Diabetic peripheral neuropathy (DPN) is characterized by progressive loss of peripheral nerves, which causes numbness, weakness, and severe pain. The medications available currently provide only modest relief from the pain of DPN and are associated with various side effects, which has generated an enormous demand for research on new therapeutic approaches. Dysregulation of the endocannabinoid system has been reported in DPN. Cannabinoid-based medications have gained increasing attention as a potential therapy to alleviate DPN pain. Endocannabinoids and cannabinoids’ actions are mediated primarily by cannabinoid receptor 1 (CB₁R) and cannabinoid receptor 2 (CB₂R). Cannabinoids that activate CB₁R have demonstrated a profound antinociceptive effect, although CB₁R is associated with undesirable psychoactive effects. Peripherally restricted CB₁R agonists help overcome this problem; however, adverse metabolic and cardiovascular effects limit its therapeutic use. In contrast, CB₂R antagonists, selective CB₁R agonists, and endocannabinoid metabolizing enzymes inhibitors alleviate DPN pain effectively with minimal side effects. This article provides a concise overview of the preclinical and clinical studies that have tested the therapeutic potential of targeting the endocannabinoid system to treat painful DPN.

Keywords: Cannabinoid receptor 1, cannabinoid receptor 2, cannabinoids, diabetic peripheral neuropathic pain, endocannabinoid system
enormous demand for research on new therapeutic approaches to treat this condition.

Diabetic mouse models are useful tools in understanding diabetes’ pathogenesis and treatment, and several display neurological impairments associated with DPN.[7,8] The model used most frequently to study diabetic neuropathy is the streptozotocin (STZ)-induced Type 1 diabetic rodent model.[7,8] This model involves injecting rodents with STZ systemically, which results in irreversible degeneration of the β-cells of Langerhans’ pancreatic islets. An STZ-induced diabetic rodent develops peripheral neuropathy slowly (over 4 weeks) and exhibits thermal and mechanical hyperalgesia, together with cold and mechanical allodynia.[7]

The Cannabis sativa plant has been exploited to manage chronic pain for centuries.[9,10] Over the past two decades, cannabinoids, natural compounds found in Cannabis sativa, have gained popularity rapidly as an analgesic to manage inflammatory and neuropathic pain, including pain associated with DPN.[9,10] The two most abundant cannabinoids in Cannabis sativa are Δ9-tetrahydrocannabinol (THC), the primary psychoactive, and cannabidiol (CBD), a nonpsychoactive.[11,12] Cannabinoids exert potent antinociceptive, antihyperalgesic, and antiallodynic effects at peripheral, spinal, and supraspinal sites. Several animal studies and clinical trials have demonstrated the efficacy of cannabinoids in managing chronic inflammatory and neuropathic pains, such as pain associated with fibromyalgia, cancer, multiple sclerosis, and diabetes.[13-15] This review provides the current state of knowledge of cannabinoids’ therapeutic potential to relieve pain associated with DPN in animals and clinical trials.

THE ENDOCANABINOID SYSTEM

The endocannabinoid system (ECS) is an endogenous signaling system that is comprised of endocannabinoids (endogenous ligands), their receptors, and anabolic and catabolic enzymes that maintain the endocannabinoids’ levels.[16-18] The endocannabinoids, N arachidonylethanolamine (AEA), and 2-arachidonoylglycerol (2-AG), are lipid mediators synthesized postsynthetically.[19,20] AEA’s synthesis is catalyzed through N-acyltransferase and N-acyl-phosphatidylethanolamine (NAPE)-hydrolyzing phospholipase D (NAPE-PLD), while 2-AG’s synthesis is catalyzed largely by diacylglycerol lipase. The brief action of AEA and 2-AG is attributable to their fast degradation by fatty-acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively.[16-18]

Endocannabinoids and cannabinoids bind and activate two well-characterized G-protein coupled receptors (GPCRs), i. e., cannabinoid receptors 1 (CB1R) and 2 (CB2R).[16-18] Both couple with Gαq protein and their activation suppresses adenylyl cyclase-mediated cAMP production and activates mitogen-activated protein kinases. Further, activation of CB1R has been shown to activate the G protein-coupled inwardly rectifying K+ channel, while it inhibits voltage-gated Ca2+ channels, thereby suppressing neuronal firing and alters neurotransmitter release.[16-18] In addition to CB1R/CB2R, the endocannabinoids, AEA and 2-AG, also activate CB1R splice variants and non-CB1R/CB2R GPCRs, such as GPR18, GPR55, and GPR119, which play an important role in the sensory transmission and integration of pain.[19,21] AEA interacts and activates the transient receptor potential vanilloid 1 (TRPV1) channel as well, which is implicated in pain regulation.[22]

The cannabinoid receptors, CB1R and CB2R, are expressed in several areas of the pain pathway.[19,23] In the central nervous system (CNS), the CB1R are found in several sites associated with modulating and transmitting pain, including the rostral ventromedial medulla, the periaqueductal gray, thalamus, and amygdala.[24-26] The CB2R are also expressed in regions involved with processing pain, such as the spinal trigeminal nucleus caudalis and spinal dorsal horn.[25,27-29] In the peripheral nervous system (PNS), CB1R are expressed in sensory neurons’ cell bodies located in the dorsal root ganglia,[30-32] while in the nociceptive primary sensory neurons, the CB2R are colocalized with TRPV1 channels.[33,34] The CB1R are also expressed in myelinated and unmyelinated nerve fiber bundles in the human skin.[35] CB2R are found predominantly in the immune cells, including macrophages, mast cells, B-lymphocytes, and microglia,[36,37] where the activation of the CB1R expressed in these cells mediates cannabinoids’ immunosuppressive effects. In addition, CB2R is also expressed in the skin’s sensory neurons.[35,38-41]

ENDOCANNABINOID SYSTEMS IN DIABETIC PERIPHERAL NEUROPATHIC PAIN

Alterations in endocannabinoid functions have been documented in several neuropathic pain conditions, including DPN. Numerous studies have reported that CB1R mRNA expression and protein levels change in several areas of the pain pathway in neuropathic pain conditions.[42,43] An increase in the CB1R protein level has been documented in the spinal cord and thalamus in mice with STZ-induced DPN.[44-46] The increased CB1R expression under neuropathic pain conditions may augment the endocannabinoids’ or CB1R agonists’ potency or efficacy.[47] In contrast, in the PNS, CB2R expression was reduced in the dorsal root ganglia of diabetic rodents. The activation of CB1R with an agonist attenuated neural damage in an in vitro experimental diabetic neuropathy model, which suggests that cannabinoids exert neuroprotective effects.[48,49] Future research is required to determine whether CB1R’s loss in the PNS contributes to diabetic neuropathy’s pathogenesis.

CB1R are found in immune cells, which are unregulated in neuropathic pain conditions.[50-52] Microglia play an essential role in neuropathic pain, as reactive microglia interact with neurons and are involved in neuropathic pain’s pathophysiology.[50-52] In STZ-induced diabetic mice, CB2R proteins’ expression was increased in spinal cord microglial cells.[46] Increased CB2R expression may assist...
in neuroprotection from neuroinflammatory insults reactive microglia produce. CB$_{1}$R protein and mRNA expression are also elevated in T-lymphocytes and macrophages in the skin epidermal and dermal layers in neuropathic conditions.\cite{93} The increased CB$_{1}$R expression in microglia and inflammatory cells in DNP suggests that CB$_{1}$R might represent an attractive target drug to reduce pain.\cite{54,55}

Changes in the endocannabinoid levels have also been observed in neuropathic pain conditions.\cite{56-58} Augmented levels of AEA and 2-AG have been reported in pain modulating pathways (including the periaqueductal gray and rostral ventromedial medulla) and the spinal cord in neuropathic pain animal models.\cite{57-59} While in the periphery, both AEA and 2-AG levels were increased considerably in the dorsal root ganglia.\cite{43} Hence, the increase in endocannabinoid levels may be a neuroprotective mechanism in neuropathic pain conditions. Moreover, immune cell recruitment at the nerve damage site may increase endocannabinoid levels further.\cite{115} N-palmitoylethanolamine (PEA) is a non-endocannabinoid lipid mediator that activates peroxisome proliferator-activated receptor $\alpha$ (PPAR$\alpha$). PEA has an affinity for the GPR55 and GPR119 receptors as well. One study found an elevated PEA level in the paw skin of mice with DNP.\cite{60}

### Cannabinoids’ Modulation of Diabetic Peripheral Neuropathic Pain in Preclinical Animal Studies

Numerous preclinical studies have reported that synthetic and naturally occurring cannabinoids effectively attenuate inflammatory and neuropathic pain, including DPN pain.\cite{14,15} Table 1 summarizes the preclinical studies that have investigated the potential benefits of modulating ECS to attenuate pain in rodents with STZ-induced DPN. An earlier study reported that oral administration of THC, a nonselective CB$_{1}$/CB$_{2}$R agonist, to STZ-induced neuropathic rodents reduced thermal hyperalgesia.\cite{61} Subsequent studies have found that systemic or intrathecal administration of the synthetic nonselective CB$_{1}$/CB$_{2}$R agonist, WIN-55,212-2, decreased thermal and mechanical hyperalgesia drastically in STZ-induced neuropathic rodents in a dose-dependent manner.\cite{14,46,62,63} Similarly, the systemic or local administration of WIN-55,212-2 to either STZ-induced neuropathic rats or Zucker diabetic fatty rats (Type 2 diabetes) alleviated mechanical allodynia,\cite{64} while pretreatment with the CB$_{1}$R-selective antagonist AM251 or the CB$_{2}$R-inverse agonist SR144528 reversed WIN 55,212-2’s antinociceptive properties. This finding suggests that WIN 55,212-2’s antinociceptive effects are mediated through the activation of CB$_{1}$R and CB$_{2}$R.\cite{64} Another study reported that chronic administration of 2-Methyl-2’-F-anandamide, a CB$_{2}$R selective agonist, attenuated mechanical hyperalgesia in STZ-induced diabetic neuropathy.\cite{62} However, the uses of nonselective cannabinoids that activate the CB$_{1}$/CB$_{2}$R in the CNS and the PNS are associated with numerous unwanted CNS side effects, including sedation, hypothermia, catalepsy, hypolocomotion, and psychological problems that are caused by CB$_{1}$R activation present in the brain.\cite{77}

Therefore, peripherally restricted cannabinoid agonists may help avoid these adverse side effects. Activation of peripherally expressed CB$_{2}$Rs plays a vital role in cannabinoid-induced antinociceptive. Peripherally, restricted CB$_{2}$Rs agonists were found to alleviate pain effectively by activating CB$_{2}$Rs expressed on peripheral nociceptors.\cite{14,64} Numerous peripherally restricted synthetic cannabinoid agonists have been synthesized and showed analgesic effects in neuropathic pain animal models.\cite{15} Oral administration and local injection

### Table 1: Targeting the endocannabinoid system in streptozotocin-induced diabetic peripheral neuropathic pain rodent models

| Target                  | Compounds          | Species       | Route              | Effect on pain thresholds | References |
|-------------------------|--------------------|---------------|--------------------|---------------------------|------------|
| CB$_{1}$/CB$_{2}$R agonists | THC                | Mouse/rat     | Oral               | +                         | [61]       |
|                         | WIN 55,212-2       | Rat           | Intrathecal/systemic | +  +  +                   | [46,62-64] |
| CB$_{1}$R agonists      | Met-F-AEA          | Rat           | Systemic           | +                         | [62]       |
| CB$_{2}$R antagonists   | SR141716 (rimonabant) | Mice         | Systemic           | +                         | [65,66]    |
| CB$_{1}$R agonists      | L759,656           | Mice          | Intrathecal        | +                         | [46]       |
|                         | MT178              | Mouse         | Systemic           | +                         | [67]       |
|                         | AM1241             | Rat           | Systemic           | +                         | [62]       |
|                         | JWH-015            | Mouse         | Intraplanter       | +  +  +                   | [68]       |
| TRPV1 agonists          | Capsaicin          | Mouse         | Topical            | +  +  +                   | [69]       |
| FAAH                    | Alpha-lipoic acid  | Rat           | Systemic           | +  +  +                   | [70]       |
|                         | URB597             | Rat           | Systemic           | +  +  +                   | [71]       |
|                         | ST4070             | Rat/Mice      | Oral               | +                         | [72]       |
|                         | URB937             | Rat           | Systemic           | +                         | [73]       |
| MAGL                    | MJN110             | Rat           | Systemic           | +  +  +                   | [74]       |
| PPAR$\alpha$            | PEA                | Mouse         | Systemic/oral      | +  +  +                   | [75,76]    |

CB$_{1}$R: Cannabinoid receptor 1, CB$_{2}$R: Cannabinoid receptor 2, FAAH: Fatty acid amide hydrolase, MA: mechanical allodynia, MAGL: Monoacylglycerol lipase, Met-F-AEA: 2-Methyl-2’-F-anandamide, MH: Mechanical hyperalgesia, PEA: N-palmitoylethanolamine, PPAR$\alpha$: Peroxisome proliferator-activated receptor $\alpha$, TH: Thermal hyperalgesia, TRPV1: Transient receptor potential vanilloid 1
of CRA13, a peripherally acting nonselective CB$_R$/CB$_R$ agonist, reduced both thermal hyperalgesia and mechanical allodynia in rodents with neuropathic pain. CRA13 did not produce the CNS side effects observed with CB$_R$ agonists.\cite{78} Further, CRA13’s antinociceptive effect was diminished by the coadministration of rimonabant (SR141716), a CB$_R$ selective antagonist. However, the antinociceptive effect of CRA13 was still observed when the CB$_R$/inverse agonist, SR144528, was coadministered. These findings confirmed that this compound’s antinociceptive action is attributable to the activation of peripheral CB$_R$s.\cite{78} In a neuropathic pain model, the administration of the peripherally acting nonselective CB$_R$/CB$_R$ agonist AZ11713908 reduced mechanical allodynia.\cite{79} The analgesic effect of AZ11713908 was observed in CB$_R$ knockout mice but diminished in CB$_R$ knockout mice. This finding indicates that the activation of CB$_R$s in the periphery contributes to this compound’s analgesic effects.\cite{79} However, these compounds’ ability to attenuate DPN pain effectively has not yet been evaluated in rodent models.

Another strategy to avoid unwanted CB$_R$-mediated CNS side effects is the use of CB$_R$ positive allosteric modulators (PAMs).\cite{80,81} CB$_R$ PAMs bind to the CB$_R$ at an allosteric site (s) on the CB$_R$ that are distinct from the orthosteric-binding site. The binding of a PAM to CB$_R$ leads to conformational changes within the receptor, which enhances the affinity and/or efficacy of the orthostatic ligand for the CB$_R$. Unlike CB$_R$ orthosteric agonists, CB$_R$ PAMs do not have psychoactive effects or lead to tolerance or dependence.\cite{80,82} GAT221 (racemic mixture of GAT228 and GAT229), a CB$_R$ allosteric modulator characterized recently, has shown promising results in suppressing pain in chemotherapy-induced neuropathic mice and did not lead to tolerance or dependence.\cite{83} Whether CB$_R$ PAMs are efficacious in attenuating neuropathic pain in a PDN pain model has not been evaluated to date.

Similar to other GPCRs, CB$_R$ can interact physically with other receptors, such as dopamine, adenosine, and opioid receptors.\cite{84-86} Cannabinoid dimerization can expand cell signaling diversity in response to ligands via various mechanisms of allosteric control among receptor heteromers.\cite{87,88} In diabetic mice, the coadministration of THC and morphine was found to enhance morphine’s antinociceptive properties.\cite{61} Although the CB$_R$-opioid heteromer-specific mechanisms probably are responsible for these effects, more research is needed to confirm this finding. Given that CB$_R$ heteromers can exert effects that are unique from its constituent receptors, it may be promising to target CB$_R$ heteromers to attenuate DPN pain.

Emerging evidence from preclinical studies has suggested that activation of the peripheral CB$_R$s enhances the oxidative stress and inflammatory processes and results in microvascular and neuronal impairment.\cite{15,49,89} In diabetic rodents, CB$_R$ stimulation has been attributed to cannabinoids’ adverse metabolic and cardiovascular effects. These adverse effects of CB$_R$ agonists are the primary hindrance to their successful use to manage DPN pain.\cite{15,49,89} Indeed, studies have found that CB$_R$s’ inhibition may be beneficial in DPN rodent models. For example, the chronic administration of rimonabant (SR141716), a CB$_R$-selective antagonist, to STZ-induced diabetic mice reduced intraepidermal nerve fiber density loss significantly. In addition, rimonabant treatment decreased skin capillary loss, improved skin blood flow, and decreased tumor necrosis factor-alpha (TNF-$\alpha$) levels in STZ-induced diabetic mice’s skin tissue. These findings suggest that rimonabant exerts anti-inflammatory and vasoprotective effects and might be a beneficial treatment for PDN pain.\cite{65} Consistent with this finding, Comelli et al. reported that rimonabant treatment attenuated mechanical allodynia in a time-and dose-dependent manner.\cite{66} Further, it reduced TNF-$\alpha$ overproduction in the spinal cord and oxidative stress in the peripheral nerves, while it neutralized the nerve growth factor deficit in STZ-induced diabetic rodents. These findings imply that CB$_R$ antagonists interfere with neuronal impairment pathways and promote nerve regeneration.\cite{66} Rimonabant has shown promising results in clinical trials, as it improved several metabolic risk factors and reduced weight loss.\cite{90} Although CB$_R$ antagonists may have benefits in treating DPN pain, their use has been hindered largely by their adverse psychiatric effects, such as anxiety and depression.\cite{49,92} The development of peripherally restricted CB$_R$ antagonists could be a promising strategy to alleviate painful DPN without these adverse CB$_R$-mediated CNS effects.

Together, the activation of peripheral CB$_R$s produces robust antinociceptive properties; however, some studies have revealed that activation of the CB$_R$ is associated with undesirable diabetic complications. In contrast, recent studies have reported the beneficial effects of blocking CB$_R$s to treat DPN. These conflicting findings might be attributable to the different experimental designs, animal species, and bias agonists.\cite{91,92} Further research is required to determine what type of CB$_R$ modulation is favorable to manage DPN.

In preclinical studies, activation of CB$_R$ has been shown to exert neuroprotective effects and attenuate neuropathic pain by inhibiting immune cells and microglia-driven inflammation.\cite{15} For example, intrathecal administration of WIN-55,212-2 to STZ-induced diabetic mice reduced thermal hyperalgesia significantly.\cite{46,65} The coadministration of AM630, a CB$_R$ antagonist, but not AM251, a CB$_R$ inverse agonist, diminished WIN-55,212-2’s antinociceptive effects significantly. These findings suggest that the activation of CB$_R$ in the spinal cord mediates cannabinoids’ antinociceptive properties.\cite{46} Notably, CB$_R$’s activation by its selective agonists is not associated with unwanted CB$_R$-mediated CNS side effects. A study found that the selective CB$_R$ agonist, L-759,656 reduced thermal hyperalgesia in mice with STZ-induced diabetic neuropathy considerably, and AM63 reversed this effect.\cite{46} Similarly, the CB$_R$ agonists, MT178 and AM124, reduced mechanical hyperalgesia in dose-related manners in diabetic mice.\cite{62,93} Further studies have found that the intra-planter injection of
the CB₂R agonist JWH-015 attenuated mechanical allodynia in mice with STZ-induced-diabetic neuropathy. A CB₂R antagonist inhibited the antinociceptive action of JWH-015, which suggests that peripheral CB₂R is involved in this compound’s antinociceptive action. All of these studies have highlighted the important role that CB₂ receptors play over CB₁R in the antinociceptive effects of cannabinoids and further support the hypothesis that selective CB₁R agonists may offer an exciting approach to reduce pain in DPN.

The upregulation of TRPV1 channels in the dorsal root ganglia and the myelinated primary afferent neurons have been reported to mediate diabetic thermal hyperalgesia. The topical application of the TRPV1 agonist capsaicin attenuated thermal and mechanical hyperalgesia observed in STZ-induced diabetic mice in a dose-dependent manner, while pre-treatment with the TRPV1 antagonist capsazepine blocked capsaicin’s effects. Further, a study of STZ-induced diabetic rats showed that alpha-lipoic acid, a TRPV1 agonist, attenuated neuropathic pain and normalized TRPV1 expression in the dorsal root ganglion through the inhibition of the nuclear factor NF-κB. These studies demonstrated that stimulation of the TRPV1 channels is a useful approach to attenuate painful DPN.

Elevation of endocannabinoids has been observed in both the CNS and the periphery in rodents with DPN. Compounds that inhibit the endocannabinoid metabolizing enzymes, FAAH and MAGL, increase the endocannabinoid levels by inhibiting their degradation. Research based on preclinical neuropathic animal models has reported that FAAH and MAGL inhibitors produce antinociceptive effects with fewer side effects relative to CB₁R/CB₂R agonists. Systemic administration of URB597, a FAAH inhibitor, decreased both mechanical allodynia and formalin-induced cold allodynia in mice with diabetic neuropathic pain. Similarly, significant anti-allodynic effects were observed following the oral administration of the reversible FAAH inhibitor, ST4070, to mice with STZ-induced neuropathic pain. The coadministration of selective CB₁R and CB₂R antagonists and the PPARα antagonist diminished this compound’s anti-allodynic effects. Further, the systemic administration of the peripherally restricted FAAH inhibitor, URB937, attenuated STZ-induced hyperalgesia and allodynia. Recently, several MAGL inhibitors have been developed and examined in neuropathic pain models. For example, the selective MAGL inhibitor, MJN110, was reported to reduce mechanical allodynia in rodents with DPN. These studies have provided evidence that supports the beneficial effects of modulating endocannabinoid levels to treat pain associated with DPN.

PEA is the endogenous ligand for PPARα, and it also has an affinity for the GPR55 and GPR119 receptors. Acute and repeated PEA administration alleviated mechanical allodynia, neutralized the nerve growth factor deficit, and improved insulin levels in STZ-induced diabetic mice. Importantly, PEA produces an antinociceptive effect without causing tolerance. A further study by Impellizzeri et al. reported that oral administration of a micronized PEA formulation attenuated mechanical and thermal hyperalgesia and reduced mast cell and microglial activation in mice with DPN. This has been linked to an inhibition of the nuclear factor NF-κB inflammatory pathway. PEAs antinociceptive and neuroprotective properties are mediated primarily by the activation of PPARα.

**Clinical Studies of Cannabinoids’ Modulation of Diabetic Peripheral Neuropathic Pain**

Preclinical studies have provided promising evidence of the antinociceptive properties of selective CB₁R agonists, peripherally restricted CB₁R agonists, and FAAH and MAGL inhibitors in DPN rodent models. However, although cannabinoids have shown promising antinociceptive effects in animals, this does not necessarily indicate efficacy in humans. In a very early trial, Sativex®, which contains equimolar THC with CBD, did not relieve patients’ DPN pain. In 2012, a placebo-controlled clinical trial was conducted to assess the antinociceptive properties of Nabilone®, a synthetic THC, on patients with DPN pain, and showed that it diminished pain effectively. The patients tolerated Nabilone® well and it yielded an overall improvement in their status as well. Further, a randomized, placebo-controlled crossover study was conducted to evaluate the effectiveness of inhaled cannabis in patients with painful DPN, which produced adequate dose-dependent antinociceptive effects in patients. However, smoked cannabis was also associated with dose-dependent cognitive impairments. In a later clinical trial, the selective FAAH inhibitor ASP8477 failed to produce significant antinociceptive properties relative to the placebo in patients with DPN pain. Interestingly, ASP8477 did not show evidence of cannabinoid-related adverse effects. A recent randomized, placebo-controlled trial was conducted to test topical CBD oil’s efficacy in alleviating DPN pain in the lower extremities. The topical application of CBD was tolerated well and improved pain in patients with PDN significantly. However, all trials to date have been relatively brief, with very limited sample sizes. It is possible that different agents and doses and a longer treatment duration could produce significant pain relief in patients with DPN.

**Conclusion**

Targeting the ECS provides a promising way to modulate neuropathic pain associated with diabetes. The peripherally restricted CB₁R agonist is an attractive strategy to treat DPN pain that lacks the adverse CNS side effects. CB₁R agonists and endocannabinoid-metabolizing enzyme inhibitors attenuate DPN pain with limited side effects as well. The primary limitation of the preclinical studies is that most were conducted with STZ-induced diabetic mice; further, a limited number of studies have been conducted using diabetic rodents that are representatives of the human disease. However, few clinical trials to date have supported cannabinoid-based medications’ safety and efficacy to alleviate pain associated with DPN.
Hence, future clinical studies are vital to further establish cannabinoid-based medications’ ability to treat painful DPN.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Zakin E, Abrams R, Simpson DM. Diabetic neuropathy. Semin Neurol 2019;39:560-9.
2. Said G. Diabetic neuropathy A review. Nature Clin Pract Neurol 2007;3:331-40.
3. Schreiber AK, Nones CF, Reis RC, Chichorro JG, Cunha JM. Diabetic neuropathic pain: Physiopathology and treatment. World J Diabetes 2015;6:432-44.
4. Javed S, Petropoulos IN, Alam U, Malik RA. Treatment of painful diabetic neuropathy. Therap Adv Chronic Dis 2015;6:15-28.
5. Snyder MI, Gibbs LM, Lindsay TJ. Treating painful diabetic peripheral neuropathy: An update. Am Fam Physician 2016;94:227-34.
6. Sommer C, Cruccu G. Topical treatment of peripheral neuropathic pain: Applying the Evidence. J Pain Symptom Manage 2017;53:614-629.
7. Courteix C, Eschalier A, Lavarenne J. Streptozocin-induced diabetic rats: Behavioural evidence for a model of chronic pain. Pain 1993;53:81-8.
8. Brien PD, Sakowski SA, Feldman EL. Mouse models of diabetic neuropathy. ILAR J 2014;54:259-72.
9. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006;58:389-462.
10. Russo EB. Cannabinoids in the management of difficult to treat pain. Ther Clin Risk Manag 2008;4:245-59.
11. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an cannabinoid. Science 1964;142:1646-7.
12. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM. Cannabidiol in the management of difficulty to treat pain. Clin Ther 2014;36:259-72.
13. Donvito G, Nass SR, Wilkerson JL, Curry ZA, Schurman LD, et al. Cannabinoid receptor Cb2. Ann New York Acad Sci 2003;996:10-6.
14. Bridges D, Rice AS, Egertová M, Elphick MR, Winter J, Michael GJ, et al. Localization of cannabinoid receptor 1 in rat dorsal root ganglion using in situ hybridization and immunohistochemistry. Neuroscience 2003;119:803-12.
15. Lynn AB, Herkenham M. Localization of central cannabinoid CB1 receptor messenger RNA in neuronal subpopulations of rat dorsal root ganglia: A double-label in situ hybridization study. Neuroscience 1999;90:923-31.
16. Bridges D, Rice AS, Egertová M, Elphick MR, Winter J, Michael GJ, et al. Localization of cannabinoid receptor 1 in rat dorsal root ganglion using in situ hybridisation and immunohistochemistry. Neuroscience 2003;119:803-12.
17. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
18. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
19. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
20. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
21. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
22. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
23. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
24. Anandamide and the cannabinoid CB1 receptor in the central nervous system. J Pain Symptom Manage 2017;53:614-629.
CB1 agonist. Pain 2006;124:175-83.

43. Mittrittakanakul S, Ramakul N, Guerrero A V, Matsuka Y, Ono T, Iwase H, et al. Site-specific increases in peripheral cannabinoid receptors and their endogenous ligands in a model of neuropathic pain. Pain 2006;126:102-14.

44. Siegling A, Hofmann HA, Denzer D, Mauler F, De Vry J. Cannabinoid CB1 receptor upregulation in a rat model of chronic neuropathic pain. Eur J Pharmacol 2001;415:R5-7.

45. Lim G, Sung B, Ji RR, Mao J. Uptregulation of spinal cannabinoid-1 receptors following nerve injury enhances the effects of win 55,212-2 on neuropathic pain behavior in rats. Pain 2003;105:275-83.

46. Ikeda H, Ikemagi M, Kai M, Ohsawa M, Kamei J. Activation of spinal cannabinoid CB2 receptors inhibits neuropathic pain in streptozotocin-induced diabetic mice. Neuroscience 2013;250:446-54.

47. Spiegelman I. Therapeutic targeting of peripheral cannabinoid receptors in inflammatory and neuropathic pain states. In: Translational Pain Research: From Mouse to Man. Boca Raton (FL): CRC Press/Taylor and Francis; 2009.

48. Zhang F, Challapalli SC, Smith PJ. Cannabinoid CB1 receptor activation stimulates neurite outgrowth and inhibits capsaicin-induced Ca2+ influx in an in vitro model of diabetic neuropathy. Neuropharmacology 2009;57:88-96.

49. Gruden G, Baruta F, Kunos G, Pacher P. Role of the endocannabinoid system in diabetes and diabetic complications. Br J Pharmacol 2016;173:1116-27.

50. Hsieh GC, Pai M, Chandran P, Hooker BA, Zhu CZ, Salyers AK, et al. Central and peripheral sites of action for CB2 receptor mediated analgesic activity in chronic inflammatory and neuropathic pain models in rats. Br J Pharmacol 2011;162:428-40.

51. Naguib M, Xu JJ, Diaz P, Brown DL, Cogdoll D, Bie B, et al. Prevention of paclitaxel-induced neuropathy through activation of the central cannabinoid type 2 receptor system. Anesth Analg 2012;114:1104-20.

52. Xu J, Tang Y, Xie M, Bie B, Wu J, Yang H, et al. Activation of cannabinoid receptor 2 attenuates mechanical allodynia and neuroinflammation responses in a chronic post-ischemic pain model of complex regional pain syndrome type 1 in rats. Eur J Neurosci 2016;44:3046-55.

53. Zhang J, Chen L, Su T, Cao F, Meng X, Pei L, et al. Electroacupuncture increases CB2 receptor expression on keratinocytes and infiltrating inflammatory cells in inflamed skin tissues of rats. Pain 2010;11:1250-8.

54. Bie B, Wu J, Foss JF, Naguib M. An overview of the cannabinoid type 2 receptor system and its therapeutic potential. Curr Opin Anesthesiol 2018;31:407-14.

55. Turcotte C, Blanchet MR, Laviolette M, Flamand N. The CB2 receptor and its role as a regulator of inflammation. Cell Mol Life Sci 2016;73:4499-70.

56. Jahanabadi S, Hadian MR, Shamsaee J, Tavangar SM, Abdollahi A, et al. Site-specific increases in peripheral cannabinoid receptors and their endogenous ligands in a model of neuropathic pain. Pain 2006;124:175-83.

57. Petrosino S, Palazzo E, de Novellis V, Bisogno T, Rossi F, Maione S, et al. The neuroprotective effects of win 55,212-2 on neuropathic pain behaviors in rats. Pain 2010;637:70-6.

58. Comelli F, Bettoni I, Colombo A, Fumagalli P, Giagnoni G, Costa B, et al. Rimonabant, a cannabinoid CB1 receptor antagonist, attenuates mechanical allodynia and counters oxidative stress and nerve growth factor deficit in diabetic mice. Eur J Pharmacol 2010;637:62-9.

59. Vencenzi F, Targa M, Coricuilo C, Tabrizi MA, Merighi S, Gessi S, et al. Anioccipitive effects of the selective CB2 agonist MT178 in inflammatory and chronic rodent pain models. Pain 2013;154:864-73.

60. Castany S, Carcelé M, Leánez S, Pol O. The role of carbon monoxide on the anti-nociceptive effects and expression of cannabinoid 2 receptors during painful diabetic neuropathy in mice. Psychopharmacology (Berl) 2016;233:2209-19.

61. Palazzo E, Luongo L, de Novellis V, Berrino L, Rossi F, Maione S, et al. Moving towards supraspinal TRPV1 receptors for chronic pain relief. Mol Pain 2010;6:66.

62. Bujalska M. Effect of cannabinoid receptor agonists on streptozotocin-induced hyperalgesia in diabetic neuropathy. Pharmacology 2008;82:193-200.

63. Jahanabadi S, Hadian MR, Shamsae J, Tavangar SM, Abdollahi A, Dehpour A, et al. The effect of spinally administered WIN 55,212-2, a cannabinoid agonist, on thermal pain sensitivity in diabetic rats. Iran J Basic Med Sci 2016;19:394-401.
81. Laprairie RB, Bagher AM, Rourke JL, Zrein A, Cairns EA, Kelly MEM, et al. Positive allosteric modulation of the type 1 cannabinoid receptor reduces the signs and symptoms of huntington’s disease in the R6/2 mouse model. Neuropharmacology 2019;151:1-2.

82. Mitjavila J, Yin D, Kulkarni PM, Zanato C, Thakur GA, Ross R, et al. Enantiomer-specific positive allosteric modulation of CB1 signaling in autaptic hippocampal neurons. Pharmacol Res 2018;129:475-81.

83. Slivicki RA, Xu Z, Kulkarni PM, Pertwee RG, Mackie K, Thakur GA, et al. Positive allosteric modulation of cannabinoid receptor type 1 suppresses pathological pain without producing tolerance or dependence. Biol Psychiatry 2018;84:722-33.

84. Carriba P, Ortiz O, Patkar K, Justinova Z, Strok J, Themann A, et al. Striatal adenosine A2A and cannabinoid CB1 receptors form functional heteromeric complexes that mediate the motor effects of cannabinoids. Neuropsychopharmacology 2007;32:2249-59.

85. Fernández-Ruiz J, Hernández M, Ramos JA. Cannabinoid-dopamine interaction in the pathophysiology and treatment of CNS disorders. CNS Neurosci Ther 2010;16:e72-91.

86. Hojo M, Sudo Y, Ando Y, Minami K, Takada M, Matsubara T, et al. Mu-opioid receptor forms a functional heterodimer with cannabinoid CB1 receptor: Electrophysiological and FRET assay analysis. J Pharmacol Sci 2008;108:308-19.

87. Bagher AM, Laprairie RB, Kelly ME, Denovan-Wright EM. Antagonism of dopamine receptor 2 long affects cannabinoid receptor 1 signaling in a cell culture model of striatal medium spiny projection neurons. Mol Pharmacol 2016;89:652-66.

88. Bagher AM, Laprairie RB, Toguri JT, Kelly ME, Denovan-Wright EM. Bidirectional allosteric interactions between cannabinoid receptor 1 (CB1) and dopamine receptor 2 long (D2L) heterotetramers. Eur J Pharmacol 2017;813:66-83.

89. Eid BG. Cannabinoids for treating cardiovascular disorders: Putting together a complex puzzle. J Microse Ultrastruct 2018;6:171-6.

90. Pi-Sunyer FX, Aronne LJ, Ernault E, Liosatos M, Tracy K, Moseley J, et al. The MOBILE study-A phase Ila enriched enrollment randomized withdrawal trial to assess the analgesic efficacy and safety of ASP8477, a fatty acid amide hydrolase inhibitor, in patients with peripheral neuropathic pain. Pain Med 2017;18:2388-400.

91. Xu DH, Cullen BD, Tang M, Fang Y. The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. Curr Pharm Biotechnol 2020;21:390-402.