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Editorial

The neuropathic pain: An overview of the current treatment and future therapeutic approaches

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Abstract

Neuropathic pain is characterized by abnormal hypersensitivity to stimuli (hyperalgesia) and nociceptive responses to non-noxious stimuli (allodynia). The conditions and the pathophysiological states that determine the onset of neuropathic pain are heterogeneous, such as metabolic disorders, neuropathy caused by viral infections, and autoimmune diseases affecting the central nervous system (CNS). Neuropathic pain in the general population is estimated to have a prevalence ranging between 3% and 17%. Most of the available treatments for neuropathic pain have moderate efficacy and present side effects that limit their use; therefore, other therapeutic approaches are needed for patients. In this article, the current standard of care treatment, the emerging pharmacological approaches from the completed phase III clinical trials, and the preclinical studies on novel promising therapeutic options will be reviewed.

Keywords

animal models, neuropathic pain, phase III clinical trials, therapy

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Introduction

Neuropathic pain can be defined as a process occurring after a primary lesion or disease of the somatosensory nervous system.[1] This condition is the result of a series of different pathological mechanisms and it is usually described based on the anatomic localization or etiology. The conditions and the pathophysiological states that determine the onset of neuropathic pain mostly involved are metabolic disorders (e.g. peripheral diabetic neuropathy (PDN)), neuropathies associated with viral infections (e.g. post-herpetic neuralgia, HIV, leprosy), autoimmune disorders affecting the central nervous system (e.g. multiple sclerosis and Guillain–Barre syndrome), chemotherapy-induced peripheral neuropathies, damage to the nervous system of traumatic origin (e.g. spinal cord injury (SCI) and amputation), inflammatory disorders, hereditary neuropathies, and channelopathies.[2]

Among the signs and the symptoms connected to the presence of neuropathic pain are allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (an increase in the perception of pain generated by a stimulus that causes pain), and paresthesia (a condition that determines the perception of anomalous sensations comparable to needle bites, tingling, itching, reduced, or even loss of sensitivity). In patients suffering from

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neuropathic pain, the perceived pain is usually spontaneous, manifesting itself without needing a stimulus. This pathological condition substantially affects the quality of life of patients, compromising their psychological state.[3]

In the global population, the incidence and prevalence of neuropathic pain are difficult to estimate due to the lack of consensus on the definition of neuropathic pain. In a systematic review of the epidemiology of chronic pain, a prevalence between 3% and 17% was found, while the incidence was calculated in 3.9–42.0/100,000 person-years for post-herpetic neuralgia; 12.6–28.9/100,000 person-years for trigeminal neuralgia; 15.3–72.3/100,000 person-years for PDN, and 0.2–0.4/100,000 person-years for glossopharyngeal neuralgia. Moreover, neuropathic pain was more prevalent among women (60.5% of patients), reached a peak at 50–64 years of age, and was more frequently reported by manual workers, as well as among people from rural areas.[4]

In this article, after a brief summary of drugs recommended for neuropathic pain, we focused on completed phase III clinical trials and on the preclinical studies performed in the last 2 years.

We have evaluated the completed phase III clinical studies available on http://clinicaltrial.gov, excluding the recommended drugs and the combination therapies. We also investigated the spinal cord stimulation (SCS) as a non-pharmacological approach. The researches were conducted on PubMed using "spinal cord stimulation" and "pain" as keywords and including only data that were published from January 2018 to December 2018. Preclinical studies were selected on PubMed using the following keywords: "neuropathic pain" and "animal model" and "treatment." The results of the available studies concerning new therapeutic strategies, published in the last 2 years, have been discussed.

Pharmacological guidelines for the treatment of neuropathic pain

Neuropathic pain management focuses on treating symptoms, and only in some pathological condition, the etiological causes can be treated relieving pain. The most recent meta-analysis on the drug's efficacy included a total of 229 studies.[5] The Special Interest Group on Neuropathic Pain (NeuPSIG) proposed gabapentinoids, tricyclic antidepressants (TCAs), and selective serotonin–norepinephrine reuptake inhibitors (SNRI) as the first-line drugs for neuropathic pain. Lidocaine, Capsaicin, and Tramadol have been proposed as the second-line treatment, while strong opioids (Morphine and Oxycodone) and botulinum toxin-A (BTX-A) were included as third-line treatments for peripheral neuropathic pain (Table 1).

Gabapentin and Pregabalin have been approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain. Given their similar structure to the gamma-aminobutyric acid neurotransmitter, they bind to the $\alpha 2$-δ subunit of Ca^{2+} voltage-dependent channels reducing Ca^{2+} influx to the cells. Both gabapentin and pregabalin have obtained excellent responses in the treatment of diabetic pain, herpetic neuralgia, SCI, and phantom limb syndrome.

TCAs were found efficient in the treatment of painful neuropathy, nerve injury pain, post-herpetic neuralgia, central postpartum pain, and in the treatment of pain following SCI. Among them, Amitriptyline achieved their effects by inhibiting serotonin and noradrenaline reuptake from the presynaptic terminals as well as inhibiting effects on cholinergic, adrenergic, and histaminergic receptors and ionic channels. TCAs are contraindicated in patients with some cardiac conduction disturbances and also in patients with glaucoma and prostate hypertrophy.

SNRIs inhibit the reuptake of serotonin and norepinephrine at the synaptic level. Duloxetine is the most effective in reducing neuropathic pain. Duloxetine and venlafaxine are associated with increased blood pressure and cardiac conduction abnormalities and therefore should be used cautiously in patients with cardiac disease. The opioids are widely used for pain management and inhibit nociceptive transmission through the presynaptic and post-synaptic μ-opioid receptors. Tramadol is a μ-opioid agonist, but also exerts effects that may contribute to its analgesic properties in neuropathic pain, including serotonin and norepinephrine reuptake inhibition. Tapentadol is the only opioid FDA approved for the management of neuropathic pain associated with diabetic peripheral neuropathy.[7]

Lidocaine and Capsaicin are recommended as second-line drugs in patients with peripheral neuropathic pain. Lidocaine patches blocking voltage-gated sodium channels locally reduce spontaneous ectopic nerve discharge. Capsaicin is a potent receptor

Table 1. Pharmacotherapy for neuropathic pain.

		Drugs	Dose range	Adverse effect
First-line therapy	Gabapentinoids	Gabapentin	150–600 mg/day	Lethargy, vertigo, peripheral swelling, blurred vision
		Pregabalin	300–3600 mg/day	Lethargy, vertigo, peripheral swelling, increased body weight
	Tricyclic antidepressants (TCAs)	Amitriptyline	10–150 mg/day	Anticholinergic effects, QT prolongation (arrhythmia), suicide risk, urinary retention
	Serotonin–norepinephrine reuptake inhibitors (SNRI)	Duloxetine	20–120 mg/day	Nausea, lethargy, constipation, ataxia, dry mouth
		Venlafaxine	150–225 mg/day	Nausea, vertigo, lethargy, hyperhidrosis, hypertension
Second-line therapy	Opioids	Tramadol	25–400 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia
		Tapentadol	50–600 mg/day	Nausea/vomiting, constipation, lethargy, seizures, ataxia
	Topical treatment	Lidocaine	5% patches or gel	Local erythema, itching and rash
		Capsaicin	8% patches	Pain, erythema, itching; rare cases of high blood pressure
Third-line therapy	Strong opioids	Morphine	10–120 mg/day	Nausea, vomiting, constipation, dizziness and lethargy
		Oxycodone	10–120 mg/day	Nausea/vomiting, constipation, lethargy, respiratory control
	Neurotoxin	Botulinum toxin	25–300 U BTX-A 0.9% saline	Pain at injection site

Table 1 reports the dose range and the side effects in accordance with Electronic Medicines Compendium (eMC).[6]

agonist (transient receptor potential cation channel subfamily V member 1 also known as vanilloid receptor 1 (TRPV1)). Oxycodone and morphine are two strong opioids recommended as third-line for their complexity of follow-up and monitoring and for their potential adverse side effects of abused drugs.[8]

BTX-A, also included as a third-line treatment, is a potent neurotoxin commonly used to treat the spasticity, based on its ability to inhibit synaptic exocytosis and therefore the neural transmission. Subcutaneous injection of BTX-A has been shown to be effective in patients with focal peripheral neuropathic pain and allodynia. BTX-A in accordance with NeuPSIG recommendations should be used as the last choice in refractory cases for peripheral neuropathic pain[5] (Table 1).

Phase III clinical trials—emerging therapeutic strategies for the treatment of neuropathic pain

Several clinical trials have been carried out to test the efficacy of new therapeutic approaches to the treatment of neuropathic pain. The researches selected the Completed Phase III Clinical trials that include the new investigational drugs not recommended as first-, second-, or third-line of treatment (see Table 2).

Ketamine, memantine, and N-methyl-D-aspartate receptor (NMDAR) antagonists have been employed in several preclinical and clinical studies, but they are not approved by the FDA. NMDARs are ionotropic glutamate receptors that play a role in synaptic transmission, neuroplasticity, and processes underlying learning and memory. Alterations of NMDARs functions are involved in some of the nervous system disorders, such as neuropathic pain; for this reason, they are extensively investigated as possible therapeutic targets in pain management. Memantine, a derivative of Adamantane, is a noncompetitive NMDAR antagonist, and it has been approved by FDA and by the Euroepan Agency for the Evaluation of Medicinal Products (EMEA) for the treatment of Alzheimer's disease. The trial NCT01536314 has investigated Memantine effects in post-mastectomy neuropathic pain; 3 months post mastectomy, patients treated with Memantine (administered 5–20 mg/day for 4 weeks beginning 2 weeks before surgery) reported significantly less pain. The trial NCT00313378 included patients with chronic neuropathic pain after thoracotomy treatment with ketamine. The treatment given in 24-h infusion rate at an antihyperalgesic dose failed to prevent chronic neuropathic pain.

Table 2. Phase III Clinical Trials.

NCT number	Study title	Drug	Results
NCT01536314	Prophylaxis of neuropathic pain by memantine	*Memantine EBIXA®* *Placebo: lactose*	*Memantine prevented post-mastectomy pain and diminished chemotherapy-induced pain symptoms*
NCT00313378	Effects of perioperative systemic ketamine on development of long-term neuropathic pain after thoracotomy	*Ketamine*	*Ketamine did not prevent chronic pain after thoracotomy*
NCT00224588	KETOR: Effects of peri-operative administration of ketamine on long-term post thoracotomy pain	*Ketamine*	*Data not available*
NCT00872144	Sativex for the treatment of chemotherapy-induced neuropathic pain	*Sativex®*	*Sativex reduced chemotherapy-induced neuropathic pain in five participants that trended toward statistical significance*
NCT01604265	A study of Sativex in the treatment of central neuropathic pain due to multiple sclerosis	*Sativex®*	*Sativex reduced pain and sleep disturbance in patients with multiple sclerosis*
NCT01606202	A study of cannabis-based medicine extracts and placebo in patients with pain due to spinal cord injury	*GW-1000-02* *Placebo*	*GW-1000-02 improved pain score*
NCT00713817	A study to determine the maintenance of effect after long-term treatment of Sativex® in subjects with neuropathic pain	*Sativex®* *Placebo*	*Sativex showed no effect*
NCT00713323	A study to compare the safety and tolerability of Sativex® in patients with neuropathic pain	*Sativex®* *Placebo*	*Sativex improved pain score*
NCT00711880	A study of Sativex® for relief of peripheral neuropathic pain associated with allodynia	*Sativex®* *Placebo*	*Sativex reduced global neuropathic pain score, sleep disturbance, dynamic and punctate allodynia*
NCT00710554	A study of Sativex® for pain relief of peripheral neuropathic pain, associated with allodynia	*Sativex®* *Placebo*	*Sativex reduced the peripheral neuropathic pain NRS scores and the sleep quality score*
NCT00391079	Sativex versus placebo when added to existing treatment for central neuropathic pain in MS	*Sativex®* *Placebo*	*Sativex reduced neuropathic pain and improved sleep and quality of life*
NCT00710424	A study of Sativex® for pain relief due to diabetic neuropathy	*Sativex®* *Placebo*	*Sativex improved diabetic neuropathy pain*
NCT00959218	Efficacy and safety of the pain relieving effect of dronabinol in central neuropathic pain related to multiple sclerosis	*Dronabinol®* *Placebo*	*Dronabinol reduced pain intensity and adverse events over time*
NCT01555983	Vaporized cannabis and spinal cord injury pain	*Vaporization of cannabis*	*Vaporized cannabis decreased pain associated with injury or disease of the spinal cord*
NCT01872481	Effects of repetitive transcranial magnetic stimulation in the treatment of phantom limb pain in landmine victims: ANTARES	*Device: rTMS* *Device: Sham rTMS*	*High-frequency rTMS induced a significant pain reduction up to 15 days after treatment without any secondary effect*
NCT00443469	Spinal magnetic stimulation (SMS) in neuropathic pain	*Device: magnetic stimulation* *Device: magnetic stimulation with tilted coil*	*SMS reduced mean pain of 62.3% post-procedure*
NCT00337324	Electromagnetic stimulation (FREMS) in patients with painful diabetic neuropathy	*Device: frequency-modulated electromagnetic neural stimulation*	*FREMS induced an enhancement of microvascular blood flow measurable at 4 months of follow-up*

Table 2 shows the completed phase-III clinical trials (available on http://clinicaltrial.gov).

Several clinical studies suggest the efficacy of *Cannabis sativa* derivatives in the modulation of neuropathic pain. *Cannabis sativa* is a complex plant that contains around 100 cannabinoids. The most investigated among cannabinoids is the delta-9-tetrahydrocannabinol (Δ-9-THC) for its psychoactive properties. Recently, a mixture (1:1) of the Δ-9-THC and cannabidiol (CBD) in an oromucosal spray formulation (Sativex®; GW Pharma Ltd, Salisbury, UK) licensed for spasticity symptom improvement in multiple sclerosis has been developed. Sativex has been used in nine clinical trials, controlled with placebo, and its beneficial effect has been revealed in multiple sclerosis central pain (NCT01604265; NCT00391079), neuropathic pain after peripheral injury (NCT00711880; NCT00710554), and diabetic neuropathy (NCT00710424). In a study that recruited patients with chemotherapy-induced neuropathic pain (NCT00872144), no statistically significant difference was found. Another option for treatment of neuropathic pain in multiple sclerosis patients has been the (−) trans-Δ-9-tetrahydrocannabinol (dronabinol oral solution) administered daily at a dose of 12.7 ± 2.9 mg (range: 0–15.9 mg; NCT00959218). Another trial has shown the antinociceptive effect of vaporized cannabis with both low doses (2.9%) and high doses (6.7%) of Δ-9-THC in patients with SCI (NCT01555983).

Noninvasive transcranial brain stimulation techniques are a therapeutic approach useful in patients with refractory neuropathic pain and included repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS produces electrical currents in the cortex through a transient magnetic field.[9] The study of phantom limb pain (PLP) in landmine victims (NCT01872481) showed the ability of high-frequency rTMS (10 Hz) to reduce the pain significantly up to 15 days after treatment. The clinical trial NCT00443469 showed the use of repetitive spinal magnetic stimulation (SMS) as a therapeutic option in patients with intractable neuropathic pain of the lower limbs. The analgesic effect was evident immediately after the treatment (200 trains of five pulses delivered at 10 Hz) and a residual effect was observed up to 4 days' post-treatment. The clinical trial NCT00337324 investigated the effects of frequency-modulated electromagnetic stimulation (FREMS) in patients with diabetic neuropathy. Each patient received two series of 10 treatments of FREMS, and each series lasting no more than 3 weeks. FREMS treatment reduced pain with an enhancement of microvascular blood flow. The tDCS stimulation (electric current of 1–2 mA) has been reported as having a beneficial effect in the treatment of neuropathic pain associated with diabetes, traumatic SCI, and fibromyalgia syndrome.[10]

SCS

SCS constitutes another alternative therapy useful for patients who are not responsive to standard treatment. SCS or dorsal column stimulation is an invasive technique that involves stimulation of spinal cord dorsal columns by administering electrical impulse at frequencies of around 50 Hz (by an implanted pulse generator) which are able to suppress the central neuronal hyperexcitability. The electrodes can be inserted percutaneously through an epidural needle or surgically implanted by laminotomy. SCS has resulted in effective treatment for various neuropathic pain conditions.

Zhang TC et al. have reported the beneficial effect of SCS in chronic refractory pain, including failed back surgery syndrome (FBSS), and in idiopathic conditions, such as fibromyalgia and irritable bowel syndrome.[11] The study conducted by de Vos CC et al. reported the effectiveness of SCS in patients with refractory PDN. The electrode implanted in the thoracic epidural space was able to relieve pain and reactivate the microcirculation.[12]

SCS treatment is effective in around 50% of patients with a tolerance in the long-term treatment. The stimulation of the large-diameter fibers in the dorsal column induces paresthesia which is related by the stimulation parameters used. To avoid the side effect of paresthesia, several new electrical parameters have been proposed.[13] A new innovative technique of SCS is burst stimulation, which consists of administering five intermittent high-frequency pulses delivered at 500 Hz. Burst stimulation significantly reduced pain in patients with painful diabetic neuropathy and FBSS.[14]

Thomson SJ et al. conducted a multicenter, double-blind, crossover, randomized controlled trial (NCT02549183). The aim of the study was to evaluate the analgesic effects of high-frequency SCS (1–10 kHz). For this study, patients with persistent or recurrent low back pain and with or without equal or lesser leg pain have been recruited. The authors reported an equivalent pain relief measured

by a numeric rating scale and an improvement in the quality of life on all evaluated frequencies.[15]

The study conducted by Al-Kaisy A et al. is a prospective, randomized, sham-controlled double-blind crossover study (NCT01750229). The purpose was to verify the safety and efficacy of SCS at four different high frequencies (sham, 1200 Hz, 3030 Hz, and 5882 Hz) in subjects suffering from FBSS. After 12 weeks, the stimulation at 5882 Hz reduced pain significantly compared to lower frequencies and sham stimulation.[16]

Van Beek M et al. reported the results of two prospective multicenter clinical trials including patients affected by painful diabetic peripheral neuropathy (PDPN). In around 50% of patients, SCS treatment reduced chronic pain symptoms in the lower extremities up to 5 years of follow-up; 80% of patients with PDPN still use their SCS device after 5 years.[17]

SCS can be considered a valid, effective, and safe treatment option in patients suffering from neuropathic pain and resistant to pharmacological treatment. Studies are currently underway to validate this technique and to deepen the effectiveness of its variants such as burst and high-frequency stimulation.

Preclinical studies

The animal models of neuropathic pain facilitate the studies on the mechanism of pain and are central to the development of effective therapy for its management. Many preclinical data obtained using these animal models have led to the development of new therapeutic agents that have been translated in the clinical setup. The preclinical studies performed in the last 2 years offer new compounds and new therapeutic targets in neuropathic pain management. Numerous studies indicate that neuroinflammation plays an important role in the pathogenesis of neuropathic pain. The inhibitors of neuroinflammation might, therefore, open new avenues for the development of new pharmacological target for pain management.

Demartini C and collaborators have studied the efficacy of ADM_12—an antagonist of the Transient Receptor Potential Ankyrin 1 (TRPA1), to counteract the neuropathic pain induced in the model of a chronic constriction injury (CCI) of the infraorbital nerve of the rat (IoN-CCI). TRPA1 are channels present in dorsal and trigeminal root ganglia and are involved in neuropathic pain as they release neuromodulators such as Substance P (SP) and Neurochin-A; 28 days after the induction of IoN-CCI, a single administration of ADM_12 (30 mg/kg intraperitoneal injected) reduced the gene expression of TRPA1 and TRPV1, the nonselective cation channels involved in the transmission and modulation of pain. These results correlated with the reduction of pro-inflammatory cytokines' expressions such as interleukin (IL)-1β, IL-6, and tumor necrois factor (TNF)-α. The authors also report that treatment with ADM_12 reduces mechanical allodynia assessed through numerous behavioral tests.[18]

Lin J-P et al. evaluated whether the modulation of the purinergic receptor 7 (P2X7R) and of extracellular signal-regulated (ERK) kinases could be important in the treatment of neuropathic pain. P2X7R is a subtype of the purinergic receptor predominantly expressed on microglia. With this aim, a rat model of CCI of the sciatic nerve was induced to test the efficacy of Dexmedetomidine, a selective α2-adrenoceptor agonist. Dexmedetomidine was administered daily intrathecally (2.5 μg), 1 week after CCI induction. The results of behavioral and molecular tests showed that the treatment with Dexmedetomidine reduced neuropathic pain with inhibition of P2X7R expression and ERK phosphorylation.[19]

Afshari K et al. showed the anti-inflammatory and anti-allodynic effect of Metformin, a drug for controlling blood sugar in diabetes type 2, in a rat model of SCI. Tactile and heat stimulation tests were performed weekly beginning 1 week after SCI surgery for 28 days. Metformin administered intraperitoneally (50 mg/kg) reduced the histopathological signs of neuroinflammation and the level of inflammatory cytokines (TNF-α and IL-1β) in the spinal cord tissue, consequently decreasing sensitivity to mechanical and thermal allodynia in treated rats compared to the vehicle group.[20] Nevertheless, further investigations of the potential clinical therapeutic effects of metformin on SCI in human are required.

Vieira G et al. have evaluated simvastatin effect on complex regional pain syndrome (CRPS), using a chronic post-ischemia pain (CPIP) mouse model. Simvastatin is a synthetic compound belonging to the statin family, a class of lipid-lowering drugs. The simvastatin treatment was able to block the nociceptive response induced by intraplantar injection of

methanol, a selective Transient Receptor Potential cation channel subfamily M member 8 (TRPM8) activator, demonstrating the involvement of this receptor in the antinociceptive effects. Moreover, the treatment with simvastatin inhibited the hypersensitivity induced both by the intraplantar injection of an acidified saline, an acid-sensing ion channels (ASIC) activator, and by injection of the bradykinin, demonstrating even the involvement of ASIC and bradykinin signaling pathways.[21]

Marcondes Sari MH and collaborators demonstrated the antinociceptive action of the organoselenium compound p,p′-methoxyl-diphenyl diselenide ((OMePhSe)2) in an animal model of chronic pain induced by the partial sciatic nerve ligation (PSNL). They also reported the involvement of the supraspinal GABAergic system in the antinociceptive efficacy of (MeOPhSe)2. The treatment with (OMePhSe)2, free or incorporated into nanocapsules, in a single (25 mg/kg) or repeated administration (25 mg/kg, once a day for 7 days), reduced mechanical hypernociception as well as the pro-inflammatory cytokines (IL-1β and TNF-α) and the pro-apoptotic protein Bax. Moreover, the nanoencapsulation increased the bioavailability of the (OMePhSe)2 compared to the free compound.[22] However, further studies are needed to clarify their mechanism of action.

Chung E et al. have investigated the analgesic effect of SP injected in the CCI experimental model of chronic neuropathic pain. The SP is a neuropeptide and member of the tachykinin family. Their biological actions are mediated by Neurokinin-1 (NK1) receptor. SP is released from the sensory neurons and plays an essential role in pain transmission. SP intravenously administered every 3 days (1 nmol/kg) was able to attenuate mechanical allodynia in treated mice by reducing phospho-ERK levels in the spinal cord. Moreover, SP treatment has inhibited the glial activation by reducing glial fibrillary acidic protein levels, by increasing the expression of IL-10, and by reducing the TNF-α. In order to demonstrate the involvement of the NK1 receptor in the reduction of mechanical allodynia, its antagonist RP67580 was administered. RP67580 administered in association with SP reversed the analgesic effect of SP, demonstrating the involvement of the NK1 receptor. SP might represent a good drug candidate for neuropathic pain management; however, further investigations should be performed to determine its exact mechanism of action.[23]

Natural compounds have been investigated for the management of many diseases, and some of them may present therapeutic candidates for the development of new drugs to alleviate neuropathic pain.

Heng-Tao Xie et al. evaluated the effect of Puerarin to counteract the neuropathic pain induced by PSNL. Puerarin, a compound isolated from *Radix puerariae*, is a potent antioxidant and anti-inflammatory agent used in traditional chinese medicines for the myocardial and cerebral ischemia treatment. Puerarin (30 or 60 mg/kg, intraperitoneally administered daily for 1 week) dose-dependently ameliorates mechanical allodynia in rats with peripheral nerve injury. The treatment decreased the TRPV1 and TRPA1 expression levels in dorsal root ganglion (DRG) neurons. It is possible that Puerarin prevents TRPV1 and TRPA1 upregulation through protein kinase C modulation; however, these mechanisms remain unclear and further studies are required.[24]

Bingjie Qin et al. have investigated the analgesic effects of Gastrodin, a bioactive constituent of the traditional chinese herbal medicine, in peripheral neuropathy induced by anti-tumor treatment with Vincristine, a chemotherapy medication administered in the rat model of breast cancer. Gastrodin administered to the cancer group restored the mechanical and thermal pain threshold decreased by vincristine treatment without reducing the anti-tumor effect. The highest concentration of Gastrodin (120 mg/kg) was more effective than a lower concentration (60 mg/kg) and also even promotes the anti-tumor effect of vincristine. Gastrodin reduced the peripheral inflammation by inhibiting the activation of microglia cells, via the Chemokine CX3CL1 (Fractalkine) and its Receptor CX3CR1 (CX3CL1/CX3CR1) and mitogen-activated protein kinase (MAPK) pathway.[25]

Araújo-Filho HG et al. have evaluated the anti-hyperalgesic effect of the D-limonene (LIM) alone or complexed with β-cyclodextrin (βCD) in an animal model of fibromyalgia. LIM is a monocyclic monoterpene extracted from oranges and lemons. The βCD complexed to LIM (1:1 ratio) improves the solubility and stability of the LIM. Oral administration of LIM-βCD (50 mg/kg) significantly increases the paw withdrawal threshold compared to the control group. This analgesic effect was lower

in LIM compared to LIM-βCD at the same dose. The treatment with LIM or LIM-βCD decreased the number of Fos-positive cells in the dorsal horn of the spinal cord suggesting a role in the modulation of pain transmission. Moreover, the involvement of the gamma-aminobutyric acid (GABA) system in the antinociceptive effect of LIM-βCD using Flumazenil (2 mg/kg), an antagonist to GABA receptors, has been demonstrated. In addition, the hot-plate test has demonstrated the contribution of TRPV1 receptors to the LIM-βCD antihyperalgesic effect.[26]

The study conducted by Kandhare AD and colleagues showed the possible involvement of the *Azadirachta indica* (AI), a tree of the *Meliaceae* family, in the treatment of peripheral neuropathy induced by PSNL. After PSNL, the rats were treated with an extract of AI for 28 days (100, 200, and 400 mg/kg). All doses significantly attenuate mechanical allodynia, thermal hyperalgesia, motor coordination, and motor nerve conduction velocity. AI extract has also shown anti-inflammatory and antioxidant properties. In particular, the AI increased the expression of superoxide dismutase and glutathione while significantly reduced the malondialdehyde, nitric oxide, and the expression of the pro-inflammatory cytokines TNF-α and IL-1β. The treatment also showed anti-apoptotic properties, decreasing the mRNA expression of Bax and caspase-3 and increasing the expression of the anti-apoptotic protein Bcl-2. These results are very hopeful for the possibility of the neuroprotective effect of AI for the treatment of neuropathic pain.[27]

Jones M and collaborators have examined the therapeutic effect of indomethacin morpholine amide (IMMA), a novel substrate-selective Cyclooxygenase-2 (COX-2) inhibitor, in the CCI mouse model. In chronic pain states, the therapeutic effect of endocannabinoids can be counteracted by the metabolites of endocannabinoid oxygenation mediated by COX-2. Stated the demonstrated efficacy of the inhibitors of endocannabinoid hydrolysis in the management of the neuropathic pain, the researchers speculated that inhibition of 2-Arachidonyl Glycerol and Anandamide oxygenation by IMMA could provide a novel strategy for pain treatment. IMMA (10 mg/kg) reduced thermal withdrawal latency and increased mechanical thresholds in the treated mice.[28] COX-2-mediated oxygenation is thought to be an alternative route for endocannabinoid metabolism and therefore provides a new strategy for pain treatment, but further studies are required.

Berrocoso E et al. evaluated the effectiveness of new oral delivery systems for a synthetic cannabinoid, the Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (also known as CB13), a potent receptor CB1/CB2 agonist. The poly(lactic-co-glycolic acid) (PLGA)-based nanoparticles and two PLGA nanoparticles enhanced with polyethylene glycol (PEG) were tested in the CCI murine model. CB13 (3.4 mg/kg) and PLGA-CB13 (1.7, 3.4, and 6.8 mg/kg CB13) were orally administrated on day 7 after CCI induction. CB13 and the three nanosystems showed the same analgesic potency, but the PLGA-CB13 maintains the analgesic effect for a longer time. PEG surface modification has increased oral bioavailability compared to free compound.[29]

Discussion

Neuropathic pain is a disorder that is difficult to treat, therefore affecting the quality of life of many patients, and for this reason, it is pivotal to identify new potential drug targets in order to develop novel pharmaceutical agents. The recommended first-line treatments are based on the use of antidepressants and antiepileptic drugs, which are reported in Table 1 with relative doses.[6] Opioids are generally recommended to be used in second- and third-line treatment due to their adverse related effects. In particular, tramadol and the FDA-approved tapentadol[7] are used in second-line treatment, while the strong opioids, oxycodone, and morphine[8] are used in the third-line treatment.

Several clinical trials have shown the potential effectiveness of cannabis-derived compounds in the treatment of pain associated with diabetes, chemotherapy, and multiple sclerosis. Sativex already approved by the FDA for the treatment of spasticity in multiple sclerosis patients is considered as an alternative for patients suffering from neuropathic pain. NMDAR antagonist agents might be considered for treatment of neuropathic pain, even if in some cases do not prove adequate symptomatic relief or their use is limited by their side effects. Nevertheless, to evaluate the efficacy of these drugs, further investigation is needed. The rTMS and the high-frequency SCS have proven efficacy in refractory patients to conventional medical management, but it is a field still extensively investigated.[10,15] Nanotechnology-based drug delivery systems are

promising tools to resolve the low solubility and the bioavailability of some compounds.[22] The use of nanocarriers in the management of pain is a novel area of research, with great potential for growth and clinical benefit.[29] It is relevant to point out the possibility of repurposing drugs currently approved for other indications that have already shown efficacy in animal models of neuropathic pain. Metformin and simvastatin were effective in decreasing pain by reducing neuroinflammation.[20,21] Certainly, the neuroinflammation offers potential therapeutic targets in neuropathic pain, and among them, the receptors expressed in microglia (e.g. P2X7R and CX3CR1) might be the targets for treating the chronic pain state.[19,25] The natural compounds are widely investigated for the treatment of chronic pain.[26,27] The modulation of pro- and anti-inflammatory mediators trigger a cycle of neuroinflammation and cellular activation that is usually resistant to pharmacological therapy. Abnormal activation of these cells precipitates the development of neuropathic pain. For this reason, some preclinical studies investigated the treatments able to modulate the neuroinflammation and downregulate the inflammatory cytokines. Despite the multiple preclinical studies, most of the evidences have identified the involvement of the supraspinal GABAergic system and the antagonist of TRPA1; two studies reported the reduction of pro-inflammatory cytokines expressions such as IL-1 β, IL-6, and TNF-α.[18,22] For these reasons, it is still necessary to identify new effective therapeutic strategies in neuropathic pain management. Combination therapy may provide benefits compared to single-drug treatments, increasing safety and effectiveness in order to develop personalized treatments with an individual plan for each patient.

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