

Cannabinoids for Neuropathic Pain

Perry G. Fine · Mark J. Rosenfeld

Published online: 28 August 2014

© Springer Science+Business Media New York 2014

Abstract Treatment options for neuropathic pain have limited efficacy and use is fraught with dose-limiting adverse effects. The endocannabinoid system has been elucidated over the last several years, demonstrating a significant interface with pain homeostasis. Exogenous cannabinoids have been demonstrated to be effective in a range of experimental neuropathic pain models, and there is mounting evidence for therapeutic use in human neuropathic pain conditions. This article reviews the history, pharmacologic development, clinical trials results, and the future potential of nonsmoked, orally bioavailable, nonpsychoactive cannabinoids in the management of neuropathic pain.

Keywords Cannabinoids · Endocannabinoid system · Neuropathic pain

Introduction

Forty-five years ago, commenting on the inadequate state of understanding of potentially therapeutic vs adverse health effects of cannabinoids, Raphael Mechoulam, a pioneer in cannabinoid pharmacology, said: “It is a sad truth, however, that in spite of the voluminous literature on the subject, critical scientific evaluation of the different aspects of the problem are few” [1]. PubMed indexed publications referencing cannabis and cannabinoids ran at a rather steady rate of about 200 per year for several decades, until about 10 years ago. Since then,

there has been more than an 8-fold increase in such citations. Nevertheless, were Mechoulam’s words of almost one-half a century ago uttered today, they would be as accurate in describing our depth of applied pharmacologic understanding, largely because of social and regulatory constraints that have trumped both knowledge and potential welfare of innumerable patients living with intractable conditions for which cannabinoids may have therapeutic benefit.

The more recent explosion of literature does signal both a rapidly growing interest in and understanding of the endocannabinoid system, cannabinoids, and the relationship between cannabinoids and potential medical applications. This foray into cannabinoid science coupled with a rapidly evolving re-evaluation of prohibitions surrounding use of cannabis can now complement a vast anecdotally-based oral and written history, derived from millennia of cannabis use for recreational and health-related purposes [2]. Although this article’s focus is on current pharmacologic and clinical science related to cannabinoids and the medical indication of neuropathic pain, it is useful to provide a brief overview of the historical context undergirding our current understanding of the endocannabinoid system and cannabinoids.

Early History of Cannabis for Pain

Historical accounts of cannabis use as an analgesic are inconsistent. Egyptian relics dating to the 16th century BC appear to ascribe medicinal benefit to cannabis. In India, the medical and religious use of cannabis probably began together around 3000 years ago. The plant was used for many pain-related purposes, including neuralgia, headache, and toothache. Evidence from a 4th century BC tomb near Jerusalem suggests use of cannabis to ease the pain of childbirth. Intoxicating effects were recognized and memorialized in Sanskrit, Hindu, and Chinese writings starting about 2000 years ago. In 2nd century China, cannabis resin, mixed with wine, was used with apparent success as an anesthetic in

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

P. G. Fine (✉)
Pain Research and Management Centers, School of Medicine,
Department of Anesthesiology, University of Utah, Suite 200, 615
Arapeen Drive, Salt Lake City, UT 84108, USA
e-mail: perry.fine@hsc.utah.edu

M. J. Rosenfeld
ISA Scientific, Inc., Draper, UT 84020, USA

order to perform major surgical procedures. The first comprehensive writings in western society are found in the “*material medica*” written by the Greek physician Dioscorides in the 1st century CE who was accompanying the Roman army. Cannabis is listed as an herbal remedy, especially useful for ear aches. Later, in the 2nd century CE, Galen described the analgesic effects of cannabis. Although hemp was cultivated widely throughout many geographic areas, there is little medical documentation until centuries later.

In Europe, during the early 19th century, science-minded soldiers in Napoleon Bonaparte’s army published papers extolling the virtues of cannabis for pain and other virtues. George Washington is reported to have used cannabis for tooth pain. The mid-1800s saw a great surge of interest in potential medical benefits of cannabis resin and extracts, administered in a variety of forms to treat acute and chronic pain and alcohol withdrawal, among other conditions. Cannabis was accepted into the U.S. Pharmacopoeia in 1850 and was included in many compounds marketed by major mainstream pharmaceutical companies of the era.

During the temperance movement of the late 19th century and early 20th century, along with fears related to racial and ethnic prejudices, the term cannabis became conflated with the Spanish term *marihuana*, which was used to describe recreational use. Eventually, and in the absence of any scientific understanding of cannabinoid pharmacology, concerns about medical benefits vs adverse side effects and abuse liability dominated policy around cannabis use. This led to the 1937 *Marihuana Tax Act* that imposed untenable regulatory barriers to medical use or research. The 1970 *Controlled Substances Act*, listing any and all cannabinoids as Schedule I substances, effectively closed the door on therapeutic investigation for many years [2–6]. Extraordinary efforts are required to obtain authorization for cannabinoid research in the United States, under the aegis of the National Institute on Drug Abuse (NIDA). As a direct result, almost all reports of cannabinoid use for pain in the modern era have come from very limited trials or anecdotal reports [7]. Notwithstanding these severe shortcomings, there appears to be compelling evidence that some cannabinoids may fill an important treatment gap in the management of neuropathic pain [8, 9].

Present Day Cannabinoid Science

The endogenous cannabinoid system has been described as “an ancient lipid signaling network, which in mammals modulates neuronal functions, inflammatory processes, and is involved in the etiology of certain human lifestyle diseases, such as Crohn’s disease, atherosclerosis, and osteoarthritis. The system is able to downregulate stress-related signals that lead to chronic inflammation and certain types of pain, but it is also involved in causing inflammation-associated symptoms,

depending on the physiological context [10].” Within this system, 2 distinct receptor types have been identified, that serve as binding sites for endogenous and exogenous cannabinoids.

CB₁ Receptors

The CB₁ receptor has been cloned from humans [11]. Activation of CB₁ receptors leads to dose-dependent and stereo-selective inhibition of adenylate cyclase activity, with effects on memory, perception, and movement. The CB₁ receptor appears to be responsible for the mood enhancing effects of cannabis as well as negative psychotomimetic effects, including anxiety, paranoia, and dysphoria, in susceptible individuals.

CB₁ receptor distribution has been well-characterized in the human brain [12]. The receptors are expressed in high abundance in the hippocampus and associational cortical regions, the cerebellum, and the basal ganglia. This widespread distribution in the brain matches well with the known pharmacodynamic effects of cannabinoids. In contrast, binding is sparse or absent from the brain stem, medulla, and thalamus. The paucity of CB₁ receptors in these areas helps explain the absence of life-threatening effects on vital physiological functions associated with extremely high doses of cannabinoids.

Outside of the brain, CB₁ receptors occur in the testis, and on presynaptic sympathetic nerve terminals [13]. CB₁ receptor mRNA has been identified in the adrenal gland, heart, lung, prostate, bone marrow, thymus, and tonsils [14, 15].

CB₂ Receptors

Although CB₁ and CB₂ receptors share considerable structural similarities, their distribution and activity diverge. Among other actions, including pain modulation, CB₂ receptors are thought to serve an important role in immune function and inflammation [16]. There is ample evidence that CB₂ receptor activation reduces nociception in a variety of preclinical models, including those involving tactile and thermal allodynia, mechanical, and thermal hyperalgesia, and writhing [17]. With regard to their role in modulating neuropathic pain, the presence of CB₂ receptors on microglia within the nervous system may explain the putative benefits of cannabinoids in reducing cytokine-mediated neuroinflammation.

CB₁ and CB₂ receptors inhibit adenylate cyclase via interactions at the G-protein complex. However, their activation and consequent inhibition of various ion channels differs [18]. The key point is that differential binding of CB₁ or CB₂ receptors, either separately or in combination by their respective endogenous or exogenous ligands, leads to varied physiological effects, mediated via several neurotransmitters, including acetylcholine, glutamate, and dopamine.

Endogenous Cannabinoids and Pain Signal Processing

The first compound to be identified as an endogenous cannabinoid receptor ligand was given the name anandamide, after the Sanskrit word for bliss. Anandamide bears no chemical resemblance to the aromatic phytocannabinoids such as THC and CBD, but rather is an arachidonic acid derivative [19]. Several other endogenously generated moieties (endocannabinoids) have been identified that bind to cannabinoid receptors, but their roles in homeostatic functions and in disease states remain poorly defined. The physiologic role of anandamide continues to be actively explored, having been identified in central and peripheral tissues of man [20].

It appears that the endocannabinoid system is intimately involved in tissue healing in the face of inflammatory conditions, correlating clinically with prevention and treatment of inflammation-mediated pain [21]. With regard to potential pain-modulating activity, anandamide has been shown to be a full agonist at vanilloid (TRPV₁) receptors, and may play a modulating role at other transient receptor potential (TRP) receptor types [22]. Anandamide is reported to produce effects similar to THC at CB₁ receptors, via G-protein coupled inhibition of adenylate cyclase. These effects include antinociception, hypomotility, and reduced memory [23].

There are distinct differences between anandamide and other cannabinoids with respect to their antinociceptive properties and other physiological effects, which vary as a function of route of administration. It is not known whether anandamide acts at the same sites as phytocannabinoids to produce antinociception. The behavioral effects of THC and anandamide after administration suggest that they act, at least in part, in the brain and/or spinal cord. These studies suggest that anandamide is less potent and has a shorter duration of action than THC [24].

Studies have demonstrated that antinociceptive effects of cannabinoids are mediated through mechanisms distinct from those responsible for other behavioral effects. For instance, THC has additive analgesic efficacy with kappa opioid receptor agonists. This effect is blocked by kappa antagonism but opioid receptor antagonism does not alter psychoactive effects of THC [25]. Investigations into the endogenous cannabinoids and their effector sites (including CB₁ and CB₂ along with other noncannabinoid receptors) have exploded in recent years and insights reveal this area of pharmacology to be highly complex and dynamic. For instance, there is mounting evidence that endogenous and exogenous cannabinoids exert some influence on opioid, 5HT₃, N-methyl-d-aspartate, and most recently, α 3 glycine receptors. These interactions suggest a role for endocannabinoids in homeostatic pain modulation (antinociception), thus, their use as exogenous agents in pain management [26].

Evidence now suggests that by binding effects at CB₁ and CB₂ receptors, respectively, the cannabinoid agonists

anandamide and N-palmitoyl-ethanolamine (PEA) induce peripheral antinociception through activation of the central endogenous noradrenergic pathway and peripheral adrenoreceptors [27]. Other studies have demonstrated the expression of functional CB₂ receptors in areas of human dorsal root ganglion (DRG) sensory neurons. CB₂ receptor expression also has been demonstrated in the spinal cord as well as in other brain regions particularly relevant for nociceptive integration [28–30].

These findings implicate CB₂ receptors in the analgesic effects produced by CB₂ agonists [31, 32]. Other evidence for the involvement of the endocannabinoid system in peripherally-mediated pain control includes the finding that CB₂ receptor agonists can evoke analgesia by triggering the release of beta-endorphin in response to the stimulation of CB₂ receptors expressed in human keratinocytes [33]. Many other studies have linked cannabinoid and opioid effects through primary receptor interactivity as well as downstream second messenger effects. From a clinical standpoint, this may provide an opportunity for therapeutic synergy [34].

The role of CB₂ receptors in antinociception has been demonstrated in inflammatory and neuropathic pain models. Investigations involving carrageenan-induced inflammatory pain in rodents demonstrate that activation of CB₂ receptors by CB₂ selective agonists suppresses neuronal activity in the dorsal horn via reduction in C-fiber activity and wind-up involving wide dynamic range (WDR) neurons [35, 36]. The involvement of cannabinoid receptors in modulating pain has been supported further by findings that there are increases in peripheral CB₂ receptor protein or mRNA in inflamed tissues and in the dorsal root ganglion in neuropathic states [37–39]. Data from studies investigating viscerally-induced pain due to colorectal distention indicate that peripheral CB₁ receptors mediate the analgesic effects of cannabinoids on visceral pain from the gastrointestinal tract [40].

Not all of the pain-relieving effects of cannabinoids can be explained by interactions at CB₁ and CB₂ receptors. Xiong et al [41] have shown that both systemic and intrathecal administration of CBD suppress chronic inflammatory and neuropathic pain without the development of tolerance in a rodent model. The mechanism of pain relieve appears to be through significant potentiation of glycine currents in dorsal horn neurons, and this analgesic effect does not correspond to CB₁ and CB₂ binding affinity. Corroborating this extra-CB-receptor phenomenon is the observation that analgesic efficacy of CBD is diminished in mice lacking the α 3 glycine receptor.

Several additional animal models have established a strong basis for cannabinoid attenuation of neuropathic pain. Neuropathic pain models evaluating the role of cannabinoids as analgesics include chronic constriction injury, partial sciatic nerve ligation, and spinal nerve ligation, among others. Similarly, disease-related animal models have also demonstrated

reduction or elimination of mechanical allodynia and/or hyperalgesia, common and unifying phenomena underlying neuropathic pain. Efficacy of cannabinoids in reducing these signs and symptoms has been shown in streptozotocin-induced diabetic neuropathy, chemotherapy-induced neuropathy (vincristine, cisplatin, and paclitaxel), HIV-associated neuropathy, demyelination-induced neuropathy, and in postherpetic neuralgia (PHN) [42].

The sum of these data strongly suggest that cannabinoids play a pivotal role in homeostatic modulation of nociception, and that exogenous cannabinoids may offer an important therapeutic opportunity as nontraditional analgesics in various pain states [43]. With this foundation to build upon, the proceeding section will explore the role of cannabinoids in clinical pain relief in humans. Much has been learned since a decade ago when there was significant doubt about translating research findings linking cannabinoids to antinociception with pain relief in actual patients [44]. But there are now methodically sound studies that may lead to important therapeutic advances for people living with neuropathic pain.

Cannabinoids and the Management of Pain

Evidence continues to accumulate suggesting that cannabinoids can impact normal inhibitory pathways and pathophysiological processes influencing nociception in humans [37, 45]. When cannabinoids do have an analgesic effect, it is more likely to occur in hyperalgesic and inflammatory states [46]. Clinical trials lasting from days to months, involving more than 1000 patients, have shown efficacy in different categories of chronic pain conditions but the vast majority of controlled trials have involved patients with chronic neuropathic pain (Table 1).

When cannabinoids lead to a reported reduction in pain, it remains unclear where the effects are triggered, or which aspect of the pain experience is most affected and under what circumstances. As well, different cannabinoids may lead to mechanistically different pain relieving effects. For instance, a recent study of functional brain imaging in human volunteers investigated the means by which THC may influence pain resulting from capsaicin-induced hyperalgesia. The study results suggest that “peripheral mechanisms alone cannot account for the dissociative effects of THC on the pain that was observed. Instead, the data reveal that amygdala activity contributes to inter-individual response to cannabinoid analgesia, and suggest that dissociative effects of THC in the brain are relevant to pain relief in humans” [47]. In other words, cannabinoids, and THC in particular, may have differential effects on the sensory (eg, intensity; quality) vs affective (eg, unpleasantness; suffering) components of pain.

The 2 best studied cannabinoids implicated as having potential analgesic properties are THC and cannabidiol (CBD)

(Fig. 3). THC was first isolated from cannabis by Raphael Mechoulam and colleagues in 1964 at the Hebrew University of Jerusalem, identifying it as the major psychoactive component of cannabis, with preferential binding at CB₁ receptors [48]. Synthetic forms of THC, like dronabinol and nabilone, are commercially available in several countries, and are considered controlled substances. These have indications for treating anorexia in AIDS patients and as a therapy for intractable nausea and vomiting during cancer chemotherapy. In a wide range of oral doses, dronabinol, which is chemically identical to the THC extracted from plants, has not demonstrated significant pain relief in several naturally occurring and experimental pain conditions [49–51]. In contrast, nabilone, which is chemically similar to THC but not identical [52] has demonstrated modest efficacy in fibromyalgia [53] but with dose-limiting adverse effects. Its use has led to paradoxical increases in pain in the postoperative setting [54].

Cannabidiol is a major constituent of cannabis. It has virtually no psychoactivity compared against THC [55]. Cannabidiol has low affinity for both cannabinoid CB₁ and CB₂ receptors. Limited pharmacodynamic effects due to relatively weak receptor binding (low affinity) may be overcome with higher doses of agonist. Whereas the dose-limiting factor with THC resides in the highly variable propensity among individuals to experience and tolerate negative affective, cognitive and psychotomimetic effects, the ability of cannabidiol to behave as a CB₁ receptor inverse agonist may contribute to its documented mitigating action on THC psychotomimetic effects. More recently it has been postulated that cannabidiol may exert its effects via inhibition of anandamide deactivation or otherwise enhancing anandamide signaling [56].

Cannabidiol agonist activity at CB₂ receptors seems to account for its anti-inflammatory properties and both primary and secondary influences on pain [57, 58]. As well, memory impairments associated with THC are not apparent with CBD, and when combined, CBD reduces the negative impact of THC on memory. This mitigating effect also has been attributed to the inverse agonist effect at CB₁ receptors by CBD. Anxiolytic effects of CBD may also be attributed to its agonist effect at the 5-HT_{1A} receptor [59].

A pharmaceutical combination product of THC and CBD now exists as an oral spray consisting of 27 mg Δ⁹-tetrahydrocannabinol and 25 mg cannabidiol per ml (100 microliters per administered dose; ie, 2.7 mg THC and 2.5 mg CBD), extracted from *Cannabis sativa* L. This formulation is approved in Canada, New Zealand, Israel, and several European countries for the management of central pain and spasticity in multiple sclerosis (MS). There are several ongoing trials on its efficacy in treating MS-related pain [60]. The therapeutic value of THC and THC-CBD via oral mucosal delivery in the treatment of various other neuropathic pain conditions show promising, albeit, modest results [61, 62]. The limited efficacy is likely due to the relative low dose of

Table 1 Clinical trials: cannabinoid and NP pain

NP type	Number of subjects	Cannabinoid type, preparation	Dosage and route	Treatment duration	Study design	Results	Author, reference
HIV	50	Marijuana	3.56 % THC, smoked 3 times per d	5 d	RCT	Significant pain reduction in active treatment group.	Abrams et al [78]
Chronic NP pain	34	THC+CBD 1:1	Oral mucosal, variable dose	12 wk	RCT	Positive pain relieve (not otherwise specified).	Notcutt et al [79]
Chronic NP pain	21	CT-3 (THC analog)	Oral, 20 mg twice daily × 4 d, then 40 mg twice daily × 3 d	7 d	RCT cross-over	Significant decrease in hyperalgesia, allodynia and VAS pain intensity scores.	Karst et al [80]
MS	630	THC cannabis extract	Oral, variable dose	15 wk, with 52 wk continuation	RCT	Statistically significant reduction in pain scores and clinically meaningful sense of improvement.	Zajicek et al [81]
MS	24	Dronabinol	Oral 10 mg	3 wk	RCT cross-over	Significant pain reduction with active treatment.	Svenden et al [82]
MS	137	THC+CBD 1:1 (Sativex)	Oral mucosal, variable dose	10 wk controlled trial followed by 52 wk open label	RCT and open label	Significant pain reduction with active treatment; continued pain relieve in about half of long-term use patients.	Wade et al [83]
MS	66	THC+CBD 1:1 (Sativex)	Oral mucosal, variable dose	4 wk	RCT	Significant pain reduction with active treatment.	Rog et al [84]
Chronic NP pain conditions	24	THC+CBD 1:1	Oral mucosal, variable dose	2 wk	RCT cross-over	Significant pain reduction with active treatment.	Wade et al [85]
Brachial plexus injury	48	THC+CBD 1:1 (Sativex) vs THC vs placebo spray	Oral mucosal, variable dose	Three 2-wk treatment period	RCT cross-over	Significant pain reduction with both active treatments	Berman et al [86]
Peripheral NP pain	125	THC+CBD 1:1 (Sativex)	Oral mucosal, variable dose	5 wk controlled trial followed by 52 wk extension	RCT	Significant pain reduction with active treatment	Nurmikko et al [87]

MS multiple sclerosis, NP neuropathic pain

this combination of cannabinoids. It is important to note that the dose-limiting factor is how much THC may be tolerated. With higher doses via smoking marijuana or inhaling vaporized cannabis, hyperalgesic, and cognitive effects become more pronounced and problematic, especially in cannabis-naïve individuals [63–67]. Beyond these trials involving CBD and THC, comparative or head-to-head studies of individual cannabinoids or various cannabinoid combinations and routes of administration evaluating clinical outcomes are lacking.

Combining Phytocannabinoids and Terpenes: the Entourage Effect

The entourage effect is the term used to describe enhancement of efficacy, with related improvement in overall therapeutic effectiveness, derived from combining phytocannabinoids and other plant-derived molecules [68]. Besides CBD, phytocannabinoids that have been identified as exerting clinically-useful effects without psychoactivity include tetrahydrocannabinol, cannabigerol, and cannabichromene. Innovative conventional plant breeding has been yielding Cannabis chemotypes expressing high titres of each component for future study.

A chemical class known as the terpenes share a precursor molecule with phytocannabinoids, and are all flavor and fragrance components common to human diets. Terpenes have been designated Generally Recognized as Safe (GRAS) by the US Food and Drug Administration and other regulatory agencies. Cannabis-derived terpenes include limonene, myrcene, α -pinene, linalool, β -caryophyllene, caryophyllene oxide, nerolidol, and phytol. These terpenes are also found in other plants [69].

Terpenes are quite potent, and affect animal and even human behavior when inhaled in very low concentrations. They display unique therapeutic effects that may contribute meaningfully to the entourage effects of cannabis-based medicinal extracts. Of particular interest are the phytocannabinoid-terpene interactions that could produce synergy with respect to treatment of pain and inflammation. Phytocannabinoid-terpene synergy increases the likelihood that an extensive pipeline of new therapeutic products is possible from this age-old plant.

The synergistic contributions of cannabidiol to Cannabis pharmacology—and specifically analgesia—have been scientifically demonstrated. Preclinical and clinical data indicates that cannabinoids administered together are more effective at ameliorating neuropathic pain than the use of a single agent [68].

The terpene β -caryophyllene is found in a number of commonly available plants, including black pepper, cinnamon, clove and other spices. It selectively binds to the CB₂ receptor at nanomolar concentrations and acts as a full agonist.

β -caryophyllene and cannabidiol abundantly occur in Cannabis sativa [70]. So, this plant species produces at least 2 entirely different chemical substances able to differentially target CB₂ receptors. Although studies on the pharmacokinetics of β -caryophyllene are still ongoing, it is already clear that this terpene is readily bioavailable. Unlike many polyphenolic natural products, it is not metabolized immediately but shows a T_{max} >1 hour after 1 single oral administration. Orally administered β -caryophyllene (<5 mg·kg⁻¹) produces strong anti-inflammatory and analgesic effects in wild type mice but not in CB₂ receptor knockout mice, which is a clear indication that it may be a functional CB₂ ligand [71].

Ongoing studies show that β -caryophyllene is effective at reducing neuropathic pain in a CB₂ receptor-dependent manner [72]. Like other CB₂ ligands β -caryophyllene inhibits the pathways triggered by activation of the toll-like receptor complex CD14/TLR4/MD2, which typically lead to the expression of pro-inflammatory cytokines (eg, IL-1 beta, IL-6; IL-8, and TNF alpha), is synergistic with opioid analgesic effects, and promotes a Th1 immune response that plays a critical role in neuroinflammation, sensitization, and pain [73]. Therefore, the FDA approved food additive β -caryophyllene seems an attractive candidate for clinical trials targeting the CB₂ receptor. Indeed, in cases of intractable or difficult-to-control pain, combination therapy with small doses of opioid and nonpsychoactive cannabinoid receptor agonists may be an alternative way to circumvent the undesirable side effects of opioids alone, yet obtain far greater analgesic efficacy than achieved with cannabinoids alone [74–77].

Conclusions

Great progress has been made in understanding the pharmacology of the endocannabinoid system and elucidating the structures of several phytocannabinoids and many of their physiological effects. These steps have provided a rational foundation upon which to test the efficacy of high therapeutic index cannabinoids such as cannabidiol in experimental neuropathic pain models, as well as in several difficult-to-control human neuropathic pain conditions. These early trials suggest that cannabidiol may offer a safe and effective alternative or adjunct to currently used pharmacotherapies (eg, tricyclic antidepressants, anticonvulsants, opioids, and local anesthetics). With a rapidly-emerging shift toward a less stringent regulatory environment, there is a widening window of opportunity for methodologically sound research to explore the role of phytocannabinoids—especially nonpsychoactive and orally bioavailable formulations—in the treatment of neuropathic pain.

Compliance with Ethics Guidelines

Conflict of Interest Perry G. Fine and Mark J. Rosenfeld serve on the Board of Directors of ISA Scientific, Inc., a medicinal cannabinoid research and development company.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Mechoulam R. Marijuana chemistry. *Science*. 1970;168:1159–66.
 2. Adams R. Marijuana. *Science*. 1940;92:115–9.
 3. Abel EL. Marijuana: the first twelve thousand years. New York: Phenum Press; 1980.
 4. Zias J, Stark H, Sellgman J, Levy R, Werker E, Breuer K, et al. Early medical use of cannabis. *Nature*. 1993;363:215.
 5. Mikuriya TH, editor. Marijuana medical papers: 1839–1972. Berkeley: Medicomp Press; 1972.
 6. Zuardi AW. History of cannabis as medicine: a review. *Rev Bras Psiquiatr*. 2006;28:1253–7.
 7. Nicoll RA, Alger BN. The brain's own marijuana. *Sci Am*. 2004;21:45–51.
 8. Mandavilli A. Marijuana researchers reach for pot of gold. *Nat Med*. 2003;9:1227.
 9. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annu Rev Neurosci*. 2009;32:1–32.
 10. Gertsch J. Anti-inflammatory cannabinoids in diet: towards a better understanding of CB(2) receptor action? *Commun Integr Biol*. 2008;1:S26–8.
 11. Gerard CM, Mollereau C, Vassart G, Parmentier M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochem J*. 1991;279:129–34.
 12. Glass M, Faull RLM, Dragunow M. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study on the fetal, neonatal and adult human brain. *Neuroscience*. 1997;77:299–318.
 13. Ishac EJN, Jiang L, Lake KD, Varga K, Abood ME, Kumos G. Inhibition of exocytotic noradrenergic release by presynaptic cannabinoid CB1 receptors on peripheral sympathetic nerves. *Br J Pharmacol*. 1996;118:2023–8.
 14. Galiegue S, Mary S, Marchand J, et al. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur J Biochem*. 1995;232:54–61.
 15. Rice W, Shannon JM, Burton F, Fiedelkey D. Expression of a brain type cannabinoid receptor (CB1) in alveolar type-II cells in the lung-regulation by hydrocortisone. *Eur J Pharmacol*. 1997;327:227–32.
 16. Hulsebosch CE. Special issue on microglia and chronic pain. *Exp Neurol*. 2012;234:253–4. *The role of microglial proliferation on neuroinflammation is gaining importance in understanding mechanisms involved in inciting and maintaining neuropathic pain. Recognition of cannabinoid receptors on microglia adds 1 more element for potential therapeutic manipulation to prevent or treat neuropathic pain.*
 17. Beltramo M. Cannabinoid type 2 receptor as a target for chronic pain. *Mini Rev Med Chem*. 2009;9:11–25.
 18. Felder CC, Joyce KE, Briley EM, et al. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. *Mol Pharmacol*. 1995;48:443–50.
 19. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258:1946–9.
 20. Felder CC, Nielsen A, Briley EM, et al. Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide in brain and peripheral tissues of human and rat. *FEBS Lett*. 1996;393:231–5.
 21. Kozono S, Matsuyama T, Biwasa KK, et al. Involvement of the endocannabinoid system in periodontal healing. *Biochem Biophys Res Commun*. 2010;394:928–33.
 22. De Petrocellis L, Bisogno T, Maccarrone M, et al. The activity of anandamide at vanilloid VR1 receptors requires facilitated transport across the cell membrane and is limited by intracellular metabolism. *J Biol Chem*. 2001;276:12856–63.
 23. Vogel Z, Barg J, Levy R, Saya D, Heldman E, Mechoulam R. Anandamide, a brain endogenous compound, interacts specifically with cannabinoid receptors and inhibits adenylate cyclase. *J Neurochem*. 1993;61:352–5.
 24. Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Martin BR. The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. *J Pharmacol Exp Ther*. 1994;270:219–27.
 25. Welch SP. Blockade of cannabinoid-induced antinociception by norbinaltorphimine, but not N-, N-, diallyltyrosine-Aib-phenylalanine-leucine, ICL 174,864 or naloxone in mice. *J Pharmacol Exp Ther*. 1993;265:633–40.
 26. Pertwee RG, Howlett AC, Abood ME, et al. International union of basic and clinical pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacol Rev*. 2010;62:588–631.
 27. Thiago RL, Romero L, Resende LC, Guzzo LS, Duarte IDG. CB1 and CB2 cannabinoid receptor agonists induce peripheral antinociception by activation of the endogenous noradrenergic system. *Anesth Analg*. 2013;116:463–72. *This research report provides insight into one of the several putative mechanism by which peripherally acting cannabinoids reduce pain in both experimental models and clinical syndromes of neuropathic pain.*
 28. Beltramo M, Bernardini N, Bertorelli R, et al. CB2 receptor-mediated antihyperalgesia: possible direct involvement of neural mechanisms. *Eur J Neurosci*. 2006;23:1530–8.
 29. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science*. 2005;310:329–32.
 30. Jhaveri MD, Elmes SJ, Richardson D, et al. Evidence for a novel functional role of cannabinoid CB(2) receptors in the thalamus of neuropathic rats. *Eur J Neurosci*. 2008;27:1722–30.
 31. Anand U, Otto WR, Sanchez-Herrera D, et al. Cannabinoid receptor CB2 localisation and agonist mediated inhibition of capsaicin responses in human sensory neurons. *Pain*. 2008;138:667–80.
 32. Jhaveri MD, Sagar DR, Elmes SJ, Kendall DA, Chapman V. Cannabinoid CB2 receptor-mediated anti-nociception in models of acute and chronic pain. *Mol Neurobiol*. 2007;36:26–35.
 33. Ibrahim MM, Porreca F, Lai J, et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. *Proc Natl Acad Sci U S A*. 2005;102:3093–8.
 34. Bushlin I, Rozenfeld R, Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Curr Opin Pharmacol*. 2010;10:80–6.
 35. Nackley AG, Zvonok AM, Makriyannis A, Hohmann AG. Activation of cannabinoid CB2 receptors suppresses C-fiber

- responses and windup in spinal wide dynamic range neurons in the absence and presence of inflammation. *J Neurophysiol.* 2004;92:3562–74.
36. Quartilho A, Mata HP, Ibrahim MM, et al. Inhibition of inflammatory hyperalgesia by activation of peripheral CB2 cannabinoid receptors. *Anesthesiology.* 2003;99:955–60.
 37. Richardson D, Pearson RG, Kurian N, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Res Ther.* 2008;10:R43.
 38. Walczak JS, Pichette V, Leblond F, Desbiens K, Beaulieu P. Behavioral, pharmacological and molecular characterization of the saphenous nerve partial ligation: a new model of neuropathic pain. *Neuroscience.* 2005;132:1093–102.
 39. 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;135:235–45.
 40. Brusberg M, Arvidsson S, Kang D, et al. CB1 Receptors mediate the analgesic effects of cannabinoids on colorectal distension-induced visceral pain in rodents. *J Neurosci.* 2009;29:1554–64.
 41. Xiong W, Cui T, Cheng K, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting $\alpha 3$ glycine receptors. *J Exp Med.* 2012;209:1121–34. *This insightful research study supports a previously undisclosed, novel mechanism for observed clinical efficacy of cannabinoids.*
 42. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics.* 2009;6:713–37.
 43. Pertwee RG. Cannabinoid receptors and pain. *Prog Neurobiol.* 2001;63:569–611.
 44. Campbell FA, Tamer MR, Carroll D, et al. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systemic review. *BMJ.* 2001;323:1–6.
 45. Dogrul A, Seyrek M, Yalcin B, Ulugol A. Involvement of descending serotonergic and noradrenergic pathways in CB1 receptor-mediated antinociception. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012;38:97–105.
 46. Iversen L, Chapman V. Cannabinoids: a real prospect for pain relief? *Curr Opin Pharmacol.* 2002;2:50–5.
 47. Lee MC, Ploner M, Wiech K, et al. Amygdala activity contributes to the dissociative effect of cannabis on pain perception. *Pain.* 2013;154:124–34.
 48. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc.* 1964;86:1646–7.
 49. Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain.* 2003;106:169–72.
 50. Holdcroft A, Smith M, Jacklin A, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia.* 1997;52:483–6.
 51. Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain.* 2003;105:79–88.
 52. Lemberger L, Row H. Clinical pharmacology of nabilone, a cannabinol derivative. *Clin Pharm.* 1975;18:720–6.
 53. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain.* 2008;9:164–73.
 54. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. *Can J Anaesth.* 2006;53:769–75.
 55. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol.* 2002;42:11S–9S.
 56. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry.* 2012;2:1–7.
 57. Thomas A, Baillie GL, Phillips AM, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol.* 2007;150:613–23.
 58. Morgan C, Curran H. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry.* 2008;192:306–7.
 59. Morgan C. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. *Br J Psychiatry.* 2010;197:285–90.
 60. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin.* 2007;23:17–24.
 61. Russo EB. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag.* 2008;4:245–59.
 62. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized crossover clinical trial. *Neuropsychopharmacology.* 2009;34:672–80.
 63. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology.* 2007;107:785–96.
 64. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain.* 2008;9:506–21.
 65. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain.* 2013;14:1236–48.
 66. St Gieringer D, Laurent J, Goodrich S. Cannabis combines efficient delivery of THC with effective suppression of pyrolytic compounds. *J Cannabis Ther.* 2004;4:2–27.
 67. Michalski CW, Oti FE, Erkan M, et al. Cannabinoids in pancreatic cancer: correlation with survival and pain. *Int J Cancer.* 2008;122:742–50.
 68. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol.* 2011;163:1344–64.
 69. Gertsch J, Pertwee RG, Di Marzo V. Phytocannabinoids beyond the Cannabis plant—do they exist? *Br J Pharmacol.* 2010;160:523–9.
 70. Gertsch J, Leonti M, Raduner S, et al. Beta-caryophyllene is a dietary cannabinoid. *Proc Natl Acad Sci U S A.* 2008;105:9099–114.
 71. Zimmer A, Racz I, Klauke AL, Markert A, Gertsch J. Betacaryophyllene, a phytocannabinoid acting on CB2 receptors. IACM 5th Conference on cannabinoids in medicine. Cologne, Germany; 2009. Available at: <http://www.cannabis-med.org/meeting/Cologne2009/reader.pdf>. Accessed March 23, 2013.
 72. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol.* 2009;27:519–50.
 73. Cichewicz DL, McCarthy EA. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther.* 2003;304:1010–5.
 74. Zutler M, Holty JC. Opioids, sleep and sleep-disordered breathing. *Curr Pharm Des.* 2011;17:1443–9.
 75. Carley DW, Pavlovic S, Janelidze M, Radulovacki M. Functional role of cannabinoids in respiratory stability during sleep. *Sleep.* 2002;25:388–95.
 76. Walker JM, Huang SM. Cannabinoid analgesia. *Pharmacol Ther.* 2002;95:127–35.
 77. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. *Ann Pharmacother.* 2006;40:251–60.
 78. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology.* 2007;68:515–21.
 79. Notcutt W, Price M, Miller A, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 ‘N of 1’ studies. *Anaesthesia.* 2004;59:440–52.

80. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA*. 2003;290:1757–62.
81. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow-up. *J Neurol Neurosurg Psychiatry*. 2005;76:1664–9.
82. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*. 2004;329:253.
83. Wade DT, Makela PM, House H, et al. Long-term use of a cannabis based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler*. 2006;12:639–45.
84. Rog DJ, Nurmiko T, Friede T, et al. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. *Neurology*. 2005;65:812–9.
85. Wade DT, Robson P, House H, et al. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*. 2003;17:18–26.
86. 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 randomised controlled trial. *Pain*. 2004;112:299–306.
87. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133:210–20.