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The endocannabinoid system and neuropathic pain

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Abstract

The research of new therapeutic strategies for neuropathic pain represents a major current priority. Important drawbacks to advance in the development of these therapies are the limited translational value of the animal models now available and the elucidation of the complex neuronal and immune pathophysiological mechanisms underlying neuropathic pain. One of the neurotransmitter systems participating in neuropathic pain control that has recently raised a particular interest is the endocannabinoid system. This system is highly expressed in neurons and immune cells, and it plays a crucial role in the development of neuropathic pain. Preclinical studies have provided important findings, revealing the potential interest of the endocannabinoid system for the treatment of neuropathic pain. These studies have reported the analgesic effects of cannabinoid agonists in multiple neuropathic pain models, and they have identified specific targets within this system to develop more effective and safe analgesic compounds. However, further studies using more relevant neuropathic pain animal models are required to confirm these interesting results. Several clinical studies suggest that cannabinoids significantly reduced neuropathic pain, although most of these trials fail the required standards of quality. The different pain patient populations included in the systematic reviews also make it difficult to get adequate conclusions. Therefore, additional clinical trials that consider an adequate number of patients, the use active treatments as controls, and longer duration of administration are required to have an adequate profile of the effectiveness and safety of cannabinoids in neuropathic pain.

Keywords: Neuropathic pain, Animal models, Cannabinoid, Clinical research, CB1 receptor, CB2 receptor, Nociception, Emotional alterations, Cognition

1. Introduction

Chronic neuropathic pain is a devastating pain syndrome affecting 7% to 10% of the general population,[40] with higher incidence in the aged people.[14] Neuropathic pain patients have lower labor productivity, use more health resources, and are more likely to develop mental disorders compared with those with other chronic pain.[57] It has been estimated that cost related to neuropathic pain could amount to as much as $160 billion per year only in the United States, which represents approximately one quarter of all chronic pain costs.[36] An important limitation at the present moment is the absence of effective treatment for neuropathic pain. Indeed, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and anticonvulsants constitute the first-line treatment for neuropathic pain.[4] However, the efficacy is only modest, and the number of patients needed to treat for 50% pain relief is estimated in 3 to 9.4.[32] Topical capsaicin and lidocaine are second-choice agents with discrete efficacy recommended for peripheral neuropathies, and other treatments such as opioids or botulinum toxin-A are weakly recommended because of the side effects or poor evidence of efficacy.[32] Therefore, the research of new therapeutic strategies for neuropathic pain represents a major current priority.

2. Significance and limitations of the animal models

The existence of appropriate animal models is crucial for understanding the biological basis of the different diseases. The limited translational value of the animal models currently available to investigate neuropathic pain represents an important drawback to advance in understanding the pathophysiological mechanisms involved and to develop new therapeutic strategies. Neuropathic pain is characterized by the presence of spontaneous pain and signs of sensory loss, which can sometimes be accompanied by the gain of function, ie, allodynia and hyperalgesia. Sensory manifestations are often associated to emotional and cognitive alterations. A number of disorders affecting the somatosensory system have been modeled to investigate neuropathic pain, although the most common neuropathic pain models mimic traumatic injuries to the nervous system (**Table 1**). Injury and disease-based models are successful in reproducing allodynia and hyperalgesia associated to neuropathic pain.[49,93] Although allodynia and hyperalgesia are important complaints affecting up to 64% of the patients, the cardinal symptom of neuropathic pain is spontaneous pain that affects 96% of patients,[8] and it has not been evaluated in appropriate animal models until recently. Direct measures of spontaneous pain, such as changes in facial expression, locomotor activity, or rearing, are transient in models of peripheral neuropathic pain, and they have not been widely used to evaluate drug efficacy.[55,71,107] Recent operant self-medication paradigms or conditioned place preference tests are promising indirect measures useful to evaluate

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Table 1

Summary of animal studies evaluating efficacy of cannabinoids in neuropathic pain.

Name of the model	Principle of the model	Cannabinoid behavioral responses
Traumatic models—peripheral nerve injury		
Chronic constriction injury	3-4 loose ligatures around sciatic nerve[22]	Mixed CB1R/CB2R and CB2R agonists, cannabinoid-reuptake and FAAH*/MAGL inhibitors reduced thermal and mechanical nociception. Acute rimonabant (selective CB1R antagonist) showed pronociceptive effects. CB2R agonist showed antidepressant effect.[93] Intrathecal CB1R/CB2R but not CB2R agonist inhibited mechanical nociception.[13] FAAH and MAGL–KO mice showed unaltered nociception*; wild-type mice developed tolerance to antinociception after repeated treatment with high doses of MAGL but not with FAAH inhibitors.[99] A CB1R-positive allosteric modulator reduced mechanical sensitivity.[45]
Partial sciatic nerve ligation (Seltzer model)	Tight ligation of cranial 1/3 of sciatic nerve[22]	Mixed CB1R/CB2R,* CB2R agonists,* cannabinoid-reuptake and FAAH*/MAGL inhibitors reduced thermal and mechanical nociception. CB2R-KO mice showed contralateral hypernociception*. Rimonabant and CB2R inverse agonists induced pronociceptive effects.[93,104] CB1R-KO mice showed enhanced anxiety and depression-like behavior.*,[92]
Spinal nerve ligation or transection	L5-L6 ligation or transection[22,93]	Mixed CB1R/CB2R*, CB2R agonists,* and FAAH inhibitors reduced thermal and mechanical nociception. Mixed CB1R/CB2R agonist–mediated antinociception and motor impairment were abolished in CB1R-KO mice.* Treatment with CB1R antagonist enhanced CB2R-mediated antinociception.[87,93] MAGL-KO and wild-type mice showed similar mechanical and thermal nociception.*,[17]
Saphenous nerve injury	Saphenous nerve partial ligation, demyelination, or constriction with 2 loose ligatures[93]	Mixed CB1R/CB2R agonist suppressed thermal and mechanical nociception.[93]
Orofacial pain, trigeminal neuralgia	Two loose ligatures around infraorbital nerve[49]	Mixed CB1R/CB2R agonist reduced mechanical nociception, without developing tolerance.[93]
Spared nerve injury	Transection of tibial and common peroneal nerves[22]	Mixed CB1R/CB2R agonists suppressed thermal and mechanical nociception, an effect reduced in mice lacking CB1* in nociceptors.[93] A CB2R agonist maintained an operant behavior associated to spontaneous pain relief and inhibited mechanical nociception[39] MAGL-KO and wild-type mice showed similar mechanical nociception.*,[86]
Sciatic nerve axotomy	Ligation and transection of sciatic nerve[22]	—
Tibial nerve injury	Axotomy of tibial branch of sciatic nerve[93]	Mixed CB1R/CB2R attenuated thermal and mechanical nociception.[93]
Traumatic models—spinal cord injury		
Spinal cord clip–compression injury	Compression of T6-T8 segment with microaneurysm clip[93]	Mixed CB1R/CB2R agonist suppressed mechanical nociception.[93]
Weight drop or contusive spinal cord injury	Drop of a weight onto exposed spinal cord[49]	Mixed CB1R/CB2R agonist suppressed thermal nociception.[3]
Spinal hemisection	Hemisection cranial to L1 dorsal root[49]	—
Drug-induced models		
Streptozocin-induced diabetic neuropathy	Subcutaneous streptozocin administration[22,49]	Mixed CB1R/CB2R, CB1R, and CB2R agonists suppressed mechanical sensitivity. THC enhanced analgesic effect of morphine. A mixed agonist reversed cognitive impairment.[93]
Alcohol-induced neuropathy	Chronic dietary ethanol consumption[49]	
Chemotherapy-induced neuropathy	Repeated administration of paclitaxel, vincristine, oxaliplatin, cisplatin[22,49]	Mixed CB1R/CB2R and CB2R agonists inhibited mechanical and thermal sensitivity.[93] FAAH inhibitor reduced mechanical nociception.[111]
Antiretroviral-induced neuropathy	Zalcitabine, didanosine, stavudine administration[49,51,93]	FAAH inhibitor reduced mechanical sensitivity.[93]
Viral neuropathy		
Postherpetic neuralgia	Subcutaneous hind paw inoculation of Varizella zoster virus–infected cells[49]	Mixed CB1R/CB2R agonist and FAAH inhibitor reduced mechanical and thermal sensitivity.[93]

(*continued on next page*)

Table 1 (*continued*)

Name of the model	Principle of the model	Cannabinoid behavioral responses
HIV-related neuropathy	Perineural HIV-gp120 administration[49]	Mixed CB1R/CB2R agonist reduced mechanical and cold sensitivity.[77,93]
Chemically induced models		
Sciatic inflammatory neuropathy	Injection of zymosan or TNF-alpha around sciatic nerve[49]	—
Excitotoxic spinal cord injury	Spinal administration of excitatory amino acids[49]	—
Orofacial pain	Application of CFA to the infraorbital nerve[49]	—
Transgenic models		
Diabetic polyneuropathy	Diabetic BB or Wistar rats, leptin-deficient mice[22,49]	—
Cancer neuropathy		
Neuropathic cancer pain	Inoculating Meth A sarcoma cells to the proximity of sciatic nerve[49]	—
Vascular models		
Central poststroke pain	Hemorrhagic stroke lesion in the ventral posterolateral nucleus of the thalamus[121]	—
Photochemical spinal cord or sciatic nerve injury	Thrombosis in sciatic nerve or spinal cord blood vessels, using photosensitive dye and laser[49]	—
Autoimmune models		
Experimental autoimmune encephalomyelitis	Immunization by subcutaneous injection of myelin oligodendrocyte glycoprotein[93]	—

* Demonstrated through genetic approach.

CFA, complete Freund adjuvant; FAAH, fatty acid amide hydrolase; KO, knockout; MAGL, monoacylglycerol lipase; CB1R, CB1 receptor; CB2R, CB2 receptor; THC, tetrahydrocannabinol; HIV, human immunodeficiency virus; HIV-gp120, envelope glycoprotein GP120 of the HIV envelope; TNF-alpha, tumor necrosis factor alpha.

both the rewarding effect of pain relief and the abuse potential of candidate drugs.[70,78]

Neuropathic pain is more common in old people and women.[7,14] However, most basic research studies have been performed only in young male rodents, although this tendency is changing partially due to the failure of clinical trials.[20] Recent works taking into account these important experimental conditions have found striking differences depending on sex and age.[60,106]

Sleep disturbances (37%-60% prevalence), emotional disorders (33%-42% prevalence), cognitive impairment (11.4% prevalence), pain-related fear, or deficits in social behavior[57,89,98,105] are important comorbid manifestations of neuropathic pain that should also be evaluated in animal models. These alterations and their pharmacotherapy may be independent of hyperalgesia and allodynia,[27] and an additional effort must be made to evaluate them in basic research studies. Taking into account not only the nociceptive manifestations but also the emotional and the cognitive consequences of neuropathic pain will allow to embrace the complexity of neuropathic pain syndromes and should improve the translational value of animal models.

In addition, a frequent problem of neuropathic pain animal models is the interpretation of results without considering the timing of treatment. Indeed, most failures in phase-II clinical trials are due to lack of efficacy (50%) or drug toxicity (25%).[47] Therapeutic efficacy could be different when the consequences of the injury to the nervous system are not fully developed, which could lead to overestimations of the results.[25] Using appropriate animal models to elucidate the mechanisms of action of the candidate drugs, establishing clinically validated targets, and finding correlation between the alleviation of neuropathic pain and the inhibition of the proposed target should increase the predictability of these models and facilitate the understanding of the neurobiological mechanisms underlying this syndrome.

3. Pathophysiological mechanisms

The pathophysiological mechanisms underlying neuropathic pain include complex peripheral and central sensitization processes mainly involving neurons and immune cells. Peripheral nerve injury involves damage to primary afferents and recruitment of immune cells releasing cytokines, nerve growth factor, and other signaling substances.[100] Nerve fibers develop ectopic activity and become hyperexcitable and pharmacologically dysfunctional. Several specific changes at the peripheral level could underlie this nerve sensitization, including dysregulation or redistribution of potassium and voltage-gated sodium channels,[54,110,129] increase functionality of purinergic receptors[19] and calcium channel subunit $\alpha_2\delta1$,[10] and reductions in opioid receptor expression.[82] In contrast, an enhancement of cannabinoid receptors has been reported at the peripheral and spinal levels during neuropathic pain.[68,128]

After peripheral nerve injury, heightened firing from primary afferents render postsynaptic spinal cord neurons hyperexcitable, mainly through the activation of glutamate receptors.[58] Loss of GABA and glycinergic interneurons and a change in the polarity of GABA or glycinergic transmission also contribute to this activation.[34,69] Serotonergic, noradrenergic, opioid, and cannabinoid bulbospinal neurons constitute a descending inhibitory input over the spinal cord dorsal horn under these pathological conditions.[83,93] Important adaptive changes also occur in other somatosensory areas, such as thalamus and somatosensory cortex.[38,69] However, plastic changes are increasingly reported in brain areas involved in emotional and cognitive aspects of neuropathic pain, including cingulate cortex, amygdala, hippocampus, prefrontal cortex, or nucleus accumbens.[16,76,79]

Immune mechanisms are also highly intertwined during neuropathic pain. Nerve growth factor, chemokine ligands, and leukotriene-b4 released by primary afferents and denervated Schwann cells rapidly attract neutrophil granulocytes and resident macrophages to the injured site. Immune cells increase the levels of proinflammatory mediators, facilitating regrowth and repairing and also promoting peripheral sensitization.[100] In the dorsal root ganglia, activated satellite glial cells contribute to neuronal sensitization.[113,120] This is accompanied by disruption of the nerve-blood barrier by matrix metalloproteases and vascular endothelial growth factor[61,100] and infiltration of circulating macrophages and lymphocytes.

In the spinal cord, neuronal damage is followed by microglial cell activation through purinergic, toll-like, or brain-derived neurotrophic factor (BDNF) receptors. Microglia phagocyte cell debris and release numerous inflammatory mediators.[9] These spinal cord immune responses are modulated by the endocannabinoid system (ECS) during neuropathic pain.[90,91] Increasing evidence also suggests an important role of astrocytes in the advanced stages of neuropathic pain, through the release of pronociceptive mediators.[18,67] Finally, oligodendrocyte damage can impair axonal repairing, reflected in alterations in conduction velocity and neuropathic pain phenotype.[37] Immune or glial response may be similar in limbic system areas, and it may participate in the emotion-like manifestations of neuropathic pain.[97,127]

One of the neurotransmitter systems involved in the pathophysiology of neuropathic pain that has recently raised a particular interest for the development of new therapeutic strategies is the ECS. This system is highly expressed in neurons and immune cells that are crucial for the development of neuropathic pain.

4. The endocannabinoid system

The ECS plays a key role in pain control and the physiopathology of neuropathic pain. It is integrated by the cannabinoid receptors, their endogenous ligands, and the enzymes involved in the synthesis and degradation of these ligands. At least 2 different cannabinoid receptors, CB1 receptor (CB1R) and CB2 receptor (CB2R), have been identified. Both receptors are 7 transmembrane domain receptors coupled to inhibitory G proteins, and their distribution and physiological role are quite different.[85] Generally, CB1R are highly expressed in neurons of central nervous system (CNS),[26] whereas CB2R are mainly located in immune cells,[73] although they are also expressed in CNS neurons.[103] The most important endogenous ligands for cannabinoid receptors are N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG).[85] These endocannabinoids are synthesized from cell membrane phospholipids mainly postsynaptically, acting as retrograde messengers that regulate the release of multiple presynaptic neurotransmitters, and they are inactivated by reuptake mechanisms followed by enzymatic degradation.[126] The ligand 2-AG is synthesized from diacylglycerol by diacylglycerol lipase and is primarily metabolized by monoacylglycerol lipase (MAGL).[28] Anandamide is synthesized from the phosphatidylethanolamine by the action of N-acyltransferase and phospholipase D, and it is mainly degraded by fatty acid amide hydrolase (FAAH).[65]

The ECS plays a crucial role in the inhibitory control of the nociceptive stimuli by acting at peripheral, spinal, and supraspinal levels (**Figure 1**). At the periphery, CB1R located in nociceptive terminals inhibit nociceptive transmission, whereas CB2R located in immune cells and keratinocytes reduce the release of pronociceptive agents.[44] Moreover, CB1R are expressed in the dorsal root ganglia and in the nociceptive and nonnociceptive sensitive terminals in the spinal cord dorsal horn, where they inhibit neurotransmitter release and pain transmission.[75] CB2R in the spinal cord modulates the immune responses, leading to neuronal sensitization during chronic pain.[88,91] At the supraspinal level, CB1R inhibit ascending nociceptive transmission, mainly at the thalamus level, modify the emotional pain component acting at the limbic system and cortical areas, and activate the descending inhibitory pathway through the inhibition of GABA release in the periaqueductal gray and rostral ventral medulla.[75,112]

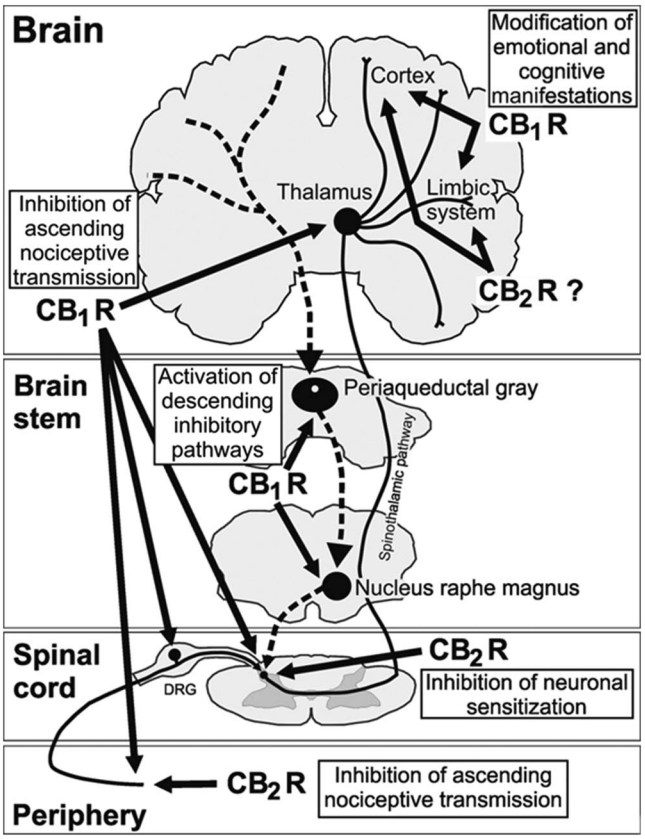

Figure 1. Role of the endocannabinoid system in the control of pain at the peripheral, spinal, and supraspinal levels. Cannabinoid receptor activity inhibits the ascending nociceptive transmission, activates the inhibitory descending pathway, and modifies the emotional component of pain.

5. Preclinical studies on endocannabinoid system and neuropathic pain

Animal studies have provided important findings revealing the role of the ECS in the pathophysiology of neuropathic pain and its potential interest to identify new pharmacological tools for neuropathic pain treatment. These studies have mainly used genetically modified mice with selective mutations in specific ECS components and pharmacological agents that modify the ECS activity (**Table 1**).

Several studies have demonstrated that the constitutive deletion of CB1R did not significantly modify the manifestations of neuropathic pain in mice.[75] In contrast, the selective CB1R deletion in peripheral nociceptors enhanced neuropathic pain manifestations and reduced the analgesic effects of systemic cannabinoid agonists underlying the role of peripheral CB1R in neuropathic pain.[2] However, the constitutive suppression of CB1R enhanced anxiety-like and depression-like behavior promoted by chronic neuropathic pain, suggesting a prominent role in these emotional manifestations.[92] The constitutive deletion of CB2R generates a clear enhancement of neuropathic pain manifestations revealed by a mirror image of pain in the contralateral unaffected side.[91] In agreement, the overexpression of CB2R in the CNS attenuates neuropathic pain manifestations.[91] An immune response involving the release of microglia and interferon-γ seems responsible of these CB2R-mediated effects.[90] The endocannabinoids that could be involved in these mechanisms have not been yet clarified. Indeed, the development and expression of neuropathic pain was not modified in

FAAH- and MAGL-knockout mice[75,99]; CB1 desensitization could underlie the absence of antinociceptive effects in MAGL-knockout mice.[99]

Pharmacological studies revealed that nonselective cannabinoid agonists and selective CB1R and CB2R agonists induced antinociceptive effects in multiple animal models of neuropathic pain,[75] whereas the acute blockade of CB1R or the inverse CB2R agonism produced pronociceptive effects[93,104] (**Table 1**). Most of the studies have reported these effects on classical animal models of evoked allodynia or hyperalgesia or both. However, few studies have used animal models evaluating more relevant aspects of neuropathic pain.[93] Thus, recent studies have revealed that nonselective cannabinoid agonists reduce the cognitive impairment associated with diabetic neuropathy,[24] and selective CB2R agonists reduced the depression-like behavior[43] and alleviated spontaneous neuropathic pain in an operant model of self-medication.[39] Interestingly, these CB2R agonists are devoid of the cannabimimetic effects of CB1R agonists.[74]

The blockade of endocannabinoid reuptake and the pharmacological inhibition of FAAH produce antinociceptive effects that did not develop tolerance in neuropathic pain models,[99] although these effects were less consistent than in chronic inflammatory pain models[50,96] and some contradictory results have been reported depending on the experimental conditions.[59] In contrast, MAGL inhibition produced clear antinociceptive effects in neuropathic pain models, which underwent tolerance with CB1R desensitization after repeated treatment. Both FAAH and MAGL inhibitors produced limited cannabimimetic effects.[46,99]

Therefore, preclinical studies have underlined the interest of the ECS for neuropathic pain treatment, and they have identified new possible approaches to obtain effective analgesic responses, minimizing the classical side effects related to CB1R agonists. However, the majority of studies have just evaluated the modification of the nociceptive sensitization associated with neuropathic pain. Most of these promising results must be confirmed in more relevant models of neuropathic pain allowing to evaluate the spontaneous pain manifestations, sleep disturbances, and emotional and cognitive impairments that are crucial in this complex pain syndrome. Additional efforts must also be taken to match the age and sex of the animal samples and time schedule of the experimental treatments with the real clinical conditions. In particular, further studies including these experimental conditions would be necessary to identify the potential interest that has risen from the recent results obtained with CB2R agonists and MAGL and FAAH inhibitors.

6. Cannabinoids and neuropathic pain treatment in humans

In agreement with the preclinical data, the analgesic effects of *Cannabis sativa* derivatives have also been reported in humans. Cannabis sativa contains around 70 phytocannabinoids, and the main psychoactive component is Δ9-tetrahydrocannabinol (THC). Cannabis sativa has been used for pain treatment more than 20 centuries ago in ancient China, Greece, Rome, Israel, and India.[48] More recently, cannabis use has been reported in population-based studies of patients with multiple pain syndromes, including neuropathic pain.[84,117] In the past 20 years, several cannabinoid preparations were available for neuropathic pain, including oral dronabinol and nabilone, and cannabis extracts to be administered by oromucosal, inhaled, and vaporized route.[118]

Early systematic reviews reported that cannabinoids were not better than codeine in controlling pain without advocating their widespread use.[15] However, the number of patients was limited, and a few randomized clinical trials (RCTs) were analyzed including multiple pain syndromes. They analyzed several clinical trials, but only one considered neuropathic pain and advised that more RCTs should be performed to evaluate the efficacy of cannabinoids. More recent systematic reviews have identified the existence of moderate analgesic effects of cannabinoids compared with placebo and an improvement in sleep, without serious adverse effects; they concluded that the cannabinoids were modestly effective and safe in neuropathic pain.[62,64] However, the only systematic review of cannabinoids in neuropathic pain has been recently published.[12] This study reviewed 13 high-quality RCTs and suggested that cannabinoids provide analgesia in patients with neuropathic pain who are refractory to other treatments. Another recent review included 6 trials with marijuana in 325 patients with neuropathic pain and concluded that it may be useful, although some significant side effects, such as addiction and worsening of psychiatric illnesses should be taken into account.[41] The authors also suggested that new studies were needed to evaluate the consequences of long-term treatments and to establish the best form of drug administration. A recent meta-analysis that has considered 9 clinical trials with the oromucosal administration of nabiximols (1:1 mixture of THC and cannabidiol) concluded that this cannabinoid formulation has only weak recommendations against its use in neuropathic pain.

Clinical research on cannabinoids has widely increased in the past 15 years. New designs, larger-scale studies, higher doses, and change of route of administration have allowed to accumulate evidences to clarify if cannabinoids have an opportunity as analgesics. Given the information available, we have separately considered the analysis of clinical trials depending on how cannabinoids were administered in neuropathic pain: orally (mainly nabilone and dronabinol), smoked or vaporized (marijuana), and oromucosal (THC plus cannabidiol).

7. Clinical trials with orally administered cannabinoids

The main oral cannabinoids used with medical purposes were ajulemic acid (CT3, a major metabolite of THC with CB1R activity), cannabidiol, dronabinol, levonantradol, nabilone, and THC (**Table 2**). A moderate evidence supports the use of these cannabinoids in chronic pain and spasticity.[122] Only an RCT with CT3 has been published with neuropathic pain patients of varying etiologies and demonstrated its effectiveness in reducing pain without causing cannabinoid-like CNS side effects.[53] Dronabinol was studied in 3 RCTs. No beneficial effect was seen in a pilot study with titrating dosing in refractory neuropathic pain,[5] whereas modest effects were observed in neuropatic pain patients with spinal cord injury, and a third clinical trial reported that dronabinol was no more effective than active placebo in a crossover study with only 7 adults.[94] Experience with nabilone in neuropathic pain is scarce. A study comparing dihydrocodeine with nabilone reported that the second was less effective and with a worst safety profile.[35] However, this study was criticized in the grounds of patient dropout, and because allodynia and sympathetic dysfunction were overrepresented in these patients.[21] A trial in patients with painful diabetic neuropathy showed that nabilone relieved symptoms and improved disturbed sleep and overall quality of life when compared with placebo.[109]

8. Clinical trials with smoked and vaporized cannabis

The most traditional way of consuming cannabis is by smoking because their effects are more rapid. However, the use of this

Table 2

Summary of randomized clinical trials assessing analgesic efficacy of cannabinoids in neuropathic pain.

Authors	Study design (patients)	Indication	Agent and daily dose	Control	Duration	Results	Adverse events
Oral administration							
Karst et al.[53]	Crossover (24)	Chronic Np	CT3 40-80 mg	P	1 wk	CT3 > P	Minor tiredness and dry mouth
Svendsen et al.[108]	Crossover (24)	Central Np in MS	D, up 10 mg	P	3 wk	D > P	AEs were higher during the active treatment
Frank et al.[35]	Crossover (96)	Chronic Np	Nb, up 2 mg	Dc, up 240 mg daily	14 wk	Dc > Nb	No serious AEs but slightly side effects with dihydrocodeine
Rintala et al.[94]	Crossover (7)	Np after spinal cord injury	D, 5 mg	Dp (25 mg)	28 d	D = Dp	Dry mouth, constipation, fatigue, and drowsiness for both drugs
Toth et al.[109]	Parallel (26)	Diabetic Np	Nb 1-4 mg	P	8 wk	Nb > P	Minor AEs
Smoked and vaporized administration							
Abrams et al.[1]	Parallel (55)	HIV-Np	C smoked (3.56%)	P	5 d	C > P	Mild serious effects, minimal psychoactive effects
Wilsey et al.[124]	Crossover (38)	Central and peripheral Np	C smoked (3.5%, 7%)	P	6 h sessions	C > P	Minimal psychoactive effects
Ware et al.[119]	Crossover (23)	Posttraumatic chronic Np	C smoked (2.5%, 6%, 9.4%)	P	14 d	C > P	No serious AEs
Ellis et al.[30]	Crossover (34)	HIV-Np	C smoked (1%-8%)	P	5 d	C > P	No serious AEs
Wilsey et al.[123]	Crossover (39)	Peripheral Np	C vaporized (1.29%, 3.53)	P	6 h sessions	C > P	Psychoactive effects were minimal and well tolerated
Oromucosal spray							
Wade et al.[114]	Crossover (24)	Peripheral and central Np	CBM (THC/CBD) CBD and THC up 120 mg	P	8 wk	THC > P, CBD > P	Predictable AEs generally well tolerated
Berman et al.[11]	Crossover (48)	Brachial plexus root avulsion	CBM (up THC, 129.6 mg or CBD 120 mg) and THC	P	6 wk	CBM = THC = P	Well tolerated with mild to moderate AEs
Rog et al.[95]	Parallel (63)	Central Np in MS	CBM (up THC, 129.6 mg or CBD, 120 mg)	P	4 wk	CBM > P	No serious AEs
Nurmikko et al.[81]	Parallel (125)	Peripheral Np	CBM (up THC, 21.6 mg or CBD 20 mg)	P	5 wk	CBM > P	No serious AEs
Selvarajah et al.[101]	Parallel (30)	Diabetic Np	CBM (THC:CBD 1:1 one pump = 2.5/2.5 mg)	P	12 wk	CBM = P	Six AE-related withdrawals
Langford et al.[56]	Parallel (339)	Central Np in MS	CBM (up THC, 32, 4 mg/CBM, 30 mg)	P	14 wk	CBM = P	Less than 10% withdraw in all study groups
Serpell et al.[102]	Parallel (246)	Peripheral Np	CBM (THC/CBD spray)	P	15 wk	CBM > P	Treatments were well tolerated
Lynch et al.[63]	Crossover (16)	Chemotherapy -induced Np	CBM (up THC, 32, 4 mg/CBM, 30 mg)	P	10 wk	CBM = P	Fatigue, dizziness, dry mouth or nausea or both

AEs, adverse events; C, cannabis; CBD, cannabidiol; CBM, cannabis-based medicine; CT3, ajulemic acid; D, dronabinol; Dc, dihydrocodeine; Dp,diphenhydramine; MS, multiple sclerosis; Nb, nabilone; Np, neuropathic pain; P, placebo; THC, tetrahydrocannabinol.

route of administration is complicated for the high risk of abuse and respiratory side effects. Several studies have provided evidences on the efficacy of smoked cannabis in neuropathic pain, such as human immunodeficiency virus–associated neuropathy,[1,30] central and peripheral neuropathic pain,[123,124] and posttraumatic or postsurgical neuropathic pain.[117] The analgesic effects were clear but moderate, whereas the adverse effects were frequent, although not severe.[15,66] This pharmacological profile has led to the endorsement of these cannabinoids for second-line use in the treatment of central neuropathic pain by European Federation of Neurological Societies.[6] No difference in terms of efficacy could be seen between the different cannabinoids, and smoked cannabis has been advised to be used only in severe neuropathic pain not responding to pharmaceutical cannabinoids and other analgesics.[52]

9. Clinical trials with oromucosal spray and Sativex

New ways of delivering cannabinoids have been developed to improve bioavailability and minimize side effects. The most recent way has been a 1:1 mixture of the natural phytocannabinoids THC and cannabidiol in the form of oral mucosal spray (nabiximols, Sativex, GW Pharmaceuticals Ltd, Salisbury, United Kingdom). This device has been used in several clinical trials controlled with placebo in neuropathic pain, and its beneficial effect has been revealed in multiple sclerosis central pain,[95] brachial plexus avulsion,[11] neuropathic pain after peripheral injury,[42,80,81,102,114] and diabetic neuropathy.[101] The THC-cannabidiol association as an add-on treatment may also improve neuropathic pain associated to multiple sclerosis resistant to other treatment.[56] In agreement, a recent meta-analysis concluded that this formulation of THC/cannabidiol has weak recommendation against the use in neuropathic pain treatment.[32] A recent, single, and pilot study has compared nabiximols with placebo in patients with chemotherapy-induced pain.[63] No global differences were seen, although 6 patients experienced significant decreases in pain compared with placebo. Given the difficulties of relieving this type of pain, authors concluded that these results merit a further full RCT.

10. Caveats of clinical trials

In spite of these interesting findings obtained in the RCTs, clinical research on cannabinoids in pain has been hampered by some

limitations that include the small sample size, the lack of differentiation of pain syndromes and cannabinoid responders, the absence of an adequate assessment of the clinical importance of the observed effects, the safety profiles, the characterization of adverse events, and the long-term consequences of treatments.[12] The blinding of the studies, due to the psychotropic effects of cannabinoids, is also an important limitation to adequately perform RCTs. The efficacy in multiple sclerosis patients where pain has an important spastic component also improved by cannabinoids, which complicates the final interpretation of the analgesic effects.[36]

In addition, anecdotal reports are usually a consequence of the use of smoked marijuana adding difficulties to the interpretation of results and the clarification of the effect of each different cannabinoids. Indeed, the complex interactions among the cannabinoid contained in marijuana are not fully known and may contribute to the final effectiveness of marijuana. Some individual cannabinoids, such as nabilone and dronabinol, have shown some potential interest as analgesics, although their efficacy in pain patients seems lower than the alleged effects of marijuana.[23]

11. Safety concerns and benefit to risk ratio

One of the most important barriers to the clinical use of cannabinoids arises from concerns on its safety profile. This may be a consequence of the reputation of these compounds in recreational use, even when their toxicity is clearly low compared with other drugs. Indeed, clinical trials have shown that cannabinoid adverse events are not frequent or more severe than those of other centrally acting analgesics.[116]

Repeated worries have been expressed on the possibility of chronic use of cannabinoids. The possibility of addiction, the risk of psychotic disorders, or exacerbation of previous psychiatric diseases have been invoked to justify the restriction of the use of these drugs. Other cannabinoid side effects related to mental health include symptoms of depersonalization, derealization, irrational panic and paranoia, amotivational syndrome, and cannabis withdrawal syndrome, which consists of anxiety, irritability, physical symptoms, and decreases in appetite or weight loss.[125] However, most of the evidences of these cannabinoid adverse effects come from their recreative use. The possible risks of cannabinoids on mental health must be particularly taken into consideration in long-term treatments with needs for close monitorization and appropriate exclusion criteria considering the psychiatric history of the patients. Additional concerns have been raised from the possibility of the detrimental effects of cannabinoids in brain development in young patients[23] or the possibility to reduce the olfactory acuity.[115]

The combined number of patients needed to obtain 50% relief with cannabinoids in neuropathic pain is 3.4,[33] which may justify its potential use, provided the safety is adequate. This safety to risk ratio must be always considered for every possible patient.

12. Future perspectives

New strategies for using cannabinoids more efficiently include the selective targeting of CB1R and CB2R, the inhibition of endogenous cannabinoid uptake and metabolism in selected tissues, the harnessing of cannabinoid-opioid synergies, and the delivery of cannabinoids by improved strategies.[118] Indeed, several selective CB2R agonists and MAGL and FAAH inhibitors have shown promising analgesic activity in preclinical models of neuropathic pain.[46,74] However, these promising results must be confirmed in more relevant animal models of neuropathic pain with experimental conditions closer to the clinical conditions. The widely reported synergistic effects between cannabinoid and opioid compounds[75] also open interesting possibilities to be explored in future clinical trials.

Spray preparations with a mix of THC and cannabidiol have given new perspectives on the use of cannabinoids in humans until then limited by the moderate efficacy of oral cannabinoids and safety of smoked marijuana. However, more RCTs are needed to explore a dose escalation in patients given the present relatively low dose of the combinations. The use of cannabidiol has also opened the possibility of the use of other phytocannabinoids in neuropathic pain treatment.[31] New devices that deliver cannabinoids more efficiently open promising approaches. Thus, a novel, portable, thermal-metered-dose inhaler that allows the administration of a single cannabis dose has been recently developed, showing a uniform pharmacokinetic profile and a significant reduction in pain in neuropathic pain patients.[29]

13. Concluding remarks

Preclinical studies have widely reported the potential interest of cannabinoids in neuropathic pain treatment. CB2R, FAAH, and MAGL have also been recently identified as novel targets within the ECS to develop more selective compounds devoid of the classical cannabimimetic side effects. In agreement with these preclinical data, some systematic reviews and meta-analyses have shown that cannabinoids allow modest pain reduction, but its analgesic effect may be offset by potentially serious harms; additionally, further high-quality studies are needed to establish the duration of the treatment and the optimal route of administration. However, the different patient populations with pain included in the systematic reviews make it difficult to get adequate conclusions. Use of orally administered cannabinoids fails to provide adequate relief, whereas smoked or vaporized marijuana seems more effective. Safety concerns in terms of mental health risk must be taken into consideration mainly for chronic use. Recently, the Canadian Pain Society has advanced cannabinoids to third-line agents in the management of chronic neuropathic pain based on the results of the last published RCTs.[72] However, they advised a close monitoring mainly with long-term treatments and the contraindication in patients with a history of psychosis. Large-scale RCTs that consider an adequate number of patients, use active treatments as controls, and longer duration of administration are required to have an adequate profile of the effectiveness and safety of cannabinoids in neuropathic pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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