Review Article

The Endocannabinoid System as a Therapeutic Target in Diabetic Peripheral Neuropathic Pain: A Review

Amina M. Bagher

Department of Pharmacology and Toxicology, Faculty of Pharmacy, King AbdulAziz University, Jeddah, Kingdom of Saudi Arabia

Abstract

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 (CB_1R) and cannabinoid receptor 2 (CB_2R). Cannabinoids that activate CB_1R have demonstrated a profound antinociceptive effect, although CB_1R is associated with undesirable psychoactive effects. Peripherally restricted CB_1R agonists help overcome this problem; however, adverse metabolic and cardiovascular effects limit its therapeutic use. In contrast, CB_1R antagonists, selective CB_2R 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

Introduction

Diabetic neuropathy is a devastating microvascular complication of diabetes mellitus. Diabetic peripheral neuropathy (DPN) is the most prevalent type of diabetic neuropathy, as it affects nearly 60% of all diabetic patients.[1] DPN involves distal-to-proximal degeneration of peripheral nerves. It tends to affect small nerve fibers in the skin and is manifested by hyperalgesia (excessive sensitivity to noxious stimuli) and allodynia (excessive sensitivity to nonnoxious stimuli). As DPN progresses, degeneration appears on larger myelinated nerve fibers and leads to a decrease in ankle reflexes and loss of proprioception.[1,2] Clinical manifestations vary based on the type of nerve fibers affected and include numbness, tingling, weakness, spontaneous pain, hyperalgesia, and/or allodynia.[1,2] DPN's precise pathophysiology is still not understood well; however, growing evidence suggests that chronic hyperglycemia produces metabolic abnormalities within the nerve and the microvasculature that supplies the nerves that contribute collectively to DPN development. Further, inflammation, impaired insulin signaling, production of mitochondrial reactive oxygen species, and dyslipidemia have linked to DPN progression.[3]

The medications available currently provide only modest pain relief for patients who suffer from DPN.[4] The recommended first-line treatment for DPN pain includes anticonvulsants (pregabalin), serotonin-noradrenaline reuptake inhibitors (duloxetine), and tricyclic antidepressants (amitriptyline).[4,5] If a patient responds poorly to these treatments, topical lidocaine and opioids may be prescribed.[6] Uncontrolled DPN pain can affect a patient's quality of life and increase the incidence of anxiety/depression.[6] The current medications' inability to control painful DPN and its various side effects has generated an

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Address for correspondence: Dr. Amina M. Bagher, Department of Pharmacology and Toxicology, Faculty of Pharmacy, King AbdulAziz University, P.O. Box: 80209, Jeddah 21589, Kingdom of Saudi Arabia.
E-mail: abagher@kau.edu.sa

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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 Δ^9-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 Endocannabinoid 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 arachidonoylethanolamine (AEA), and 2-arachidonoylglycerol (2-AG), are lipid mediators synthesized postsynaptically.[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 (CB_1R) and 2 (CB_2R).[16-18] Both couple with $G\alpha_i$-protein and their activation suppresses adenylyl cyclase-mediated cAMP production and activates mitogen-activated protein kinases. Further, activation of CB_1R has been shown to activate the G protein-coupled inwardly rectifying K + channel, while it inhibits voltage-gated Ca^{+2} channels, thereby suppressing neuronal firing and alters neurotransmitter release.[16-18] In addition to CB_1R/CB_2R, the endocannabinoids, AEA and 2-AG, also activate CB_1R splice variants and non-CB_1R/CB_2R GPCRs, such as GPR18, GPR55, and GPR119, which play an important role in the sensory transmission and integration of pain.[18,21] AEA interacts and activates the transient receptor potential vanilloid 1 (TRPV1) channel as well, which is implicated in pain regulation.[22]

The cannabinoid receptors, CB_1Rs and CB_2Rs, are expressed in several areas of the pain pathway.[18,23] In the central nervous system (CNS), the CB_1Rs 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 CB_1Rs 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), CB_1Rs are expressed in sensory neurons' cell bodies located in the dorsal root ganglia,[30-32] while in the nociceptive primary sensory neurons, the CB_1Rs are colocalized with TRPV1 channels.[33,34] The CB_1Rs are also expressed in myelinated and unmyelinated nerve fiber bundles in the human skin.[35] CB_2Rs are found predominantly in the immune cells, including macrophages, mast cells, B-lymphocytes, and microglia,[36,37] where the activation of the CB_2R expressed in these cells mediates cannabinoids' immunosuppressive effects. In addition, CB_2R 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 CB_1R mRNA expression and protein levels change in several areas of the pain pathway in neuropathic pain conditions.[42,43] An increase in the CB_1R protein level has been documented in the spinal cord and thalamus in mice with STZ-induced DPN.[44-46] The increased CB_1R expression under neuropathic pain conditions may augment the endocannabinoids' or CB_1R agonists' potency or efficacy.[47] In contrast, in the PNS, CB_1Rs expression was reduced in the dorsal root ganglia of diabetic rodents. The activation of CB_1Rs 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 CB_1Rs' loss in the PNS contributes to diabetic neuropathy's pathogenesis.

CB_2Rs 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, CB_2R proteins' expression was increased in spinal cord microglial cells.[46] Increased CB_2R expression may assist

in neuroprotection from neuroinflammatory insults reactive microglia produce. CB_2R protein and mRNA expression are also elevated in T-lymphocytes and macrophages in the skin epidermal and dermal layers in neuropathic conditions.[53] The increased CB_2R expression in microglia and inflammatory cells in DNP suggests that CB_2R might represent an attractive target drug to reduce pain.[54,55]

Changes in the endocannabinoid levels have also been observed in neuropathic pain conditions.[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,[57-59] while in the periphery, both AEA and 2-AG levels were increased considerably in the dorsal root ganglia.[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.[15] N-palmitoylethanolamine (PEA) is a non-endocannabinoid lipid mediator that activates peroxisome proliferator-activated receptor α (PPARα). 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.[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.[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_1R/CB_2R agonist, to STZ-induced neuropathic rodents reduced thermal hyperalgesia.[61] Subsequent studies have found that systemic or intrathecal administration of the synthetic nonselective CB_1R/CB_2R agonist, WIN-55,212-2, decreased thermal and mechanical hyperplasia drastically in STZ-induced neuropathic rodents in a dose-dependent manner.[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,[64] while pretreatment with the CB_1R-selective antagonist AM251 or the CB_2R-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_1R and CB_2R.[64] Another study reported that chronic administration of 2-Methyl-2'-F-anandamide, a CB_1R selective agonist, attenuated mechanical hyperalgesia in STZ-induced diabetic neuropathy.[62] However, the uses of nonselective cannabinoids that activate the CB_1R/CB_2R 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_1R activation present in the brain.[77] Therefore, peripherally restricted cannabinoid agonists may help avoid these adverse side effects. Activation of peripherally expressed CB_1Rs plays a vital role in cannabinoid-induced antinociceptive. Peripherally, restricted CB_1Rs agonists were found to alleviate pain effectively by activating CB_1Rs expressed on peripheral nociceptors.[34] Numerous peripherally restricted synthetic cannabinoid agonists have been synthesized and showed analgesic effects in neuropathic pain animal models.[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
				MH	TH	MA	
CB_1R/CB_2R agonists	THC	Mouse/rat	Oral		+		[61]
	WIN 55,212-2	Rat	Intrathecal/systemic	+	+	+	[46,62-64]
CB_1R agonists	Met-F-AEA	Rat	Systemic	+			[62]
CB_1R antagonists	SR141716 (rimonabant)	Mice	Systemic	+			[65,66]
CB_2R agonists	L759,656	Mice	Intrathecal		+		[46]
	MT178	Mouse	Systemic	+			[67]
	AM1241	Rat	Systemic	+			[62]
	JWH-015	Mouse	Intra-planter	+	+	+	[68]
TRPV1 agonists	Capsaicin	Mouse	Topical	+	+		[69]
	Alpha-lipoic acid	Rat	Systemic		+	+	[70]
FAAH	URB597	Rat	Systemic	+	+		[71]
	ST4070	Rat/Mice	Oral	+			[72]
	URB937	Rat	Systemic	+			[73]
MAGL	MJN110	Rat	Systemic	+	+		[74]
PPARα	PEA	Mouse	Systemic/oral	+	+		[75,76]

CB_1R: Cannabinoid receptor 1, CB_2R: 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, PPARα: Peroxisome proliferator-activated receptor α, TH: Thermal hyperalgesia, TRPV1: Transient receptor potential vanilloid 1

of CRA13, a peripherally acting nonselective CB_1R/CB_2R agonist, reduced both thermal hyperplasia and mechanical allodynia in rodents with neuropathic pain. CRA13 did not produce the CNS side effects observed with CB_1R agonists.[78] Further, CRA13's antinociceptive effect was diminished by the coadministration of rimonabant (SR141716), a CB_1R-selective antagonist. However, the antinociceptive effect of CRA13 was still observed when the CB_2R-inverse agonist, SR144528, was coadministered. These findings confirmed that this compound's antinociceptive action is attributable to the activation of peripheral CB_1Rs.[78] In a neuropathic pain model, the administration of the peripherally acting nonselective CB_1R/CB_2R agonist AZ11713908 reduced mechanical allodynia.[79] The analgesic effect of AZ11713908 was observed in CB_2R knockout mice but diminished in CB_1R knockout mice. This finding indicates that the activation of CB_1Rs in the periphery contributes to this compound's analgesic effects.[79] However, these compounds' ability to attenuate DPN pain effectively has not yet been evaluated in rodent models.

Another strategy to avoid unwanted CB_1R-mediated CNS side effects is the use of CB_1R positive allosteric modulators (PAMs).[80,81] CB_1R PAMs bind to the CB_1R at an allosteric site (s) on the CB_1R that are distinct from the orthosteric-binding site. The binding of a PAM to CB_1R leads to conformational changes within the receptor, which enhances the affinity and/or efficacy of the orthostatic ligand for the CB_1R. Unlike CB_1R orthosteric agonists, CB_1R PAMs do not have psychoactive effects or lead to tolerance or dependence.[80,82] GAT221 (racemic mixture of GAT228 and GAT229), a CB_1R allosteric modulator characterized recently, has shown promising results in suppressing pain in chemotherapy-induced neuropathic mice and did not lead to tolerance or dependence.[83] Whether CB_1R PAMs are efficacious in attenuating neuropathic pain in a PDN pain model has not been evaluated to date.

Similar to other GPCRs, CB_1R can interact physically with other receptors, such as dopamine, adenosine, and opioid receptors.[84-86] Cannabinoid dimerization can expand cell signaling diversity in response to ligands via various mechanisms of allosteric control among receptor heteromers.[87,88] In diabetic mice, the coadministration of THC and morphine was found to enhance morphine's antinociceptive properties.[61] Although the CB_1R-opioid heteromer-specific mechanisms probably are responsible for these effects, more research is needed to confirm this finding. Given that CB_1R heteromers can exert effects that are unique from its constituent receptors, it may be promising to target CB_1R heteromers to attenuate DPN pain.

Emerging evidence from preclinical studies has suggested that activation of the peripheral CB_1Rs enhances the oxidative stress and inflammatory processes and results in microvascular and neuronal impairment.[15,49,89] In diabetic rodents, CB_1R stimulation has been attributed to cannabinoids' adverse metabolic and cardiovascular effects. These adverse effects of CB_1R agonists are the primary hindrance to their successful use to manage DPN pain.[15,49,89] Indeed, studies have found that CB_1Rs' inhibition may be beneficial in DPN rodent models. For example, the chronic administration of rimonabant (SR141716), a CB_1R-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-α) 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.[65] Consistent with this finding, Comelli *et al.* reported that rimonabant treatment attenuated mechanical allodynia in a time-and dose-dependent manner.[66] Further, it reduced TNF-α 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_1R antagonists interfere with neuronal impairment pathways and promote nerve regeneration.[66] Rimonabant has shown promising results in clinical trials, as it improved several metabolic risk factors and reduced weight loss.[90] Although CB_1R antagonists may have benefits in treating DPN pain, their use has been hindered largely by their adverse psychiatric effects, such as anxiety and depression.[49] The development of peripherally restricted CB_1R antagonists could be a promising strategy to alleviate painful DPN without these adverse CB_1R-mediated CNS effects.

Together, the activation of peripheral CB_1Rs produces robust antinociceptive properties; however, some studies have revealed that activation of the CB_1R is associated with undesirable diabetic complications. In contrast, recent studies have reported the beneficial effects of blocking CB_1Rs to treat DPN. These conflicting findings might be attributable to the different experimental designs, animal species, and bias agonists.[91,92] Further research is required to determine what type of CB_1R modulation is favorable to manage DNP.

In preclinical studies, activation of CB_2R has been shown to exert neuroprotective effects and attenuate neuropathic pain by inhibiting immune cells and microglia-driven inflammation.[15] For example, intrathecal administration of WIN-55,212-2 to STZ-induced diabetic mice reduced thermal hyperplasia significantly.[46,63] The coadministration of AM630, a CB_2R antagonist, but not AM251, a CB_1R inverse agonist, diminished WIN-55,212-2's antinociceptive effects significantly. These findings suggest that the activation of CB_2R in the spinal cord mediates cannabinoids' antinociceptive properties.[46] Notably, CB_2R's activation by its selective agonists is not associated with unwanted CB_1R-mediated CNS side effects. A study found that the selective CB_2R agonist, L-759,656 reduced thermal hyperplasia in mice with STZ-induced diabetic neuropathy considerably, and AM63 reversed this effect.[46] Similarly, the CB_2R agonists, MT178 and AM124, reduced mechanical hyperalgesia in dose-related manners in diabetic mice.[62,93] Further studies have found that the intra-planter injection of

the CB_2R agonist JWH-015 attenuated mechanical allodynia in mice with STZ-induced-diabetic neuropathy. A CB_2R antagonist inhibited the antinociceptive action of JWH-015, which suggests that peripheral CB_2R is involved in this compound's antinociceptive action.[67,68] All of these studies have highlighted the important role that CB_2R receptors play over CB_1R in the antinociceptive effects of cannabinoids and further support the hypothesis that selective CB_2R agonists may offer an exciting approach to reduce pain in DPN.[15]

The upregulation of TRPV1 channels in the dorsal root ganglia and the myelinated primary afferent neurons have been reported to mediate diabetic thermal hyperalgesia.[94] 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.[69] 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.[70] These studies demonstrated that stimulation of the TRPV1 channels is a useful approach to attenuate painful DPN.[94]

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 CB_1R/CB_2R agonists.[15,49] Systemic administration of URB597, a FAAH inhibitor, decreased both mechanical allodynia and formalin-induced cold allodynia in mice with diabetic neuropathic pain.[71] Similarly, significant anti-allodynic effects were observed following the oral administration of the reversible FAAH inhibitor, ST4070, to mice with STZ-induced neuropathic pain.[72] The coadministration of selective CB_1R and CB_2R antagonists and the PPARα antagonist diminished this compound's anti-allodynic effects.[72] Further, the systemic administration of the peripherally restricted FAAH inhibitor, URB937, attenuated STZ-induced hyperalgesia and allodynia.[73] 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.[74] 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.[75] Importantly, PEA produces an antinociceptive effect without causing tolerance.[75] 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.[75,76]

Clinical Studies of Cannabinoids' Modulation of Diabetic Peripheral Neuropathic Pain

Preclinical studies have provided promising evidence of the antinociceptive properties of selective CB_2R agonists, peripherally restricted CB_1R 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.[49] In a very early trial, Sativex®, which contains equimolar THC with CBD, did not relieve patients' DPN pain.[95] 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.[96] 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.[97] 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.[98] 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.[99] 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 CB_1R agonist is an attractive strategy to treat DPN pain that lacks the adverse CNS side effects. CB_2R 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.

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Conflicts of interest

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