst F, Weinberg G, Roser P, Schnelle M, Fronk EM, et al. Randomized, double-blind, placebo-controlled study about

the effects of cannabdiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. Ther Drug Monit. 2005;27(6):799–810. https://doi.org/10.1097/01.ftd.0000177223.19294.5c.

47. Braida D, Pozzi M, Cavallini R, Sala M. Conditioned place preference induced by the cannabinoid agonist CP 55,940: interaction with the opioid system. Neuroscience. 2001;104(4):923–6. https://doi.org/10.1016/S0306-4522(01)00210-X.
48. Reilly D, Didcott P, Swift W, Hall W. Long-term cannabis use: characteristics of users in an Australian rural area. Addiction. 1998;93(6):837–46. https://doi.org/10.1046/j.1360-0443.1998.9368375.x.
49. Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 2007;107(5):785–96. https://doi.org/10.1097/01.anes.0000286986.92475.b7.
50. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein 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(5):438–49. https://doi.org/10.1016/j.jpain.2012.01.003.
51. Savage SR, Romero-Sandoval A, Schatman M, Wallace M, Fanciullo G, McCarberg B, et al. Cannabis in pain treatment: clinical and research considerations. J Pain. 2016;17(6):654–68. https://doi.org/10.1016/j.jpain.2016.02.007.
52. Hampson AJ, Bornheim LM, Scanziani M, Yost CS, Gray AT, Hansen BM, et al. Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission. J Neurochem. 1998;70(2):671–6.
53. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68(7):515–21. https://doi.org/10.1212/01.wnl.0000253187.66183.9c.
54. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672–80. https://doi.org/10.1038/npp.2008.120.
55. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. Randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9(6):506–21. https://doi.org/10.1016/j.jpain.2007.12.010.
56. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182(14):E694–701. https://doi.org/10.1503/cmaj.091414.
57.•• Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14(2):136–48. https://doi.org/10.1016/j.jpain.2012.10.009. **A RCT that demonstrated analgesia with low-dose vaporized cannabis.**
58. Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. J Pain. 2016;17(9):982–1000. https://doi.org/10.1016/j.jpain.2016.05.010.
59.•• Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015;16(7):616–27. https://doi.org/10.1016/j.jpain.2015.03.008. **RCT that demonstrated efficacy of vaporized cannabis delivery in patients with painful diabetic neuropathy.**
60.•• Abrams DI, et al. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther. 2007;82(5):572–8. **Study that demonstrated safety of cannabis vaporization.**
61. Wade DT, Robson P, House H, Makela P, Aram JA. Preliminary controlled study to determine whether whole –plant cannabis extracts can improve intractable neurologic symptoms. Clin Rehabil. 2003;17(1):21–9. https://doi.org/10.1191/0269215503cr581oa.
62.• Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomized controlled trial. Pain. 2004;112(3):299–306. **Randomized, double-blind, placebo-controlled crossover investigating efficacy of oromucousal THC:CBD (1:1) in chronic neuropathic pain secondary to brachial plexus root avulsion. Results were significant for improvement in sleep and mean pain severity score, but did not reach the goal of two point pain reduction, which was the primary outcome measure.**
63.• Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65(6):812–9. **Randomized, double-blind, placebo-controlled, parallel group trial in patients with MS and central neuropathic pain treated with oromucousal THC:CBD. Results demonstrated significant differences between cannabis based oromucousal spray and placebo in pain numerical rating and sleep disturbance in favor of cannabis based spray.**
64.• Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double-blind, placebo-controlled clinical trial. Pain. 2007;133(1–3):210–20. **Randomized, double-blind, placebo-controlled, parallel group trial in patients with peripheral neuropathic pain treated with oromucousal THC:CBD spray. Results demonstrated significant changes in pain intensity scores, sleep index, and patient's global impression of change in favor of the cannabis based spray.**
65. GW Pharmaceuticals Ltd. https://www.gwpharm.com/products-pipeline/sativex/prescriber-information-full. Accessed Feb 14 2017.
66.• Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regime in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260(4):984–97. https://doi.org/10.1007/s00415-012-6739-4. **Randomized, double-blind, placebo-controlled, parallel group trial and withdrawal study in patients with multiple sclerosis and central neuropathic pain treated with oromucousal THC:CBD spray. Results during the treatment phase were equivocal, but there was in increased time to treatment failure in patients in the THC:CBD oromucousal spray group compared to placebo.**
67.•• Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo –controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014;18(7):999–1012. https://doi.org/10.1002/j.1532-2149.2013.00445.x. **A double blind, randomized, placebo-controlled, parallel group study in patients with non-diabetic peripheral neuropathic pain with allodynia who were treated with THC:CBD oromucousal spray. Results demonstrated statistically significant decreases in 30% responder level, sleep quality, and global impression of change. Reductions in mean peripheral neuropathic pain scores were lower in the treatment group but failed to reach statistical significance.**
68. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2 year extension trial. Clin Ther. 2007;29(9):2068–79. https://doi.org/10.1016/j.clinthera.2007.09.013.

69. Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejcko J, et al. A multicenter, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. J Neurol. 2015;262(1):27–40. https://doi.org/10.1007/s00415-014-7502-9.

70.• GW Pharmaceuticals Ltd. NCT00710424. A double blind, randomized, placebo controlled, parallel group study of Sativex in the treatment of subjects with pain due to diabetic neuropathy. In: ClinicalTrials.gov (Internet). Bethesda (MD): National Library of Medicine (US). http://clinicaltrials.gov/show/NCT00710424 2006. 2000. **Randomized, double-blind, placebo-controlled, parallel group study in patients with painful diabetic peripheral neuropathy treated with oromucousal CBD:THC spray. The results did not demonstrate significant changes in pain severity score or number of 30% improvement responders between treatment and placebo groups.**

71. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33(1):128–30. https://doi.org/10.2337/dc09-1029.

72. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: systematic review of randomized controlled trials. Can Fam Physician. 2015;61(8):e372–81.

73. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ. 2008;178(13):1669–78. https://doi.org/10.1503/cmaj.071178.

74. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, et al. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012;307(2):173–81. https://doi.org/10.1001/jama.2011.1961.

75. National Academies of Sciences, Engineering, and Medicine (US); Health and Medicine Division (US); Board on Population Health and Public Health Practice (US); Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda (US). Editors. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington (DC): National Academies Press (US); 2017.

76. Wallace MS, Ware MA. Medicinal marijuana: here to stay and time to take responsibility. Clin J Pain. 2015;31(11):931–2. https://doi.org/10.1097/AJP.0000000000000217.