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Cannabinoids as Pharmacotherapies for Neuropathic Pain: From the Bench to the Bedside

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Abstract

Neuropathic pain is a debilitating form of chronic pain resulting from nerve injury, disease states, or toxic insults. Neuropathic pain is often refractory to conventional pharmacotherapies, necessitating validation of novel analgesics. Cannabinoids, drugs that share the same target as Δ^9-tetrahydrocannabinol (Δ^9-THC), the psychoactive ingredient in cannabis, have the potential to address this unmet need. Here, we review studies evaluating cannabinoids for neuropathic pain management in the clinical and preclinical literature. Neuropathic pain associated with nerve injury, diabetes, chemotherapeutic treatment, human immunodeficiency virus (HIV), multiple sclerosis (MS), and herpes zoster infection is considered. In animals, cannabinoids attenuate neuropathic nociception produced by traumatic nerve injury, disease, and toxic insults. Effects of mixed cannabinoid CB_1/CB_2 agonists, CB_2-selective agonists, and modulators of the endocannabinoid system (i.e. inhibitors of transport or degradation) are compared. Effects of genetic disruption of cannabinoid receptors or enzymes controlling endocannabinoid degradation on neuropathic nociception are described. Specific forms of allodynia and hyperalgesia modulated by cannabinoids are also considered. In humans, effects of smoked marijuana, synthetic Δ^9-THC analogs (e.g. Marinol®, Cesamet®) and medicinal cannabis preparations containing both Δ^9-THC and cannabidiol (e.g. Sativex®, Cannador®) in neuropathic pain states are reviewed. Clinical studies largely affirm that neuropathic pain patients derive benefits from cannabinoid treatment. Subjective (i.e. rating scales) and objective (i.e. stimulus-evoked) measures of pain and quality of life are considered. Finally, limitations of cannabinoid pharmacotherapies are discussed together with directions for future research.

Keywords

Endocannabinoid; marijuana; neuropathy; multiple sclerosis; chemotherapy; diabetes

Neuropathic Pain

Neuropathic pain is a debilitating form of treatment-resistant chronic pain caused by damage to the nervous system. Neuropathic pain may result from peripheral nerve injury, toxic insults, and disease states. Neuropathic pain remains a significant clinical problem because it responds poorly to available therapies. Moreover, adverse side-effect profiles may limit therapeutic

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dosing and contribute to inadequate pain relief. Drug discovery efforts have consequently been directed towards identifying novel analgesic targets for drug development. This review will evaluate the efficacy of cannabinoids as analgesics for the treatment of neuropathic pain from the bench to the bedside.

Cannabinoid Receptor Pharmacology

Evidence for the use of *Cannabis sativa* as a treatment for pain can be traced back to the beginnings of recorded history. The discovery by Gaoni and Mechoulam[1] of Δ^9-tetrahydrocannabinol (Δ^9-THC), the primary psychoactive ingredient in cannabis, set the stage for the identification of an endogenous cannabinoid (endocannabinoid) transmitter system in the brain. The endocannabinoid signaling system includes cannabinoid receptors (e.g. CB_1 and CB_2), their endogenous ligands (e.g. anandamide and 2-arachidonoylglycerol) and the synthetic and hydrolytic enzymes which control the bioavailability of the endocannabinoids. Both CB_1[2] and CB_2[3] receptors are G-coupled protein receptors that are negatively coupled to adenylate cyclase. Activation of CB_1 receptors suppresses calcium conductance and inhibits inward rectifying potassium conductance, thereby suppressing neuronal excitability and transmitter release. CB_2 receptor activation stimulates MAPK activity but does not modulate calcium or potassium conductances.[4] The development of CB_1[5] and CB_2[6] receptor knockout mice has helped elucidate the physiological roles of cannabinoid receptors in the nervous system. Generation of $CB_1^{-/-}$ mice that lack CB_1 receptors in nociceptive neurons in the peripheral nervous system while retaining CNS expression (SNS-CB_1^{-}) has also documented a role for these receptors in controlling nociception.[7]

CB_1 and CB_2 receptors exhibit disparate anatomical distributions.[3] CB_1 receptors are localized to the central nervous system (CNS) and the periphery. CB_1 receptors are found in sites associated with pain processing, including the periaqueductal gray (PAG),[8] rostral ventromedial medulla (RVM),[8] thalamus,[9] dorsal root ganglia (DRG),[10] amygdala,[8] and cortex[8]. Densities of CB_1 receptors are low in brainstem sites critical for controlling heart rate and respiration. This distribution explains the low toxicity and absence of lethality following marijuana intoxication. Activation of the CB_1 receptor also results in hypothermia, sedation, catalepsy, and altered mental status.[11] Thus, it is critical for any cannabinoid-based pharmacotherapy targeting CB_1 receptors to balance clinically-relevant therapeutic effects with unwanted side-effects. The CB_2 receptor was originally believed to be restricted to the periphery, primarily to immune cells (e.g. mast cells),[12] although they may be present neuronally in some species. CB_2 receptor protein has been reported in the DRG,[13] brainstem,[14] thalamus,[15] PAG,[15] and cerebellum[15, 16] of naive rats. CB_2 receptor levels in most CNS sites are present at only low levels under basal conditions (or are below the threshold for detection). However, an upregulation of CB_2 receptor immunoreactivity or mRNA is observed in sites implicated in nociceptive processing under conditions of induced neuropathy.[17, 18] CB_2 receptors are localized to microglia, a resident population of macrophages within the CNS that are functionally and anatomically similar to mast cells. Microglia secrete pro-inflammatory factors and induce the release of several mediators (e.g. nitric oxide (NO), neurotrophins, free radicals) that are associated with synaptogenesis and plasticity, leading to changes in neuronal excitability.

Endocannabinoids

The first endogenous ligand for cannabinoid receptors[19] was named anandamide (AEA) after the sankrit word for bliss. Several other endocannabinoids including 2-arachydonoylglycerol (2-AG),[20, 21] noladin ether,[22] virodhamine,[23] and N-arachidonoly-dopamine (NADA)[24] have been described. Fatty-acid amide hydrolase (FAAH) is the principle catabolic enzyme for fatty-acid amides including AEA and *N*-palmitoylethanolamine (PEA).[25] PEA does not bind

cannabinoid receptors and has recently been described as an endogenous ligand for peroxisome proliferator receptor-α (PPAR-α).[26] PEA may indirectly alter levels of endocannabinoids by competing with anandamide and other fatty-acid amides for degradation by FAAH or by suppressing FAAH expression at the transcriptional level.[27, 28] $FAAH^{-/-}$ mice are hypoalgesic in models of acute and inflammatory pain; these effects are blocked by a CB_1 antagonist.[29, 30] This basal hypoalgesia is absent in $FAAH^{-/-}$ mice subjected to nerve injury, where genotype differences in evoked neuropathic pain behaviors are not apparent.[30]

Anandamide also acts as an endovanalloid at the transient receptor potential cation channel (TRPV1) receptor.[31] AEA shows affinity for TRPV1 that is 5-20 fold lower than its affinity for CB_1. TRPV1 is not activated by classical, nonclassical, or aminoalkylindole cannabinoid agonists. AEA can also activate the peroxisome proliferator receptor-γ (PPARγ) receptor.[32] Thus, not all effects of AEA are mediated by cannabinoid receptors.

The metabolic pathways responsible for endocannabinoid degradation are well-characterized. Several FAAH inhibitors (e.g. OL135, URB597) have been developed and used to investigate physiological effects of increasing accumulation of AEA and other fatty-acid amides. Monoacylglycerol lipase (MGL) is a key enzyme implicated in the hydrolysis of 2-AG.[33, 34] MGL inhibitors (e.g. URB602, JZL184) have been developed and can be employed to selectively increase accumulation of this endocannabinoid. The endocannabinoid system has complex relationships with other metabolic pathways. Both AEA and 2-AG can be metabolized by cyclooxygenase-2 (COX-2), a phenomenon that may contribute to the antinociceptive properties of non-steroidal anti-inflammatory drugs (NSAIDS) that act through inhibition of COX-2.[4] Table 1 provides a summary of cannabinoids and related compounds that have been evaluated for efficacy in preclinical and clinical studies of neuropathic pain.

Cannabinoid Modulation of Neuropathic Nociception in Animal Models

W. E. Dixon was the first scientist to systematically study the antinociceptive properties of *Cannabis sativa*. Dixon reported that cannabis smoke delivered to dogs attenuated their responsiveness to pin-pricks.[35] He observed that normally “evil-tempered and savage” dogs became “docile and affectionate” following exposure to cannabis – reflecting the psychotropic and mood-altering effects of cannabinoids. Motor effects observed following high doses of cannabinoids included drowsiness, awkward gate, and ataxia. Work by Walker's group subsequently demonstrated that cannabinoids suppress nociceptive transmission (for review see[36]). Early observations of the antinociceptive properties of cannabinoids laid a foundation for future research examining the impact of cannabinoids and modulation of the endocannabinoid system on neuropathic pain.

Models of Surgically-induced Traumatic Nerve Injury

Cannabinoids suppress neuropathic nociception in at least nine different animal models of surgically-induced traumatic nerve or nervous system injury. Here, we review the literature with a focus on uncovering effects of different classes of cannabinoids on both neuropathic nociception and central sensitization in each model. We also consider the impact of nerve injury on the endocannabinoid signaling system. Where applicable, we review effects of neuropathic injury on levels of endocannabinoids and related lipid mediators and describe regulatory changes in CB_1 and CB_2 receptors induced by nerve injury. Finally, we will consider implications of the preclinical findings for cannabinoid-based pharmacotherapies for neuropathic pain in humans.

Chronic Constriction Injury (CCI)[37]

CCI produces mechanical allodynia as well as thermal allodynia and hyperalgesia in the ipsilateral paw as early as two days post-surgery.[37] Initial reports failed to find mechanical hyperalgesia, although several of the reviewed papers report its presence following surgery. Very few studies have investigated the presence of cold allodynia following this nerve injury; however those that have evaluated its presence uniformly demonstrate efficacy of cannabinoids in suppressing cold allodynia. CB_1 receptors are upregulated in the spinal cord following CCI; these effects are believed to be modulated by tyrosine kinase[38] and glucocorticoid[39] receptors. Not surprisingly, several classes of cannabinoids have been shown to suppress CCI-induced neuropathic nociception in rodents and include mixed cannabinoid agonists which target both CB_1 and CB_2 receptors, CB_2-selective agonists and modulators of the endocannabinoid system that inhibit FAAH or MGL (Tables 2 and 3).

Chronic administration of synthetic analogues of natural cannabinoid ligands containing cannabidiol attenuate or reverse established thermal and mechanical hyperalgesia in the CCI model. However, anti-hyperalgesic effects observed with these compounds are likely to be independent of cannabinoid receptors, and may be mediated through TRPV1. Those studies investigating pharmacological specificity have demonstrated blockade with the TRPV1 antagonist capsazepine, but not a cannabinoid CB_1 or CB_2 antagonist.[40, 41] The CB_1-specific antagonist SR141716 has been tested in this model with disparate results. SR141716, administered acutely, is pro-hyperalgesic and pro-allodynic in this model. [42] However, SR141716 (p.o.), administered chronically, suppresses thermal and mechanical hyperalgesia in both rats and $CB_1^{+/+}$ mice, while failing to produce an effect in $CB_1^{-/-}$ mice. [43] These reports are interspersed with a host of papers that indicate no antinociceptive or pronociceptive effects of either CB_1 or CB_2 antagonists, administered alone. Thus, it is important to emphasize that the behavioral phenotype induced by antagonist treatment may depend upon level of endocannabinoid tone present in the system, the injection paradigm (chronic vs. acute), and presence of regulatory changes in cannabinoid receptors or endocannabinoids.

Several mixed cannabinoid CB_1/CB_2 agonists have been shown to suppress all forms of neuropathic nociception observed in the CCI model, primarily through CB_1-mediated mechanisms. Several studies, including the original study by Herzberg and colleagues[42] were conducted before the development of a CB_2 antagonist and recognition that CB_2 receptor mechanisms modulate neuropathic pain.[44] Mixed CB_1/CB_2 agonists, such as CP55,940 or WIN55,212-2, typically act as CB_1-selective agonists following systemic administration,[45] although CB_2-mediated effects may be unmasked following administration of CB_2-selective agents or following local administration of the same compounds. A neurophysiological basis for these findings is derived from the observation that WIN55,212-2 (i.v.) dose-dependently inhibits windup[46] as well as CCI-induced increases in spontaneous firing[47] of spinal wide dynamic range (WDR) neurons through a CB_1-dependent mechanism. Spontaneous firing of WDR neurons is believed to contribute to behavioral hypersensitivity and neuronal sensitization in neuropathic pain states. WIN55,212-2 also normalizes prostaglandin E_2 (PGE_2) levels and nitric oxide (NO) activity, two mediators of neuropathic pain that are increased following CCI.[48]

Multiple CB_2-selective agonists have been demonstrated to suppress CCI-induced mechanical allodynia, although pharmacological specificity has not been consistently assessed (Table 2). Thus, it is noteworthy that CB_2 receptor mRNA is upregulated in the lumbar spinal cord following CCI. This upregulation is restricted to non-neuronal cells (e.g. glia).[49] Interestingly, GW405833, a CB_2-specific agonist, also reduces depression-like behavior associated with this mononeuropathy in the forced swim test.[50] Tolerance, a feature which may contribute to loss of analgesic efficacy of currently available analgesics, failed to develop following repeated administration the CB_2-specific agonist of A-836339. Thus, CB_2 agonists may show

therapeutic potential for suppressing neuropathic pain without producing tolerance when administered either alone or as adjuncts to exisiting treatments.[51]

Endocannabinoid modulators suppress neuropathic pain symptoms associated with CCI (Tables 2 and 3). AM404, an endocannabinoid transport inhibitor, increases accumulation and, hence, bioavailability, of anandamide (and potentially other endocannabinoids) through a mechanism that remains incompletely understood. AM404 also normalizes CCI-induced changes in NO activity,[52, 53] COX-2[53] activity, cytokine levels (e.g. TNF-α and IL10),[52] and NF-κB[52] levels. In CCI rats, chronic administration of either AM404 or URB597 suppresses plasma extravasation, a condition associated with neuropeptide release at peripheral levels.[54, 55] AM404, administered chronically or acutely, does not affect locomotor behavior, indicating a low propensity of this agent to produce unwanted motor side-effects associated with direct activation of CB_1 receptors.[52, 53]

CCI produces regulatory changes in endocannabinoid levels. CCI increases AEA and 2-AG levels in the PAG and RVM, sites implicated in the descending modulation of pain.[56] CCI also increases levels of endogenous AEA, but not 2-AG, in the dorsal raphe – an observation which may help explain the anti-hyperalgesic efficacy of an anandamide transport inhibitor in this model.[57] CCI increases serotonin (5-HT) levels in the dorsal raphe and this effect was suppressed by both WIN55,212-2 and AM404 in a CB_1-dependent manner.[57] CCI-induced Fos expression was observed in response to non-noxious mechanical stimulation in spinal cord laminae I and II, the site of termination of Aδ and C fibers, which carry nociceptive sensory information from the periphery to the CNS. Lower levels of evoked Fos expression were observed in laminae III and IV of CCI rats. Chronic administration of AM404 significantly decreased CCI-induced Fos expression in the lumbar spinal cord through CB_1/CB_2 and TRPV1-mediated mechanisms.[58] Antinociceptive effects of FAAH inhibitors (OL135 and URB597) have also been reported in mice following CCI. OL135 and URB597 attenuate cold and mechanical allodynia in a manner that is dependent upon activation of both CB_1 and CB_2 receptors.[59] Additionally both OL135 and URB597 are antinociceptive in $FAAH^{+/+}$ mice, but fail to produce an effect in $FAAH^{-/-}$ mice.[59] The novel MGL inhibitor, JZL184, attenuates CCI-induced mechanical and cold allodynia through indirect activation of the CB_1 receptor; JZL184 was efficacious in attenuating neuropathic nociception in both $FAAH^{+/+}$ and $FAAH^{-/-}$ mice.[59] The fatty acid PEA, administered chronically, attenuated the development of thermal hyperalgesia and mechanical allodynia in the CCI model through CB_1, PPARγ and TRPV1-mediated mechanisms.[60] Chronic administration of PEA also normalized levels of three neutrophic factors (NGF, GDNF, and NT-3) that were increased by CCI.[60] Thus, activation of CB_1 and CB_2 receptors as well as pharmacological manipulation of endocannabinoid accumulation or breakdown suppresses neuropathic nociception in rodents.

Partial Sciatic Nerve Ligation (Seltzer Model)[61]

Mechanical hyperalgesia and allodynia are observed following partial ligation of the sciatic nerve. Thermal hyperalgesia was present in all studies reviewed here that evaluated this measure with one exception.[62] Only two studies we reviewed examined the presence of cold allodynia following partial sciatic nerve ligation; the first study found that both $CB_2^{+/+}$ and $CB_2^{-/-}$ mice showed evidence of cold allodynia following surgery.[63] Cold allodynia has also been reported in rats following partial sciatic nerve ligation.[64] All classes of cannabinoids evaluated produced anti-allodynic and anti-hyperalgesic effects in the Seltzer model (Table 4).

Pro-hyperalgesic effects of SR141716 and SR144528 have been reported in the Seltzer model,[65] indicating a potential alteration in endocannabinoid tone following nerve injury. No other papers we reviewed reported similar effects of cannabinoid antagonists administered alone in this model. Exogenously applied endocannabinoids, AEA and 2-AG, suppress changes in neuropathic nociception induced by partial sciatic nerve ligation. Interestingly, anandamide

produced anti-hyperalgesic and anti-allodynic effects through a CB_1 mechanism,[65, 66] whereas 2-AG produced anti-hyperalgesic and anti-allodynic effects through activation of both peripheral CB_1 and CB_2 receptors.[67] Anandamide and PEA exerts effects, at least in part, through a peripheral mechanism; both fatty-acid amides suppressed release of calcitonin gene-related peptide and somatostatin evoked by the irritant resiniferotoxin without altering peptide release under basal conditions.[65] Anti-hyperalgesic effects of AEA and PEA were blocked by a CB_1 and CB_2 antagonist, respectively.[65] One limitation with studies employing exogenous administration of endocannabinoids is that they do not imply that endocannabinoids are released under physiological conditions to produce these effects. Several studies report efficacy of mixed cannabinoid CB_1/CB_2 agonists in this model, although CNS side-effects were nonetheless observed in the same dose range that resulted in full reversal of neuropathic nociception.[68] Ajulemic acid (CT-3), which was developed as a peripherally restricted cannabinoid analogue, also produced activity in the tetrad but anti-hyperalgesic effects occurred at doses lower than those producing side-effects.[69]

Structurally distinct CB_2-specific agonists are efficacious in suppressing neuropathic nociception in this model. Moreover, CB_2 receptors in the spinal cord contribute to CB_2-mediated suppression of mechanical allodynia.[70] $CB_2^{-/-}$ mice reportedly develop thermal hyperalgesia and mechanical allodynia in the contralateral paw following surgery, whereas $CB_2^{+/+}$ do not.[63] Microglia and astrocyte expression in the spinal dorsal horn is observed in both $CB_2^{-/-}$ and $CB_2^{+/+}$ ipsilateral to nerve injury. However, $CB_2^{-/-}$ mice notably exhibit increased microglial and astrocyte expression in the contralateral spinal dorsal horn – a mechanism which may help to explain differences in neuropathic nociception between wild-types and knockouts.[63] Further support for this hypothesis is derived from the observation that overexpression of the CB_2 receptor attenuated enhanced expression of microglia.[63] These results suggest that genetic disruption of the CB_2 receptor has a disinhibitory effect on the responses of glial cells following partial sciatic nerve ligation. The cytokine, interferon-gamma (IFN-γ), is produced by astrocytes and neurons ipsilateral to injury in both $CB_2^{+/+}$ and $CB_2^{-/-}$ mice. However, $CB_2^{-/-}$ mice exposed to partial sciatic nerve ligation exhibit IFN-γ immunoreactivity in the spinal dorsal horn contralateral to injury. IFN-$\gamma^{-/-}/CB_2^{-/-}$ mice showed no evidence of neuropathic nociception when the contralateral paw was stimulated following surgery, suggesting that immune responses underlie neuropathic pain responses observable in the contralateral paw of $CB_2^{-/-}$ mice.[71] Deletion of a putative novel cannabinoid receptor, GPR55, is also associated with the failure to develop mechanical hyperalgesia following partial sciatic nerve ligation.[72]

Compounds targeting three distinct mechanisms for modulating endocannabinoid levels also suppress neuropathic nociception following partial sciatic nerve ligation. The transport inhibitor AM404, administered systemically, suppressed mechanical allodynia in a CB_1-dependent manner, without producing motor effects.[73] The FAAH inhibitor URB597, administered locally in the paw,[67] but not systemically[62] suppressed both thermal hyperalgesia and mechanical allodynia through a CB_1 mechanism. The MGL inhibitor URB602 (which cannot be used systemically as a selective MGL inhibitor), administered locally in the paw, also suppressed neuropathic nociception in this model through activation of both CB_1 and CB_2 receptors.[67] The fatty-acid analogue of PEA, L-29, also suppressed thermal hyperalgesia and mechanical allodynia in the Seltzer model. The L29-induced suppression of thermal hyperalgesia was mediated by both the CB_1 receptor and PPAR-α, whereas suppression of mechanical allodynia was mediated by CB_1/CB_2 and PPAR-α receptors.[64] PEA abolished mechanical hyperalgesia following partial sciatic nerve ligation through a mechanism that was blocked by a CB_2 antagonist.[65] When considering the effects of PEA it is important to emphasize that PEA does not bind directly to CB_2 receptors[74]; therefore, blockade by a CB_2-specific antagonist could indicate indirect modulation of receptor activity (e.g. via activation of PPAR-α or entourage effects) or blockade of an uncharacterized cannabinoid receptor that

binds the CB_2 antagonist SR144528. Intrathecal N-arachidonoyl glycine (NaGly), the arachodonic acid conjugate, also attenuated mechanical allodynia in this model, however, the anti-hyperalgesic actions of this compound are independent of spinal cannabinoid receptors.[75] Locally injected (i.paw) paracetamol suppressed mechanical allodynia and thermal hyperalgesia present following partial sciatic nerve ligation and these effects are blocked by local administration of either a CB_1 or a CB_2 antagonist.[76] Paracetomol may undergo local metabolic transformation into AM404, resulting in increased levels of endocannabiniods.

Spinal Nerve Ligation (SNL)[77]

All studies reviewed here documented the presence of mechanical allodynia following SNL. All studies with the exception of one[78] indicated the presence of thermal hyperalgesia when animals were tested. One study evaluated the presence of cold allodynia and confirmed that animals with this injury display hypersensitivity to non-noxious levels of cold stimulation.[79] Gabapentin successfully attenuated mechanical allodynia in this model, however, several other commonly prescribed neuropathic pain medications including amitriptyline, fluoxetine and indomethacin failed to show similar effects.[80] Thus, it is noteworthy that mixed cannabinoid agonists, cannabinoid CB_2-selective agonists and FAAH inhibitors all attenuated neuropathic nociception induced by SNL (Table 5).

As with other nerve injury models, several mixed cannabinoid CB_1/CB_2 agonists suppress hyperalgesia and allodynia produced by SNL. Acute WIN55,212-2 suppresses all forms of neuropathic nociception tested in this model. Chronic administration of WIN55,212-2 also attenuates the development of mechanical allodynia and suppresses glial activation in the spinal cord following SNL with no overt motor side-effects.[81] Chronic administration of WIN55,212-2 produced anti-allodynic effects up to six days following the final injection. A reappearance of glial activation was also associated with return of neuropathic nociception in this study.[81] CP55,940 produces antinociception in $CB_1^{+/+}$, $CB_2^{+/+}$, $CB_2^{-/-}$, but not $CB_1^{-/-}$ mice subjected to SNL, suggesting that activity at CB_1 dominates the antinocieptive profile of mixed CB_1/CB_2 agonists following systemic administration.[45] Spinal, but not systemic, administration of HU-210 has been reported to reduce Aδ fiber-evoked responses on spinal WDR neurons in both shams and SNL rats, whereas HU-210 showed no effect on C-fiber responses of SNL rats.[82]

SNL produces regulatory changes in CB_1 mRNA and endocannabinoid levels. Increases in CB_1 mRNA are observed in the uninjured (but abnormal) L4 DRG ipsilateral to injury.[83] Increases in both AEA and 2-AG have also been reported in the ipsilateral injured L5, but not the uninjured L4 DRG.[83] These findings collectively document the presence of regulatory changes in endocannabinoid levels associated with SNL, a finding which may contribute to the efficacy of peripherally administered cannabinoid agonists that activate CB_1 receptors in this model.

Noxious stimulation (e.g. C-fiber mediated activity) induces phosphorylation of extracellular signal-regulated protein kinase (ERK) in dorsal horn neurons. The CB_1-specific agonist ACEA inhibits pERK expression induced by *in vitro* application of capsaicin to the spinal cords of SNL rats. This observation contrasts with effects of opioids (i.e. morphine and DAMGO) which lose the ability to inhibit C-fiber induced ERK activation in the L5 spinal cord following SNL.[84]

Multiple CB_2-specific agonists suppress neuropathic nociception induced by SNL. The CB_2 agonist AM1241 suppresses both thermal hyperalgesia and mechanical allodynia following SNL in both rats[17, 44, 85] and mice[44]. $CB_1^{-/-}$ mice receiving AM1241 showed enhanced antihyperalgesia.[44] An emerging body of literature now suggests that antinociceptive effects of CB_2 agonists may be mediated by suppression of microglial activation.[4]

Evidence for upregulation of CB_2 following SNL has been reported by several groups. CB_2 mRNA was upregulated in the lumbar spinal cord following SNL,[49] coincident with the expression of activated microglia. Colocalization studies, however, were not performed. Upregulation of CB_2 receptor immunoreactivity on sensory afferent terminals in the spinal cord has also been reported following SNL.[18] This group failed to find co-localization of CB_2 with markers for glial cells in SNL rats, and concluded that CB_2 receptors were upregulated on sensory neurons following spinal nerve ligation.[18] CB_2 mRNA was also shown to be upregulated in the ipsilateral (versus the contralateral) spinal cord and DRG following SNL and the presence of CB_2 mRNA was confirmed in spinal cord microglial cells in culture.[17]

The CB_2-specific agonist GW405833, administered chronically, suppressed the development of mechanical allodynia concomitant with suppression of glial activation at the level of the spinal cord.[81] The structurally distinct CB_2-specific agonist, JWH133, also attenuates mechanically-evoked responses of WDR neurons in both naive and spinal nerve ligated rats.[86] Local injection of JWH133 into the ventroposterolateral nucleus of the thalamus attenuated spontaneous and mechanically-evoked neuronal activity in SNL, but not sham rats, in a CB_2-dependent manner.[87] Thus, CB_2 receptor activation may exert little functional control under nonpathological conditions. Systemic and spinal administration of the novel CB_2 agonist, A-836339, also attenuates spontaneous and mechanically-evoked neuronal firing of spinal WDR neurons in a CB_2-dependent manner in SNL but not sham rats.[88] Interestingly, pre-treatment with the CB_1 antagonist, SR141716, enhanced the effects of A-836339 when applied to the L5 DRG,[88] indicating that blockade of CB_1 receptors enhanced the antinociceptive effects of a CB_2 agonist, as reported previously.[89]

Two endocannabinoid modulators have been evaluated behaviorally in this model. Compound 17, a novel FAAH inhibitor, reversed mechanical allodynia in SNL rats with the same potency as a 5-fold higher dose of gabapentin.[90] Additionally, OL135, a compound that accesses the CNS and inhibits FAAH, suppressed mechanical allodynia in a CB_2-dependent manner.[91] Low doses of locally injected URB597 (i.pl.) reduced mechanically-evoked responses of WDR neurons and increased endocannabinoid levels in ipsilateral paw tissue of sham operated rats.[92] A four-fold higher dose was required for reduction of mechanically-evoked WDR neuronal responses in SNL rats; these rats showed no corresponding increase in endocannabinoid levels, suggesting that contributions of FAAH to endocannabinoid metabolism may be modified under conditions of neuropathic nociception.[92] The antinociceptive effects of URB597 were blocked by a CB_1-specific antagonist in both sham and SNL rats.[92] In the same study, spinal administration of URB597 was equally efficacious at attenuating mechanically-evoked responses and increasing levels of endogenous cannabinoids in SNL and sham rats and these effects were CB_1-mediated.[92]

Other Nerve Injury Models

Cannabinoids alleviate neuropathic nociception in several other injury models. These studies support a role for CB_1 in the anti-hyperalgesic effects of cannabinoids, although pharmacological specificity has not been consistently assessed in the literature and high doses of cannabinoid agonists can produce motor side-effects which complicate interpretation of behavioral studies. *Chronic constriction injury of the infraorbital nerve (CCI-ION)* results in thermal hyperalgesia and mechanical allodynia (as measured by head withdrawals) ipsilateral to the site of injury.[93] WIN55,212-2 and HU-210 increased mechanical withdrawal responses and thermal withdrawal latencies on the ipsilateral side of the head in this model.[94] WIN55,212-2 was more efficacious in suppressing mechanical allodynia vs. thermal hyperalgesia in the CCI-ION model. High antihyperalgesic doses of WIN55,212-2 decreased rotarod latencies and body temperature, whereas HU210, at the singular low dose used (10

μg/kg), had no effect on these dependent measures. CB_1 receptor upregulation was observed in both the ipsilateral and contralateral superficial layer of the trigeminal caudal nucleus, and this effect was greater on the ipsilateral side. These and earlier findings from the same group[95] indicate that cannabinoids are negative modulators of nociceptive transmission at the superficial layer of the trigeminal caudal subnucleus.

CB_2 receptor immunoreactivity[96] is increased in the ipsilateral dorsal horn following *L5 spinal nerve transection (L5-SNT)*.[97] Importantly, co-localization of CB_2 immunoreactivity with markers of microglia and perivascular cells was observed on day 4 post-surgery.[96] In this study, neither neuronal cells nor astrocytes expressed immunoreactivity for CB_2 receptors.[96] CP55,940 reversed mechanical allodynia in this model 1 h following a second intrathecal injection, although this dosing paradigm was also associated with motor effects.[96] Intrathecal JWH015 dose-dependently suppressed behavioral hypersensitivity following a second injection, indicating a cumulative anti-allodynic effect of this drug. Intrathecal JWH015 reduced SNT-induced increases in activated microglia in a CB_2-dependent manner, further supporting a role for nonneuronal CB_2 receptors in anti-hyperalesic effects of CB_2 agonists.[96]

Two models developed by Walczak and colleagues[98, 99] involve injuries to the saphenous nerve in rats and mice, respectively. The advantage of injuring the saphenous nerve over other nerves is that the saphenous nerve is an exclusively sensory nerve whereas other nerve injury models typically target nerves that subserve both sensory and motor functions. The first model was produced in rats by *saphenous partial nerve ligation (SPL)*, which involves trapping 30-50% of the saphenous nerve in a tight ligature.[98] SPL rats presented with all symptoms except mechanical hyperalgesia (which was present inconsistently throughout testing). WIN55,212-2, administered systemically, suppressed all forms of hyperalgesia and allodynia present.[98] In rats, SPL increased μ-opioid, CB_1, and CB_2 receptor protein in ipsilateral hindpaw skin, DRG and lumbar spinal cord.[98] In a second injury model, *chronic constriction of the saphenous nerve (CCS)* was accomplished by tying two loose ligatures around the saphenous nerve in mice.[99] Systemic WIN55,212-2 suppressed all forms of neuropathic nociception present in this model, including thermal hyperagesia, cold allodynia, mechanical hyperalgesia and mechanical allodynia.[99] Mu-opioid, CB_1 and CB_2 receptor protein was increased in the ipsilateral spinal cord and hindpaw skin at 7 days post-surgery.[99] Additionally, increased CB_1 receptor protein was observed in contralateral hindpaw skin 7 days post-surgery and increased CB_2 receptor expression was observed in the contralateral spinal cord 1 and 7 days post-surgery. The neurobiological rearrangement of cannabinoid and mu-opioid receptors may contribute to the antinociceptive efficacy of WIN55,212-2 and morphine in this model.

The *spared nerve injury (SNI)* model reliably produces thermal hyperalgesia and mechanical allodynia in studies that tested for both measures. Initial reports of the SNI model indicated the presence of cold allodynia and mechanical hyperalgesia,[100] but none of the papers reviewed here assessed these behaviors in conjunction with cannabinoid treatment. Standard analgesics (e.g. morphine, gabapentin, amitryptiline) are efficacious in treating neuropathic nociception resulting from a crush injury of the sciatic nerve, but showed limited efficacy following SNI.[101] Two mixed cannabinoid CB_1/CB_2 agonists have been tested in this model. Acute WIN55,212-2 suppressed thermal hyperalgesia and mechanical allodynia in both mice lacking CB_1 receptors in primary nociceptors (SNS-CB_1^-) and their wild-type controls; however differences in the antinociceptive effects of WIN55,212-2 were observed between genotypes, and these effects were greater with mechanical than thermal sensitivity. Comparable responses to WIN55,212-2 were only observed at doses high enough to induce sedation and rigidity in all mice. SNS-CB_1^- mice showed exaggerated sensitivity to noxious levels of mechanical stimulation and a cold plate relative to their wild-type counterparts, whereas differential sensitivity was not observed between genotypes with non-noxious levels of mechanical

stimulation and noxious levels of thermal stimulation.[7] Thus, CB_1 receptors on nociceptors in the periphery account for much of the antinociceptive effects of cannabinoids.[7] A dose-escalation study with BAY 59-3074 in the SNI model indicated that tolerance rapidly develops to side-effects observed following chronic administration (e.g. hypothermia), whereas no loss in analgesic efficacy was observed.[78]

*Spinal cord injury (SCI)*102 produces mechanical hyperalgesia and allodynia. WIN55,212-2 is the only compound that has been evaluated in the SCI model. Acute WIN55,212-2, administered systemically, suppressed SCI-induced mechanical allodynia in a CB_1-dependent manner, although other parameters of neuropathic pain were not assessed.[103] Unlike morphine, chronic administration of WIN55,212-2 reduced mechanical allodynia in the SCI model with no decrease in effectiveness over time.[104]

Tibial nerve injury (TNI) is performed by unilaterally axotomizing the tibial branch of the sciatic nerve. Mechanical allodynia and thermal hyperalgesia were present in the initial study describing this technique[105] as well as the study we reviewed. Systemic BAY 59-3074 was shown to attenuate both forms of neuropathic nociception, although pharmacological specificity was not assessed.[78] TNI injury resulted in an upregulation of CB_1 receptor mRNA in the contralateral thalamus on day 1 post-surgery,[106] indicating cannabinoid receptor regulation within an important relay nucleus in the ascending pain pathway.

Disease-related Models of Neuropathic Pain

Cannabinoid agonists have been evaluated in animal models of disease-related neuropathic pain, although pharmacological specificity has not been consistently assessed. Here, we review effects of cannabinoids in preclinical models of neuropathic pain induced by diabetes, chemotherapeutic treatment, HIV/antiretroviral treatment, demyelination disorders, multiple sclerosis and post-herpetic neuralgia.

STZ-induced Diabetic Neuropathy

Diabetic neuropathy induced by a single injection of streptozotocin (STZ) resulted in increased sensitivity to noxious and non-noxious levels of mechanical stimulation, and failed to induce thermal hyperalgesia in the studies reviewed here (Table 6). None of the studies we reviewed evaluated the presence of cold allodynia. Met-F-AEA, a CB_1-specific agonist based upon the structure of anandamide, the mixed cannabinoid agonist WIN55,212-2 and the CB_2-specific agonist AM1241, administered chronically, suppressed mechanical hyperalgesia associated with STZ-induced diabetic neuropathy. However, mediation by cannabinoid receptors has not been assessed for agonists tested in this model. Daily pre-treatment with indomethacin (COX-1 inhibitor) or L-NOArg (non-selective NOS inhibitor) increased the anti-hyperalgesic actions of low doses of WIN55,212-2, AM1241 and MET-F-AEA in STZ rats to a greater extent than the cannabinoid administered alone, suggesting the presence of antinociceptive synergism between cannabinoid and COX pathways.[107] COX inhibitors may block oxidative metabolism of endocannabinoids, thereby increasing endocannabinoids available to interact with cannabinoid receptors.

Diabetic rats exhibit a decrease in the density of CB_1 receptor protein in DRG.[108] More work is necessary to determine whether this loss of cannabinoid receptors contributes to the neurodegenerative process in diabetes. Increased levels of endocannabinoids have been found in obese patients suffering from Type II diabetes[109] and this effect is likely to result from downregulation of FAAH gene expression, an effect which has also been observed in adipocytes sampled from obese women.[110] Lean males subjected to hyperinsulinemia show a 2-fold increase in FAAH mRNA expression whereas obese males subjected to the same conditions failed to show similar alterations in gene expression.[111] These findings are

suggestive of a negative feedback mechanism that could result in downregulation of the endocannabinoid signaling system. The CB_1 antagonist rimonabant (Acomplia®) ameliorates insulin resistance and decreases weight gain in patients suffering from metabolic syndromes.[112] In animal models, rimonabant improves resistance to insulin through pathways that are both dependent and independent of adiponectin, a hormone important for the regulation of glucose and catabolism of fatty acids.[113] Although adverse side-effects have limited the potential therapeutic efficacy of Acomplia®, drugs modulating the endocannabinoid system should not be disregarded as targets for potential treatments of diabetes and its associated syndromes. STZ-diabetic mice showed a progressive decline in the radial arm maze and reduced neurological scores, both of which were recovered following treatment with HU-210.[114] However, these effects were not blocked by a CB_1-specific agonist. HU-210 did not alter the hyperglycemia index; however, it did normalize cerebral oxidative stress present in diabetic mice.[114] An increase in the number of apoptotic cells and impaired neurite growth was observed in PC12 cells cultured under hyperglycemic conditions and these effects were effectively treated by HU-210.[114]

Cannabinoids may show greater therapeutic potential for treating painful diabetic neuropathy compared to opioids. Interestingly, Δ^9-THC exhibited enhanced antinociceptive efficacy in diabetic rats whereas morphine showed reduced antinociceptive efficacy.[115] Moreover, a non-nociceptive dose of Δ^9-THC, administered in conjunction with morphine, enhanced the antinociceptive properties of morphine in both diabetic and naive mice.[115] Thus, combinations of opioids and cannabinoids may show promise as adjunctive analgesics in humans. Diabetic rats exhibit lower levels of dynorphin and β-endorphins in cerebrospinal fluid (CSF) relative to non-diabetic rats treated under the same conditions.[115] Administration of Δ^9-THC to diabetic rats restored CSF levels of endogenous dynorphin and leu-enkephalin to levels observed following morphine administration to non-diabetic rats.[115] More work is necessary to understand the mechanism underlying these observations.

Chemotherapy-induced Neuropathy

Cannabinoid modulation of chemotherapy-induced neuropathy has been evaluated with agents from three major classes of chemotherapeutic agents (Table 6). A singular study has evaluated cannabinoid modulation of neuropathic nociception induced by cisplatin, a platinum derived agent. WIN55,212-2 prevented the development of mechanical allodynia induced by cisplatin, but failed to produce an anti-emetic benefit in this study.[116] It is possible that the dose of cannabinoid employed, the species used (rat) or toxicity of cisplatin-dosing paradigms may prevent detection of anti-emetic effects in this model. Cannabinoids have been shown to suppress cisplatin-induced emesis in the least shrew.[117]

Paclitaxel has been most frequently studied in the cannabinoid literature with three studies documenting cannabinoid-mediated suppression of paclitaxel-induced neuropathic nociception. In one study, paclitaxel[118] produced mechanical allodynia starting on day 5 that continued throughout the timecourse, although thermal hyperalgesia was only present from days 18-21.[119] WIN55,212-2 suppressed neuropathic nociception in this model but had no effect on body temperature or immobility. WIN55,212-2-induced decreases in spontaneous motor activity were nonetheless observed.[119] A more recent study using the same paclitaxel dosing paradigm[118] reported the presence of mechanical allodynia and the absence of thermal hyperalgesia.[85] Naguib and colleagues[85] demonstrated that a novel CB_2-specific agonist, MDA7, suppressed paclitaxel-induced mechanical allodynia, although mediation by CB_2 receptors was not assessed. Using the paclitaxel dosing paradigm described by Flatters and Bennett,[120] mechanical allodynia, but not thermal hyperalgesia, was observed. In this model, rats showed signs of mechanical allodynia up to 72 days post-paclitaxel.[89] Systemic administration of either the CB_2 agonist (*R*,*S*)-AM1241 or its receptor-active enantiomer (*R*)-

AM1241 produced CB_2-mediated suppressions of paclitaxel-induced mechanical allodynia. (*S*)-AM1241, the enantiomer exhibiting lower affinity for the CB_2 receptor, failed to produce an anti-allodynic effect.[89] The novel cannabilactone, AM1714, also reversed mechanical allodynia associated with paclitaxel treatment in a CB_2-dependent manner.[89] Thus, both mixed CB_1/CB_2 agonists and selective CB_2 agonists suppress paclitaxel-evoked mechanical allodynia.

Cannabinoid modulation of neuropathic nociception has also been evaluated with vincristine, an agent from the vinca-alkaloid class of chemotherapeutic agents. Vincristine produced mechanical allodynia, but not thermal hyperalgesia, in a 10 day injection paradigm[121]. Systemic and intrathecal, but not intraplantar, WIN55,212-2 suppressed vincristine-induced mechanical allodynia through activation of CB_1 and CB_2 receptors.[122] These findings implicate the spinal cord as an important site of action mediating anti-allodynic effects of cannabinoids. Systemic (*R,S*)-AM1241 also partially reversed vincristine-induced mechanical allodynia in a CB_2-dependent manner.[122] The anti-allodynic effects of WIN55,212-2 and (*R,S*)-AM1241 were observed at doses that did not produce intrinsic effects on motor behavior in the bar test.[122] Our studies suggest that clinical trials of cannabinoids for the management of chemotherapy-evoked neuropathy are warranted.

HIV-associated Sensory Neuropathy

The mixed cannabinoid agonist WIN55,212-2 is an effective anti-hyperalgesic agent in three distinct animal models of HIV-associated sensory neuropathy (Table 6). Rats treated with the antiretroviral agent zalcitabine (ddc) developed mechanical allodynia that persisted up to 43 days post-injection and peaked between days 14 and 32.[123] No hypersensitivity to thermal stimuli or motor deficits was observed following ddc treatment. HIV-1 has indirect interactions with neurons through its binding affinity to the external envelope binding protein gp120; researchers have exploited this mechanism to demonstrate development of peripheral neuropathy in rodents following exposure of the sciatic nerve to the HIV-1 gp120 protein. Perineural HIV-gp120 together with ddc treatment resulted in mechanical allodynia that was greater than either treatment alone; no changes in paw withdrawal latencies to thermal stimuli or motor deficits reported.[123] Thigmotaxis was present in animals receiving ddc, either alone or in conjunction with HIV-gp120, indicating the presence of anxiety-like behavior in these rats.[123] Rats receiving ddc displayed modest levels of gliosis whereas combined treatment with both HIV-gp120 and ddc increased levels of microglial activation.[123] Importantly, chronic WIN55,212-2 reversed mechanical allodynia induced by either ddc treatment[123] or HIV-gp120 exposure,[124] whereas animals subjected to both HIV-gp120 and ddc treatment exhibited a WIN55,212-2-induced attenuation of mechanical allodynia.[123] Increases in the density of microglia and astrocytes were observed in the ipsilateral dorsal horn following HIV-gp120 treatment. Thus, activated microglia may be a common target underlying cannabinoid-mediated suppressions of neuropathic nociception.

Demyelination-induced Neuropathy

WIN55,212-2 has been evaluated in the lysolecithin-induced demyelination model (Table 6). Heightened sensitivity to both non-noxious and noxious mechanical stimulation is observed in lysolecithin-treated rats; this hypersensitivity emerged 5 days post-exposure and peaked between 9-15 days post-exposure.[125] Recovery to baseline levels was observed by day 23 post-lysolecithin. WIN55,212-2 attenuated mechanical allodynia and thermal hyperalgesia in this model and remained efficacious for up to one hour post injection.[125] By contrast, DAMGO failed to produce an effect. Notably, the anti-hyperalgesic and anti-allodynic effects of WIN55,212-2 were reversed by a CB_1-specific antagonist in both tests.

Multiple Sclerosis-associated Neuropathy

Animal models of multiple sclerosis (MS) have been described, although to our knowledge, no study to date has evaluated cannabinoid-mediated suppression of MS-induced neuropathic nociception. Lynch and colleagues[126] reported the presence of thermal hyperalgesia (tail immersion) and mechanical allodynia in mice that were infected with Theiler's murine encephalomyelitis virus (TMEV). Interestingly, female mice showed an increased rate of development and greater allodynia than their male counterparts, a finding which mimics the greater prevalence of neuropathic pain symptoms reported by female MS patients.[127] Cold and mechanical allodynia, but not thermal hyperalgesia, have been reported in a model of autoimmune encephalomyelitis in which mice were immunized with myelin oligodendrocyte glycoprotein (MOG(35-55))[128]; autoimmune encephalomyelitis has been postulated to underlie the development of neuropathic pain in MS. Interestingly, a mouse model of MS (TMEV infection) is also characterized by an upregulation of CB_2 receptor mRNA and increases in levels of 2-AG and PEA.[129] Animals treated subchronically with PEA showed improvements in tests of motor performance, measures that were impaired following TMEV infection.[129] Thus, we postulate that cannabinoid CB_2 agonists and modulators of endogenous cannabinoids (e.g. MGL inhibitors) would exhibit anti-allodynic efficacy in this model.

Post Herpetic Neuralgia

Cannabinoids and fatty-acid amides suppress neuropathic nociception in an animal model of post herpetic neuralgia (Table 6). However, pharmacological specificity has not been consistently assessed in this model. Approximately 50% of rats exposed to the varicella-zoster virus (VZV) developed mechanical allodynia in the ipsilateral paw by 14 days post-infection; no thermal hyperalgesia or cold allodynia was observed.[64] The PEA analogue L-29 suppressed mechanical allodynia in this model with an earlier onset relative to gabapentin. However, neither a CB_1- nor CB_2-specific antagonist suppressed L-29 mediated suppression of VZV-induced mechanical allodynia.[64] This finding is perhaps unsurprising given that PPAR-α mediates effects of PEA in suppressing neuronal sensitization.[130] However, L-29 nonetheless suppressed neuropathic nociception in the Seltzer model via activation of CB_1 and CB_2 receptors (see Table 4). Systemic WIN55,212-2, administered from days 18-21 post infection, fully reversed mechanical allodynia to baseline levels in this model of post herpetic neuralgia, although pharmacological specificity was not assessed.[131]

Cannabinoid Modulation of Neuropathic Pain in Clinical Studies

Cannabinoids have been evaluated in clinical studies for their suppression of acute, postoperative and neuropathic pain. Based upon our reviews of the literature, cannabinoids exhibit their greatest efficacy when employed for the management of neuropathic pain (Tables 7 and 8).[132] There are approximately 460 known chemical constituents in cannabis. Thus, at the outset, it is important to emphasize that smoked cannabis is not the same as oral Δ^9-THC or different mixtures of Δ^9-THC and cannabidiol (e.g. Sativex® and Cannador®). Other drug delivery mechanisms (e.g. oral-mucosal sprays and rectal suppositories containing cannabinoids) have been developed. Evidence to date from clinical studies suggests that these compounds show therapeutic efficacy in suppressing neuropathic pain (Table 7 and 8).

Three of the articles reviewed here used smoking as the route of administration, whereas the other thirteen employed oral preparations in the form of pills or oral-mucosal sprays. Side-effects were reported in all studies in a proportion of patients receiving cannabinoid-based medications. The most frequently reported side-effects were dizziness, impairment of balance, feelings of intoxication, dry mouth and dysgeusia (most commonly observed with oral-mucosal sprays), sedation, and hunger. One study reported severe gastrointestinal effects for 10% of patients taking Sativex® versus 0% reporting similar problems in the placebo group.[133]

However, unwanted side-effects, in contrast to analgesic effects, may undergo tolerance.[134] Side-effects may be minimized using dosing paradigms employing low doses that are only gradually escalated. Below, we review effects of cannabinoid-based medications in clinical studies employing populations of patients presenting with neuropathic pain. Neuropathic pain induced by HIV infection and/or antiretroviral treatment, multiple sclerosis, brachial plexus avulsion, mixed treatment-resistant neuropathic pain, and others are considered.

HIV-associated neuropathy

Two studies have examined effects of smoked cannabis for the treatment of HIV-associated sensory neuropathy (resulting from HIV infection, dideoxynucleoside antiretroviral therapy, or both) and have reported positive results (Table 7). Abrams and colleagues[135] reported that 52% of patients (i.e. 13 out of 25 receiving cannabis cigarettes) experienced a greater than 30% reduction in pain (visual analogue scale daily ratings; VAS). Stimulus-evoked pain testing revealed that the group receiving cannabis experienced a reduction in the area sensitive to mechanical allodynia (with a foam brush or 26g von Frey hair) in the heat and capsaicin sensitization model. Moreover, CD4+, CD8+, and T-cell counts were not negatively impacted by cannabinoid treatment in HIV patients.[136] In 2009, Ellis and colleagues[137] reported similar results in a crossover study employing multiple concentrations of Δ^9-THC in cannabis cigarettes administered to patients. Cannabis was superior to placebo in either phase of the crossover as measured with the descriptor differential scale (DDS) or VAS. This study found no changes in heart rate, blood pressure, plasma HIV RNA (viral load; VL), or blood CD4+ lymphocyte counts following cannabis treatment, suggesting that cannabis did not negatively impact the already compromised immune system in these patients. An anonymous cross-sectional questionnaire study revealed that as many as one-third of patients suffering from HIV have used cannabis to treat symptoms.[138] Patients reported self-dosing with marijuana primarily between 6 PM and 12 AM. Among the symptoms improved following cannabis were appetite (97% reported improvement), pain (improved in 94% of the patients with pain), nausea (93% reported improvement) and anxiety (93% reported improvement).[138]

Dronabinol (Marinol®) is used to counteract AIDS-related wasting and promote appetite in patients suffering from AIDS-related anorexia.[139] The benefits of Δ^9-THC and nabilone for the treatment of chemotherapy-induced nausea and vomiting have also been validated.[140, 141] Thus, several features of cannabinoid pharmacology are particularly desirable for an analgesic intervention aimed at managing neuropathic pain in AIDS and cancer patients.

Multiple Sclerosis-induced Neuropathic Pain

Several cannabinoid-based medicines have been evaluated in patients suffering from multiple sclerosis (MS)-related neuropathic pain. Cannabinoid-based medications have more frequently been evaluated for efficacy in suppressing MS-related spasticity.[142] Dronabinol reduced spontaneous pain intensity as measured with a numerical rating scale (NRS) over a treatment period of 3 weeks[134] and improved overall pain ratings on the category-rating scale over a treatment period of 15 weeks[143]. Additionally, this drug improved median radiating pain intensity and pressure threshold,[134] sleep quality, spasms, and spasticity[143] in MS patients. Cannador® is a medicinal cannabis preparation containing Δ^9-THC and CBD in a 2:1 ratio. Cannabidiol is a natural constituent in cannabis, which has very low affinity for cannabinoid CB_1 and CB_2 receptors. It may act as a high potency antagonist of cannabinoid agonists and an inverse agonist at CB_2 receptors.[144] CBD may compete with cannabinoid agonists for cannabinoid receptor binding sites, thereby minimizing psychoactivity of drugs that employ a combination of Δ^9-THC and CBD. CBD's antinociceptive effects have additionally been attributed to inhibition of anandamide degradation, the compound's antioxidant properties, or binding to an unknown cannabinoid receptor.[144] CBD also acts as an agonist at serotonin 5-HT1a receptors.[144] Cannador®, administered over a treatment period of 15 weeks, improved

overall pain ratings as well as sleep quality, spasms, and spasticity on category-rating scales in patients suffering from MS-related neuropathic pain.[143] A one year double-blind, placebo-controlled follow up study in MS patients demonstrated improved symptoms of pain, spasms, spasticity, sleep, shakiness, energy level, and tiredness following administration of either dronabinol or Cannador®.[145] This study reported that 74% of the patients in the placebo group, versus 45% of the patients receiving cannabinoid-based medications, cited a lack of benefit derived from experimental medication as the reason for discontinuation of the trial.[145] MS patients receiving Sativex® (a medicinal cannabis extract containing approximately a 1:1 ratio of CBD:Δ^9-THC, administered as an oral-mucosal spray) reported significant reductions in pain symptoms as measured with the NRS-11 and neuropathic pain scale (NPS) in a 4-week treatment period double-blind, placebo-controlled study.[146] Ninety-five percent of the patients in the placebo-controlled study chose to enter a two year open-label study with Sativex®.[147] Fifty-four percent of the patients completed one year and 44% of patients completed two years of the study. Twenty-five percent withdrew due to adverse events and 95% experienced one or more adverse events during the course of treatment. The NRS-11, completed at the end of the trial or upon withdrawal, was not different from the earlier randomized study indicating that Sativex® was still suppressing pain. Additionally, patients did not increase the titration of their dose indicating that no tolerance developed to Sativex®. Most doses of Sativex® were administered between 6 PM and 12 AM demonstrating that pain symptoms may be at their worst during normal sleeping hours for MS patients. A recent meta-analysis examining six studies of cannabinoid-based medications used for the treatment of MS-related neuropathic pain revealed that cannabis preparations were superior to placebo.[148]

Increased CB_2 immunoreactivity has been reported in spinal cords derived from multiple sclerosis patients.[149] Here, greater numbers of microglia/macrophage cells expressing CB_2 immunoreactivity were observed relative to controls.[149] Thus, cannabinoid-based pharmacotherapies consistently show efficacy for suppressing pain due to multiple sclerosis, a disease state associated with an upregulation of CB_2 receptors in microglia.

Brachial Plexus Avulsion-induced Neuropathy

A single study has examined patients with neuropathic pain resulting exclusively from a brachial plexus avulsion (Table 8). This study[150] used a three period crossover design with patients self-administering Δ^9-THC, Sativex®, or placebo for 14-20 days per drug. Both Δ^9-THC and Sativex® reduced the primary outcome measure (Box-Scale 11 ordinal rating scale) in patients suffering from brachial plexus avulsion, indicating a reduction in pain symptoms versus placebo. Sleep quality disturbance scores were improved in patients receiving either active drug versus placebo. Eighty percent of the patients chose to enter an open-label study with Sativex® following completion of this randomized study.

CB_2 receptor immunoreactivity has been reported in normal and injured human DRG neurons, brachial plexus nerves, and neuromas as well as peripheral nerve fibers.[151] However, upregulation of CB_2 receptor immunoreactivity was specifically observed in injured human nerve specimens and avulsed DRG obtained during surgery for brachial plexus repair.[151] These observations correspond to preclinical observations of cannabinoid receptor upregulation following nerve injury.[18] However, possible changes in CB_1 receptor immunoreactivity, were not evaluated in the human tissue, and therefore cannot be excluded.

Mixed Neuropathic Pain

Recruitment of a patient population suffering from a specific form of neuropathic pain can be a difficult prospect; therefore several studies include patients in which neuropathic pain is associated with different disease states or injuries (Table 8). A 21 patient study reported that ajulemic acid (CT-3) suppressed mixed forms of neuropathic pain, as assessed with the VAS,

in the morning (3 hours after drug administration), but not in the afternoon (8 hours following drug administration).[152] Eighteen of those same patients participated in stimulus-evoked pain testing during the study and patients showed a trend towards decreased mechanical allodynia following CT-3 administration.[153] CT-3 binds with high affinity to both CB_1 and CB_2 receptors and also binds with low affinity to PPARγ receptors.[154] CT-3 has limited CNS availability,[69] which translates into fewer CB_1-mediated side-effects. Smoking cannabis cigarettes also improved spontaneous pain relief and pain unpleasantness VAS ratings in patients suffering from mixed forms of neuropathic pain, but failed to alter stimulus-evoked pain.[155] This study reported that cannabinoids compounded the decreased neurocognitive performance of patients that was present at baseline. Using an "N of 1" preparation, Notcutt and colleagues[156] determined if patients experienced improvements in pain following a 2 week open-label phase with Sativex® prior to initiation of the double-blind, placebo-controlled crossover phase of the study. Δ^9-THC and Sativex®, but not placebo or CBD, reduced the VAS rating of the two worst pain symptoms during the crossover phase.[156] Quality of sleep was improved by all cannabinoid based medications[156] and may, therefore, contribute to the therapeutic potential of the cannabinoids. By contrast, opioid analgesics produce deleterious effects on sleep architecture, including reductions in slow wave sleep and promotion of sleep apnea.[157, 158] A similarly structured study reported improved pain ratings (VAS) and spasticity severity following CBD and Δ^9-THC in patients with mixed neuropathic pain.[159] Δ^9-THC and Sativex® additionally improved muscle spasms and spasticity severity.[159]

Sativex® improved pain ratings as measured with the NRS in a five-week double-blind, placebo-controlled study performed in patients experiencing unilateral neuropathic pain.[133] In this study, Sativex® reduced mechanical dynamic and punctate allodynia, and improved sleep disturbances.[133] Seventy-one percent of the patients tested chose to continue to the open label study of Sativex® with 63% withdrawing by the end of the study for various reasons. Nabilone (Cesamet®) decreased measures of spasticity-related pain (11-Point Box Test) in patients experiencing chronic upper motor neuron syndrome (UMNS) associated with a number of pain syndromes.[160] In a retrospective review of patient charts at the Pain Center of the McGill University Health Center from 1999-2003,[161] 75% of patients received some benefit from taking nabilone (whether that came in the form of pain relief, improved sleep, decreased nausea or increased appetite).

Two studies have examined the effects of cannabinoid-based medications in patients suffering from spinal cord injuries. An early case study reported pain relief and improvement in spasticity in a patient with a spinal cord injury following oral Δ^9-THC.[162] A later study reported that 18% of the patients with spinal cord injuries reported pain relief following treatment with oral dronabinol (mean 31 mg per day), whereas 23% experienced enhancement of pain, resulting in subsequent withdrawal by several patients.[163] Changes in experimental design after initiation of the study complicate interpretation of these latter findings.[163]

Caveats

We are aware of only two clinical studies that have failed to report efficacy of cannabinoids, relative to placebo, for treatment of mixed neuropathic pain.[164, 165] Our analysis of the study by Clermont-Gnamien and colleagues [165] is restricted to information provided in the abstract, published in English. Both of these studies employed eight or fewer subjects and evaluated dronabinol titrated to a dose of 25 mg/day (where tolerated). The mean dose was 16.6 ± 6.5 mg oral dronabinol in one study[164] and 15 ± 6 mg in the other study.[165] The two studies associated with negative outcomes for cannabinoids in managing neuropathic pain shared several common features: 1) evaluation of mixed neuropathic pain syndromes known to be refractory to multiple analgesic treatments, 2) evaluation of orally-administered Δ^9-THC (dronabinol) as opposed to mixtures of Δ^9-THC and CBD, or smoked marijuana, 3) small

numbers of subjects, and 4) observation of prominent side-effects (e.g. sedation) resulting in high dropout rates. One study reported side-effects that were more prominent in older patients and did not correlate with analgesia.[164] Of course, one difficulty in evaluating efficacy of analgesics in patients with neuropathic pain refractory to all known treatments is that there is no indication that these patients would respond favorably to any analgesic under the study conditions. In a third study, effects of nabilone were compared with dihydrocodeine in a randomized, crossover double-blind study of three months duration that did not include a pharmacologically inert placebo condition. In this latter study,[166] it was concluded that the weak opioid dihydrocodeine was a statistically better treatment for chronic neuropathic pain than nabilone.[166] Patients in this study exhibited a mean baseline VAS rating of 69.6 mm on a 0-100 mm VAS scale; mean VAS ratings were 59.93 ± 24.42 mm and 58.58 ± 24.08 mm for patients taking nabilone and dihydrocodeine, respectively. However, the authors noted that a small number of subjects responded well to nabilone and side-effects were generally mild and in the expected range.[166] Benefits of an add-on treatment with nabilone have nonetheless been noted in patients with chronic therapy-resistant pain (observed in causal relationship with a pathological status of the skeletal and locomotor system).[167] Oral dronanbinol produced significant pain relief versus placebo when combined with opioid therapy in both a double-blind, placebo-controlled crossover phase and a subsequent open-label extension.[168] Patients additionally reported improvements in sleep problems and disturbances while experiencing an increase in sleep adequacy in the open-label phase of the study.[168] Thus, caution should be exerted prior to concluding that side-effects of cannabinoids seriously limit the therapeutic potential of cannabinoid pharmacotherapies for pain. Combination therapies including a cannabinoid show efficacy for treatment-resistant neuropathic pain and may be employed to limit doses of analgesics or adjuvants associated with adverse side-effects.

Side-effects

Diverse neuropathic pain states (characterized as idiopathic, diabetic, immune-mediated, cobalamin-deficiency related, monoclonal gammopathy-related, alcohol abuse-related and other) were recently examined in a prospective evaluation of specific chronic polyneuropathy syndromes and their response to pharmacological therapies.[169] Intolerable side-effects were observed in all groups of patients receiving either gabapentainoids, tricyclic antidepressants, anticonvulsants, cannabinoids (nabilone or Sativex®) and topical agents).[169] Notably, the presence of intolerable side-effects was similar amongst the different classes of medications.[169] In this study, most forms of neuropathic pain had similar prevalence rates and responsiveness to the different pharmacotherapies evaluated.[169]

A recent systematic review of adverse effects of medical cannabinoids concluded that most adverse events (96.6%) were not serious and no serious adverse events were related exclusively to cannabinoid administration. Moreover, 99% of serious adverse events from randomized clinical trials were reported in only two trials.[170] Greater numbers of nonserious adverse events were observed following cannabinoid treatment, as expected.[170] Side-effects were equally associated with the different cannabinoid pharmacotherapies; the average rate of nonserious adverse events was higher in patients receiving Sativex® or oral Δ^9-THC than controls. [170] Thus, the main burden for the clinician is to balance therapeutic efficacy with the risk of intolerable side-effects in the specific patient.[169] High quality trials of long term exposure to cannabinoid based medications, together with careful monitoring of patients, are required to better characterize safety issues related to use of medical cannabinoids. [170]

Conclusions

Cannabis has been used for pain relief for centuries, although the mechanism underlying their analgesic effects has remained poorly understood until the discovery of cannabinoid receptors and their endogenous ligands in the 1990's. During the last two decades, a large number of

research papers have demonstrated the efficacy of cannabinoids and modulators of the endocannabinoid system in suppressing neuropathic pain in animal models. Cannabinoids suppress hyperalgesia and allodynia (i.e. mechanical allodynia, mechanical hyperalgesia, thermal hyperalgesia and, where evaluated, cold allodynia), induced by diverse neuropathic pain states through CB_1 and CB_2-specific mechanisms. These studies have elucidated neuronal as well as nonneuronal (i.e. activated microglia) sites of action for cannabinoids in suppressing pathological pain states and documented regulatory changes in cannabinoid receptors and endocannabinoid accumulation in response to peripheral or central nervous system injury. Clinical studies largely reaffirm that cannabinoids show efficacy in suppressing diverse neuropathic pain states in humans. The psychoactive effects of centrally-acting cannabinoid agonists, nonetheless, represent a challenge for pain pharmacotherapies that directly activate CB_1 receptors in the brain. However, nonserious adverse events (e.g. dizziness), which pose the major limitation to patient compliance with pharmacotherapy, are not unique to cannabinoids. Approaches that serve to minimize unwanted CNS side-effects (e.g. by combining Δ^9-THC with CBD, or by targeting CB_2 receptors, peripheral CB_1 receptors or the endocannabinoid system) represent an important direction for future research and clinical evaluation. The present review suggests that cannabinoids show promise for treatment of neuropathic pain in humans either alone or as an add-on to other therapeutic agents. Further evaluation of safety profiles associated with long term effects of cannabinoids are, therefore, warranted.

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Table 1

Cannabinoids Evaluated for Suppression of Neuropathic Nociception

Natural Cannabinoid Ligands and Synthetic Analogues

- Δ9-THC (Dronabinol/Marinol®)
- Cannabidiol (CBD)
- Cannador® (cannabis extract, Δ9-THC:CBD, 2.5 mg:1.25 mg)
- Cannabis
- eCBD (Cannabis with high CBD content)
- Nabilone (Cesamet®, Δ9-THC analogue)
- Sativex® (oral-mucosal spray, Δ9-THC:CBD, 2.7 mg:2.5 mg)

Endocannabinoids

- Anandamide (AEA)
- 2-arachydonoylglycerol (2-AG)

Fatty Acids

- L-29
- N-arachidonoyl glycine (NaGly)
- Palmitoylethanolamine (PEA)

CB_1-selective Agonists

- ACEA
- Met-F-AEA

Mixed CB_1/CB_2 Agonists

- BAY59-3074
- CP55,940
- CT-3 (Ajulemic Acid)
- HU-210
- WIN55,212-2

CB_2-selective Agonists

- A-796260
- A-836339
- AM1241 ((R,S)-AM1241)
- (R)-AM1241
- (S)-AM1241
- AM1714
- Compound 27
- GW405833 (L768242)
- JWH015
- JWH133
- MDA7
- MDA19

Endocannabinoid Modulators

Uptake Inhibitors:

- AM404
- VDM11

FAAH Inhibitors:

- Compound 17
- OL135
- URB597

MGL Inhibitors:

- JZL184
- URB602

Table 2

Antinociceptive Effects of Cannabinoids following Chronic Constriction Injury in Rats

	Compound	Route	Thermal	Mechanical Hyperalgesia	Mechanical Allodynia	Mechanism		Ref
						CB_1	CB_2	
Synthetic Analogues of Natural Cannabinoid Ligands	**eCBD**	p.o.	**Yes**	—	**Yes**	—	—	41
		p.o.‡	**Yes**	—	**Yes**	No (SR1 i.p.)	No (SR2 i.p.)	
	CBD	p.o.	No	No	—	—	—	40
			No	—	No	—	—	41
		p.o.‡	**Yes**	—	**Yes**	—	—	41
			Yes	**Yes**	—	No (SR1 i.p.)	No (SR2 p.o.)	40
	Δ^9-THC	p.o.	**Yes**	—	**Yes**	—	—	41’ 171
		p.o.‡	No	—	No	—	—	41
	pCBD+pTHC	p.o.‡	**Yes**	—	**Yes**	—	—	41
Mixed CB_1/CB_2 agonists	**BAY 59-3074**	p.o.	**Yes**	—	**Yes**	—	—	78
	CP55,940	i.p.	**Yes**	—	**Yes**	—	—	171
	WIN55,212-2	s.c.	No	No	—	—	—	48
			—	No	No	—	—	172
			—	**Yes**	—	—	—	173
		s.c.‡	**Yes**	**Yes**	—	—	—	48
			Yes	—	**Yes**	**Yes** (SR1 i.v.)	**Yes** (SR2 i.v.)	54
			Yes	—	**Yes**	**Yes** (SR1 s.c.‡)	—	57
		i.p.	**Yes-heat Yes-cold**	**Yes**	**Yes**	**Yes*** (SR1 i.p.)	—	42
			Yes	—	**Yes**	**Yes** (SR1 i.p.)	—	119
		i.v.	**Yes**	—	—	—	—	47
		i.t.	**Yes**†	—	**Yes**†	**Yes** (AM281 i.t.)	—	38
			—	**Yes**	—	—	—	173
		i.pl.	**Yes**†	—	**Yes**†	—	—	119
$CB_{2\ Agonists}$	**A-796260**	i.p.	—	—	**Yes**	—	—	174
	A-836339	i.p.	—	—	**Yes**	—	**Yes** (SR2 i.p.)	51
		i.p.‡	—	—	**Yes**	—	—	
	GW405833 (L768242)	i.p.	—	—	**Yes**	—	—	50

	Compound	Route	Thermal	Mechanical Hyperalgesia	Mechanical Allodynia	Mechanism		Ref
						CB_1	CB_2	
Endocannabinoid Modulators	**AM404**	s.c.	No	—	No	—	—	52
			Yes	—	**Yes**	—	—	57
			Yes	—	—	—	—	53
		s.c.‡	**Yes**	—	**Yes**	**Yes** (SR1 i.p.)	**Yes** (SR2 i.p.)	52
			Yes	**Yes**	—	**Yes** (SR1 i.p.)	No (SR2 i.p.)	53
			Yes	—	**Yes**	**Yes** (SR1 i.v.)	No (SR2 i.v.)	54
			Yes	—	**Yes**	**Yes** (SR1 s.c.‡)	—	57
	VDM11	s.c.‡	**Yes**	—	**Yes**	—	—	52

eCBD, *Cannabis Sativa* with high CBD content; pCBD, Pure cannabidiol; pTHC, Pure Δ^9-tetrahydrocannabinol; SR1, SR141716; SR2, SR144528;

‡Chronic, post-injury;

*Only tested in thermal hyperalgesia and mechanical allodynia;

†Increased measurements in contralateral paw at dose/s tested

Table 3

Antinociceptive Effects of Cannabinoids following Chronic Constriction Injury in Mice

	Compound	Route	Thermal	Mechanical Hyperalgesia	Mechanical Allodynia	Mechanism		Ref
						CB_1	CB_2	
Endocannabinoid Modulators	**JZL184**	i.p.	**Yes-cold**	—	**Yes**	**Yes** (SR1 i.p.)	No (SR2 i.p.)	59
			Yes-cold ($FAAH^{+/+}$ and $FAAH^{-/-}$)	—	**Yes** ($FAAH^{+/+}$ and $FAAH^{-/-}$)	—	—	
	OL-135	i.p.	**Yes-cold**	—	**Yes**	**Yes** (SR1 i.p.)	**Yes** (SR2 i.p.)	
			Yes-cold ($FAAH^{+/+}$) No-cold ($FAAH^{-/-}$)	—	**Yes-cold** ($FAAH^{+/+}$) No-cold ($FAAH^{-/-}$)	—	—	
	URB597	p.o.	—	**Yes**	—	—	—	55
		p.o.‡	**Yes**	**Yes**	**Yes**	**Yes** (SR1 i.p.)	**Yes*** (SR2 i.p.)	
		i.p.	**Yes-cold**	—	**Yes**	**Yes** (SR1 i.p.)	**Yes** (SR2 i.p.)	59
			Yes-cold ($FAAH^{+/+}$) No-cold ($FAAH^{-/-}$)	—	**Yes-cold** ($FAAH^{+/+}$) No-cold ($FAAH^{-/-}$)	—	—	
Fatty Acids	**PEA**	i.p.	**Yes**	—	**Yes**	—	—	60
		i.p.‡	**Yes**	—	**Yes**	**Yes** (SR1 i.p.)	No (SR2 i.p.)	

PEA, Palmitoylethanolamine; SR1, SR141716; SR2, SR144528;

‡Chronic, post-injury;

*Only for thermal hyperalgesia and mechanical allodynia, no blockade observed for mechanical hyperalgesia

Table 4

Antinociceptive Effects of Cannabinoids following Partial Sciatic Nerve Ligation (Seltzer Model)

	Compound	Route	Thermal	Mechanical Hyperalgesia	Mechanical Allodynia	Mechanism		Ref
						CB_1	CB_2	
Exogenous Endocannabinoids	**AEA**	i.p.	—	**Yes**	—	**Yes** (SR1 i.p.)	—	65
		i.paw	**Yes**	—	**Yes**	**Yes** (AM251 i.paw)	No (AM630 i.paw)	66
	2-AG	i.paw	**Yes**	—	**Yes**	**Yes** (AM251 i.paw)	**Yes** (AM630 i.paw)	67
Mixed CB_1/CB_2 Agonists	**CT-3 (AJA)**	p.o.	—	**Yes**	—	**Yes** (SR1 s.c.)	No (SR2 s.c.)	69
		i.p.	—	—	**Yes**	—	—	175
	CP55,940	s.c.	—	**Yes**	—	—	—	68
	HU-210	s.c.	—	**Yes**	—	—	—	68
		i.p.	NP	—	**Yes**	—	—	62
			—	—	**Yes**	—	—	175
		i.t.	—	—	**Yes**	**Yes** (AM251 i.t.)	**Yes** (SR2 i.t.)	75
	WIN55,212-2	s.c.	**Yes**†	**Yes**	**Yes**	—	—	68
		S.c.$^{\$}$	**Yes**$^{+}$	—	**Yes**$^{\#}$	**Yes** (AM251 chronic s.c.$^{\#}$)	**Yes** (AM630 chronic s.c.$^{\#}$)	176
		i.t.	—	**Yes**	—	**Yes** (SR1 i.t.)	—	68
		i.pl.	—	**Yes**	—	**Yes** (blocked by SR1 s.c., but not i.t.)	—	68
CB_2 Agonists	**GW405833 (L768242)**	i.p.	—	**Yes**	—	—	—	177
			—	—	**Yes**	—	—	178
	JWH133	i.p.	—	—	No	—	—	70
		i.t.	—	—	**Yes** ($CB_2^{+/+}$) No ($CB_2^{-/-}$)	—	—	
		i.paw	—	—	No	—	—	
Endocannabinoid Modulators	**AM404**	i.p.	—	—	**Yes**	**Yes** (AM251 i.p.)	—	73
	URB597	i.p.	NP	—	No	—	—	62
		i.paw	**Yes**	—	**Yes**	**Yes** (AM251 i.paw)	No (AM630 i.paw)	67
	URB602	i.paw	**Yes**	—	**Yes**	**Yes** (AM251 i.paw)	**Yes** (AM630 i.paw)	67
Fatty Acids	**L-29**	i.p.	**Yes-heat** No-cold	—	**Yes**	**Yes** (SR1 i.p.)	**Yes*** (SR2 i.p.)	64
	NaGly	s.c.	—	—	No	—	—	75
		i.t.	—	—	**Yes**	No (AM251 i.t.)	No (SR2 i.t.)	

	Compound	Route	Thermal	Mechanical Hyperalgesia	Mechanical Allodynia	Mechanism		Ref
						CB_1	CB_2	
	PEA	i.p.	—	**Yes**	—	—	**Yes** (SR2 i.p.)	65

AEA, Anandamide; 2-AG, 2-arachydonoylglycerol; AJA, Ajulemic Acid; NaGly, N-arachidonoyl glycine; NP, Not Present; PEA, Palmitoylethanolamine; SR1, SR141716; SR2, SR144528;

†Increased measurements in contralateral paw at dose/s tested;

$Chronic, pre-emptive/post-injury or both;

+Post-injury;

#Pre-emptive and post-injury combined;

*Only observed blockade for mechanical allodynia, not thermal hyperalgesia

□ Tested in rats; ▫ Tested in mice

Table 5

Antinociceptive Effects of Cannabinoids following Spinal Nerve Ligation (Traditional and Modified)

	Compound	Route	Thermal	Mechanical Hyperalgesia	Mechanical Allodynia	Mechanism		Ref
						CB_1	CB_2	
Mixed CB_1/CB_2 agonists	**BAY 59-3074**	p.o.	NP	—	**Yes**	—	—	78
	CP55,940		—	—	**Yes**	No (SR1 i.p.)	**Yes** (SR2 i.p.)	179
		i.p.	—	—	**Yes** ($CB_1^{+/+}$) No ($CB_1^{-/-}$)	—	—	45
			—	—	**Yes** ($CB_2^{+/+}$ and $CB_2^{-/-}$)	—	—	
		i.t.	—	—	**Yes**	No (SR1 i.t.)	—	179
	WIN55,212-2	i.p.	**Yes-heat Yes-cold**	—	**Yes**†	Yes (SR1 i.p.)	No+ (SR2 i.p.)	79
			—	—	**Yes**	—	—	80
			—	—	No	—	—	81
		i.p.‡	—	—	**Yes**	—	—	81
CB_2 Agonists	**AM1241**		**Yes**	—	**Yes**	No (AM251 i.p.)	**Yes** (AM630 i.p.)	44
		i.p.	**Yes** ($CB_1^{+/+}$ and $CB_1^{-/-}$)	—	**Yes** ($CB_1^{+/+}$ and $CB_1^{-/-}$)	No (AM251 i.p.)	**Yes** (AM630 i.p.)	44
			—	—	**Yes**	—	—	85
		i.v.	—	—	**Yes**	—	**Yes** (SR2 i.p.)	17
	Compound 27	i.p.	—	—	**Yes**	—	—	180
	GW405833 (L768242)	i.p.‡	—	—	**Yes**	—	—	81
	L768242 (GW405833)	i.p.	—	—	**Yes**	—	—	17
	MDA19	i.p.	—	—	**Yes**	—	**Yes** (AM630 i.p.)	181
	MDA7	i.p.	—	—	**Yes**	No (AM251 i.p.)	**Yes** (AM630 i.p.)	85
Endocannabinoid Modulators	**Compound 17**	i.v.	—	—	**Yes**	—	—	90
	OL135	i.p.	—	—	**Yes**	No (SR1 i.p.)	**Yes** (SR2 i.p.)	91

NP, Not Present; SR1, SR141716; SR2, SR144528;

†Increased measurements in contralateral paw at dose/s tested;

‡Chronic, post-injury;

+Only cold allodynia tested

▫ Tested in rats; ▪ Tested in mice

Table 6

Antinociceptive Effects of Cannabinoids in Animal Models of Disease-related Neuropathic Pain

Model	Compound		Route	Thermal	Mechanical Hyperalgesia	Mechanical Allodynia	Mechanism		Ref
							CB_1	CB_2	
Diabetic Neuropathy	**Met-F-AEA**		i.p.	—	**Yes**	—	—	—	107
			i.p.‡	—	**Yes**	—	—	—	
	WIN55,212-2		i.p.	NP	—	**Yes**	—	—	182
				—	**Yes**	—	—	—	107
				NP	—	**Yes**	—	—	183
			i.p.‡	—	**Yes**	—	—	—	107
			i.paw	NP	—	**Yes**	—	—	183
	AM1241		i.p.	—	**Yes**	—	—	—	107
			i.p.‡	—	**Yes**	—	—	—	
Chemotherapy-induced Neuropathy	**Cisplatin**	**WIN55,212-2**	i.p.§	—	—	**Yes**	—	—	116
	Paclitaxel118, 120	**WIN55,212-2**	i.p.	**Yes**	—	**Yes**	**Yes** (SR1 i.p.)	—	119
			i.pl.	**Yes**†	—	**Yes**†	—	—	
		MDA7	i.p.	NP	—	**Yes**	—	—	85
		(*R*,*S*)-AM1241	i.p.	NP	—	**Yes**	No (SR1 i.p.)	**Yes** (SR2 i.p.)	89
		(*R*)-AM1241	i.p.	NP	—	**Yes**	—	—	
		(*S*)-AM1241	i.p.	NP	—	No	—	—	
		AM1714	i.p.	NP	—	**Yes**	No (SR1 i.p.)	**Yes** (SR2 i.p.)	
	Vincristine121	**WIN55,212-2**	i.p.	NP	—	**Yes**	**Yes** (SR1 i.p.)	**Yes** (SR2 i.p.)	122
			i.t.	NP	—	**Yes**	**Yes** (SR1 i.t.)	**Yes** (SR2 i.t.)	
			i.pl.	NP	—	No	—	—	
		(*R*,*S*)-AM1241	i.p.	NP	—	**Yes**	No (SR1 i.p.)	**Yes** (SR2 i.p.)	
	HIV-SN	**WIN55,212-2**	i.p.‡	NP-heat NP-cold	—	**Yes***	—	—	124, 123
		L-29	i.p.+	NP-heat NP-cold	—	**Yes**	**Yes** (SR1 i.p.)	**Yes** (SR2 i.p.)	64
Other	**LDPN**	**WIN55,212-2**	i.t.	**Yes**	—	**Yes**	**Yes** (AM251 i.t.)	—	125
	VZV	**L-29**	i.p.	NP-heat NP-cold	—	**Yes**	No (SR1 i.p.)	No (SR2 i.p.)	64
		WIN55,212-2	i.p.‡	NP-heat NP-cold	—	**Yes**	—	—	131

ddc, Zalcitabine; HIV-SN, HIV Sensory Neuropathy (includes antiretroviral treatment (ddc), HIV-gp120, and HIV-gp120 + antiretroviral treatment (ddc) models); LDPN = Lysolecithin-induced Demyelination-associated Peripheral Neuropathy of saphenous nerve; NP, Not Present; SR1, SR141716; SR2, SR144528; VZV, Varicella Zoster Virus-induced neuropathy;

‡ Chronic, post-injury;

$ Chronic, pre-emptive and post-injury;

† Increased measurements in contralateral paw at dose/s tested;

* In antiretroviral (ddc), HIV-gp120, and HIV-gp120 + antiretroviral (ddc) models;

+ Only tested in the antiretroviral (ddc) model

□ Tested in rats; ■ Tested in mice

Table 7

Effects of Cannabinoids on Disease-related Neuropathic Pain in Clinical Studies

	Compound/Route	Primary Outcome Measure	Stimulus Evoked Pain	Secondary Outcome Measures	Ref
HIV-SN	**Cannabis cigarettes (3.56% Δ^9-THC)**[*] Smoking	VAS daily pain ratings – *52% reported > 30% reduction in pain*	LTS – *No Effect* Heat and capasaicin sensitization model – *Reduced area sensitive to mechanical allodynia*	POMS – *No Effect*	135
	Cannabis cigarettes (1-8% Δ^9-THC)[‡] Smoking	DDS and VAS pain ratings – *46% reported ≥ 30% reduction in pain*	—	POMS/SIP/BSI/plasma VL and CD4+ lymphocyte counts – *No Effect*	137
Multiple Sclerosis-related Neuropathic Pain	**Dronabinol (Marinol®)**[‡] p.o.	NRS of median spontaneous pain intensity – *Reduction from BL on this measure was 20.5% (-0.6 pt.) with Dronabinol vs. placebo*	Median radiating pain intensity/ pressure pain threshold – *Improved* Cold and warm sensibility/tactile detection/tactile pain detection/ vibration sense/temporal summation/mechanical or cold allodynia – *No Effect*	SF-36 – *Improvements in bodily pain and mental health categories*	134
	Sativex®[*#] Oral-Mucosal Spray	[*]NRS-11 (pain) – *-1.25 pt reduction in favor of Sativex®*	—	NPS/NRS-11 pain related sleep disturbances – *Improved* PGIC – *Sativex® treated 3.9× more likely than placebo to rate themselves in an improved category* HADS/MS-related disability scale – *No Effect*	146
		[#]NRS-11 (pain) – No changes in pain scores from randomized 5-wk trial (up to 2 years) – *Sativex® still suppressing pain vs. BL*	—	*44% of patients completed approximately 2 years of open-label study.* No increase in titration of dose – *No tolerance*	147
	Dronabinol (Marinol®)[$] p.o. **Cannador®**[$] p.o.	Ashworth Spasticity Score – *No Effect*	—	Category-Rating Scales – *Improved pain, sleep quality, spasms and spasticity with CBM* 10 m walk – *Improved with CBM* Rivermead Mobility Index/Barthel Index/GHQ-30/UKNDS – *No Effect*	143
	Dronabinol (Marinol®)[†] p.o. **Cannador®**[†] p.o.	Ashworth Spasticity Score – *Improvement following Dronabinol*	—	Category Rating Scales – *Improved pain, spasms, spasticity, sleep, shakiness, energy level and tiredness with CBM* Rivermead Mobility Index/Barthel Index/GHQ-30/UKNDS/10 m walk – *No Effect*	145

BL, Baseline; BSI, Brief Symptom Inventory; CBM, Cannabinoid Based Medicine; DDS, Descriptor Differential Scale; HADS, Hospital Anxiety and Depression Scale; HIV-SN, HIV-associated Sensory Neuropathy; GHQ, General Health Questionnaire; LTS, Long-term Thermal Stimulation; MS, Multiple Sclerosis; NPS, Neuropathic Pain Scale; NRS, Numerical Rating Scale; PGIC, Patient Global Impression of Change; POMS, Profile of Mood States; SF-36, Short Form Health Questionnaire; SIP, Sickness Impact Profile; UKNDS, United Kingdom Neurological Disability Score; VAS, Visual Analogue Scale; VL, Viral Load;

[*]Double-blind, placebo-controlled;

[‡]Double-blind, placebo-controlled crossover;

[#]Open label extension of randomized double-blind, placebo-controlled study;

[$]Randomized, placebo-controlled;

[†]Double-blind, placebo-controlled 1 year extension

Table 8

Effects of Cannabinoids in Injury-Related and Mixed Neuropathic Pain in Clinical Studies

	Compound/Route	Primary Outcome Measure	Stimulus Evoked Pain	Secondary Outcome Measures	Ref
Brachial Plexus Avulsion	**Sativex®/Δ^9-THC‡** Oral Mucosal Spray	BS-11 (pain) - *Sativex® reduced pain by 0.58 boxes vs. placebo* *Δ^9-THC reduced pain by 0.64 boxes vs. placebo*	—	Pain Review BS-11/Sleep Quality BS-11/Sleep Disturbances – *Improved with CBM* GHQ-12 – *Improved with Sativex* SF-MPQ Pain Rating Index and VAS - *Improved with Δ^9-THC* PDI - *No Effect*	150
Mixed Neuropathy	**Dronabinol (Marinol®)**$^+$ p.o.	VAS daily pain ratings – *No Effect*	Brush-induced mechanical allodynia – *No Effect*	MPQ/BPI/HADS/Notingham Health Profile – *No Effect*	164
	Nabilone (Cesamet®)/DHC$^{\$}$ p.o.	VAS daily pain ratings – *DHC better than Nabilone*	—	SF-36 – *Physical Role improved with Nabilone; Bodily pain improved with DHC*	166
	CT-3 (AJA)‡ p.o.	VAS (pain) – *CT-3 reduced pain ratings in the morning (3 hrs. post-drug), but not afternoon (8 hrs. post-drug)* VRS (pain) – *No Effect*	*Decrease in mechanical hypersensitivity (von Frey) in group receiving AJA prior to placebo (P = 0.052)*	TMT; ARCI-M – *No effect*	152, 153
	Cannabis cigarettes (3.5-7% Δ^9-THC)‡ Smoking	Spontaneous Pain Relief VAS - *Improved*	Mechanical Allodynia (Foam Brush) VAS; Thermal Hyperalgesis VAS – *No effect*	Pain Unpleasantness VAS/NPS – *Improved* Degree of Pain Relief PGIC/Psychoactive effects/Neurocognitive Effects – *Greater with Cannabis* Mood VAS – *No Effect*	155
	Δ^9-THC/CBD/Sativex®‡ Oral-Mucosal Spray (Open-label phase with Sativex® prior to crossover)	VAS of 2 worst symptoms – *Decrease in symptoms following Δ^9-THC and Sativex® relative to placebo*	—	Quality of sleep – Im*proved with all CBM* Duration of sleep – *No Effect* BDI/GHQ-28– *Qualitative improvement in mood following CBM*	156
		VAS Daily Ratings of target symptoms – *CBD and Δ^9-THC improved pain; Δ^9-THC and Sativex® improved spasms; Δ^9-THC improved spasticity*	—	Numerical Symptom Scale – *Spasticity severity improved with all CBM; frequency of muscle spasms improved with Δ^9-THC and Sativex®* VAS daily ratings – *Δ^9-THC improved appetite; Sativex® improved sleep*	159
Unilateral Mixed Neuropathy	**Sativex®*** Oral-Mucosal Spray	NRS (pain) – *-1.48 pt. reduction (22%) in Sativex condition vs. -0.52 pt. (8%) reduction in placebo condition*	Mechanical Dynamic Allodynia NRS – *Reduction with Sativex®* Punctate Mechanical Allodynia – *No Effect*	Sleep Disturbances NRS/NPS/PDI/PGIC (neuropathic pain)/PGIC (pain at allodynic sites) – *Improved with Sativex®* GHQ-12/BRB-N – *No Effect*	133
UMNS	**Nabilone (Cesamet®)**‡ p.o.	11-Point Box Test of spasticity-related pain – *Decreased a median of 2 pts. with Nabilone vs. placebo*	—	Ashworth Score/Rivermead Motor Assessment/ Barthel Index – *No Effect*	160

ARCI-M, Addiction Research Center Inventory-Marijuana; BDI, Body Disability Index; BPI, Wisconsin Brief Pain Inventory; BRB-N, Brief Repeatable Battery of Neuropsychological Tests; BS-11, Box Scale; CBM, Cannabinoid Based Medication; DHC, Dihydrocodeine, GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; MPQ, McGill Pain Questionnaire; NPS, Neuropathic Pain Scale; NRS, Numerical Rating Scale; PDI, Pain Disability Index; PGIC, Patient Global Impression of Change; SF-36, Short Form Health Questionnaire; SF-MPQ, Short Form of McGill Questionnaire; TMT, Trial Making Test; UMNS, (chronic) Upper Motor Neuron Syndrome; VAS, Visual Analogue Scale; VRS, Verbal Rating Scale;

‡Double-blind, placebo-controlled crossover;

+Open-label, no placebo;

[$] Double-blind, crossover

[*] Double-blind, placebo-controlled.