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Emerging Treatments for Neuropathic Pain

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Abstract Neuropathic pain is a series of well-known conditions caused by diseases or lesions to the somatosensory system. Due to the better understanding of the pathophysiology of neuropathic pain, previously unexplored therapies have been used with encouraging results. As such, Acetyl-L-carnitine (ALC), Alpha-lipoic-acid (ALA), cannabinoids, Clonidine, EMA401, Botulinum Toxin type A, and new voltage-gated sodium channel blockers, can be cited. Furthermore, new modalities in neuromodulation such as high-frequency spinal cord stimulation, burst stimulation, dorsal root ganglion stimulation, transcranial direct current stimulation, and many others have been showing exciting results. Besides, changing paradigms may occur with the advent of optogenetics and a better understanding of epigenetic regulation. This article reviews the published literature on the treatment of NP. Despite the interesting results, randomized controlled trials are demanded for the majority of the therapies previously mentioned.

Keywords Neuropathic pain · Treatment · Trials · Somatosensory nervous system · Spinal cord

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Introduction

Neuropathic pain (NP) is a common condition due to disease or lesions affecting the somatosensory nervous system, either centrally or in the periphery [1]. Central NP includes pain due to spinal cord injury; pain is multiple sclerosis, post-stroke pain, etc. Peripheral NP is seen secondary to polyneuropathies (related to diabetes, chemotherapy, chronic alcohol abuse, infections, etc.), Charcot-Marie-Tooth disease, trigeminal neuralgia, herpes zoster infection, small fiber neuropathies, complex regional pain syndrome (CRPS), entrapment syndromes, amyloid neuropathy, and others [2].

As a consequence of this afferent transmission system defect, a loss of input to the nervous system arises, creating negative sensory symptoms related to NP. Usually, patients with NP can present with lancinating, shooting and/or burning pain along with tingling sensation. Positive sensory symptoms such as spontaneous or evoked pain in response to noxious or non-noxious stimuli (hyperalgesia and allodynia, respectively) [3, 4] may also occur.

The diagnosis of NP is still based on clinical aspects. For this reason, the history and physical examination are the basis for the correct diagnosis. Imaging, electrophysiological, and sometimes histological tests confirm the diagnosis. The management of neuropathic pain consists of initially drug therapy, an interdisciplinary approach, anesthetic techniques, and as the last resource, surgical interventions [5, 6].

This review will focus on new pharmacological treatments and neuromodulation techniques for treating NP.

Pharmacological Interventions

The pharmacological treatment of neuropathic pain is based primarily on antiepileptic and antidepressant drugs. Opioid use can also be considered, but are commonly regarded

controversial. These drugs are well-studied and established in clinical practice, but their estimated pain relief is not higher than 40–50 % [6]. Among the new therapeutic options, some studies highlight Acetyl-L-carnitine (ALC), Alpha-lipoic-acid (ALA), cannabis products, botulinum toxin, and angiotensin II type 2 receptor antagonists [6]. Additionally, the new voltage-gated sodium channel blockers, among which we highlight Nav1.7, Nav1.8, Nav1.3, and Nav1.9, are expected to be superior to other sodium channel blockers, since they are receptor-specific leading to less potential cardiac, motor, and CNS side effects [7]. In the same way, the use of specific blockers of the alpha-2-delta-1 (Cav $\alpha 2\ \delta 1$) subunit of calcium channels has been studied as a potential antinociceptive drug, basing on the concept of these channels might be overexpressed in some pain states [8]. Notably, there is a lack of enough evidence for efficacy in relation the majority of these emerging treatments for NP (Table 1). Nevertheless, the paucity of randomized controlled trials (RCTs) and clinical evidence does not mean that we should abandon these new modalities. Instead, new studies are demanded to prove their efficacy [9, 10].

Acetyl-L-Carnitine (ALC), Alpha-Lipoic-Acid (ALA)

Acetyl-L-carnitine is an ester produced by the human brain, liver, and kidney. Their effect on NP is not completely understood, but it is reported that ALC increases the uptake of Acetyl-CoA into the mitochondria, and exerts cholinomimetic effects because it is similar in structure to acetylcholine [11].

In a controlled randomized trial performed by Sima Anders et al. [12], ALC was tested in diabetic neuropathy, evaluating sural nerve morphometry, nerve conduction velocities, vibration perception thresholds, clinical symptom scores, and pain visual analog scale (VAS). The authors have demonstrated the efficacy of ALC in reducing the symptoms, especially pain, as well as the improving nerve fiber regeneration in patients with diabetic neuropathy [12].

With similar results, De Grandis and Minardi demonstrated in a multicenter, randomized, double-blind, placebo-controlled study the improvement of pain control and electrophysiological parameters in diabetic neuropathy after administrating ALC for 1 year. In this study, 333 patients with diabetic neuropathy were randomized to receive either ALC or a placebo; the active treatment group received 1 g of intramuscularly ALC for 10 days following 2 g of oral ALC for 355 days. The ALC group demonstrated a 39 % decrease in pain measured by VAS ($p<0.01$ vs. baseline) in 12 months vs. 8 % reduction in placebo group. The most significant change in nerve conduction velocity was found in the sural nerve (+7 m/s in LAC vs. +1 m/s in placebo) and in the sensory ulnar nerve (+2.9 m/s in LAC vs. +0.1 m/s in placebo) [13].

The Alpha-lipoic-acid is known for its antioxidant properties and its role in mitochondrial dehydrogenase reactions. ALA has demonstrated protection against oxidative stress in models of ischemia-reperfusion lesion, diabetes, neurodegeneration, HIV activation, and others. Recent studies suggest that ALA plays a much broader role than just simply being an antioxidant [14, 15].

Recently, a meta-analysis evaluating the benefits of ALA in symptomatic peripheral diabetes demonstrated that daily intravenous dose of 600 mg ALA for 3 weeks is efficient for these patients. Similarly, a multicenter, randomized, double-blind, placebo-controlled trial with 181 diabetic patients tested daily doses of 600, 1200, and 1800 mg of oral ALA or placebo for NP. A real pain-reducing response with fewer side effects was found with the 600 mg dose. Thus, altogether, one could affirm that ALA should have an A recommendation grade for NP in diabetic neuropathy. Additionally, thioctic acid has a functional structure very similar to ALA and can be expected to have similar benefits to that of ALA [16, 17].

Table 1 Summary of emerging therapies in NP [6, 21, 33, 78]

Pharmacological treatment
Acetyl-L-carnitine (ALC)
Alpha-lipoic-acid (ALA),
Cannabis products
Cebranopadol
Angiotensin II type 2 receptor antagonist
Neuromodulation
Dorsal root ganglion stimulation
Peripheral nerve stimulation (PNS)
Repetitive transcranial magnetic stimulation (rTMS)
Motor cortex stimulation (MCS)
Deep brain stimulation (DBS).
High-frequency spine cord stimulation
Sacral neurostimulation
Intrathecal medications
Ziconotide
Nociceptin/orphanin FQ peptide receptor (NOP) agonists
Optogenetics

Cannabinoids

A subject of some controversy, the use of cannabis products, more specifically cannabinoids, has been a matter of discussion [18]. In a randomized trial using smoked cannabis for chronic neuropathic pain, the authors selected 23 patients with post-traumatic or postsurgical neuropathic pain. Evaluating pain scores, mood, and sleep, they concluded that a single inhalation of 25 mg of 9.4 % tetrahydrocannabinol herbal cannabis three times daily for 5 days may cause pain relief and improve the quality of sleep and is well tolerated [19].

In another study addressing the use of cannabinoids for NP, patients with multiple sclerosis (MS) were tested by using an oral spray with 2.7 mg of tetrahydrocannabinol and 2.5 of delta-9- cannabidiol. After 5 weeks, cannabis spray was

superior to placebo in reducing pain and sleep disorders in multiple sclerosis patients with central pain. Despite these results, controversies related to cannabinoids use are still present, since other randomized studies did not reveal the significant results, but instead showed the same results as the placebo group [20–22].

In addition to this, two randomized studies showed the benefit of using smoked cannabis in patients with painful HIV-associated sensory neuropathy, allowing the classification as level A rating for efficacy. In both studies, the authors regarded most side effects as mild and self-limited [23, 24]. Differently, in an A systematic review and meta-analysis about cannabinoids for medical use, Whiting et al. showed only moderate evidence for the use of cannabinoids in chronic pain conditions and spasticity [25].

Clonidine

Over the last years, topical clonidine has emerged as adjuvant therapy in diabetic patients who suffer from painful diabetic neuropathy. Despite the lack of enough evidence, its usage deserves more attention. In a randomized, double-blind, placebo-controlled study, Campbell et al. randomized 179 patients with painful diabetic neuropathy to receive either 0.1 % topical clonidine gel or placebo gel. As a result, patients who received topical clonidine gel obtained pain relief in the foot when compared to placebo [6, 26].

The Selective Angiotensin II Type 2-Receptor Antagonist—EMA401

Considered a new alternative for neuropathic pain, EMA401 is a selective angiotensin II type 2-receptor antagonist. A randomized, controlled, double-blind, clinical trial evaluated 181 patients who received 100 mg EMA401 twice daily or a placebo. The researchers found significantly less pain, after a week, compared with baseline values in the EMA401 group, compared to the placebo group, leading to a new possibility of treatment for refractory NP [27].

Cebranopadol

Recently described, Cebranopadol is an analgesic nociceptin/orphanin FQ peptide (NOP) as well as opioid receptor agonist. It has strong antinociceptive and antihypersensitive effects without causing respiratory and motor side effects. In many rat models of acute and chronic pain (tail-flick, rheumatoid arthritis, bone cancer, spinal nerve ligation, diabetic neuropathy), its results have been proven positive for ameliorating NP. In spite of this, other studies are necessary before the usage in humans becomes possible [27].

Botulinum Toxin Type A

The use of botulinum Toxin type A (BTX-A) has been subject to study in the NP [28, 29]. Thus, Ranoux, Attal et al. investigated the effect of one intradermal injection of BTX-A in 29 patients with NP and allodynia of different etiologies. The BTX-A injection improved the spontaneous pain from 2 to 12 weeks (number needed to treat of 3.03 for 50 % pain relief), and reduced allodynia without decrease of sensibility to pain [28].

In a double-blind crossover trial of intradermal BTX-A for diabetic neuropathic pain in 18 patients, Yuan and Sheu et al. found a reduction in VAS ≥3 after 3 months in 44 % of the patients who received BTX-A injection compared to the placebo arm of the study. Also, improvement in sleep quality in those patients was also noted. Despite the exciting results, the authors agree that larger samples are demanded to reveal the real efficacy of BTX-A usage in diabetic NP [29].

Neuromodulation

Conceptually, neuromodulation includes some functional alterations in the central nervous system (CNS), including changes in neural activity, secondary to the electrical stimulus or pharmaceutical drugs applied directly to the CNS. Historically, Galvani described in 1786 an induced muscular contraction in frogs after an induced nerve lesion had been done. In addition to this, Duchenne, in 1852, described an experiment in a patient with facial nerve palsy in whom an electrical stimulus over the frontal branch of the facial nerve evoked response [30, 31].

From a physiological standpoint, changes in voltage-sensitive ion channels occur in response to an electrical stimulus applied directly to a nerve or the CNS. These alterations in membrane permeability might lead to an increase or decrease in the threshold needed to evoke an action potential. Depending on which site and parameters of stimulus applied, a facilitatory or inhibitory response may occur [32].

Over the last years, some new neuromodulation techniques have only recently been used, resulting in a lack of substantial data to reach a conclusion regarding their efficacy so far. The difficulties related to the lack of strong evidence in neuromodulation result from limitations in the usage of placebo in neuromodulation clinical trials. However, sham stimulation has emerged as a potential solution to this issue giving the opportunity to better understanding of such therapy. Despite that, level B recommendation may justify the usage of some procedures in the treatment of some pain conditions [33–35] (Table 2).

Recently, many neuromodulation techniques that have been used in the clinical practice including spinal cord stimulation (SCS), dorsal root ganglion stimulation, peripheral nerve stimulation (PNS), repetitive transcranial magnetic

Table 2 Evidence based neuromodulation treatment in NP

Condition	Procedure	Level of recommendation	Class of evidence
Central pain	MCS	C	IV
	rTMS	B	II
Trigeminal neuralgia	MCS	C	IV
FBSS	SCS	B	II
CRPS I	SCS	B	II
CRPS II	SCS	D	IV
Amputation pain	SCS	D	IV
Brachial plexus damage	rTMS/ MCS	B	II

stimulation (rTMS), motor cortex stimulation (MCS), and deep brain stimulation (DBS). The mention of the emerging of high-frequency spine cord stimulation, a variant of the traditional SCS, which has deserved some attention over the last years, is necessary.

High-Frequency Spinal Cord Stimulation

Considered one of the most useful tools in refractory NP, SCS is an effective way to treat failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I and has gained level B recommendation [36]. Despite this, researchers have been trying to use high-frequency stimulation (HFS; up to 10 kHz), and by doing, so they have been able to demonstrate pain relief equality even more efficient than traditional SCS. A distinct advantage of HFS is that it does cause any secondary effects, such as paresthesia, which is typically required for effective pain relief with conventional SCS. The benefits of using HFS, consistent with the absence of paresthesias during stimulation, are that it may give patients the opportunity to drive cars with active stimulation on [37, 38], and that it opens the opportunity to conduct a true placebo-controlled RCT related to SCS.

In a recently published study, the SENZA-RCT compared traditional low-frequency SCS to HFS, so-called HF 10 therapy in patients with low back and leg pain. A total of 198 patients were enrolled in that study and have been classified as "responders" when they obtained at least 50 % of pain reduction with on-stimulation. After 3 months, back and leg pain improved 84.5 and 83.1 %, respectively, in the HFS group, comparing to just 43.8 and 55.5 % in the traditional SCS group. Those improvements were maintained until 12 months ($p<0.001$), without any side effects or paresthesias [39].

In a follow-up study, the same authors published the 18-month results again, the discrepancies between the group treated with HFS and the one treated with traditional SCS were significant (64.9±30.8 % for back pain, against 42.5±35.9 % in the traditional group, $p<0.001$). Similar results were found for leg pain (65.4±35.2 % for HF10 therapy, against 45.0±40.3 % in the traditional SCS arm, $p<0.001$). That having been said, one can consider a shifting paradigm in SCS, considering nowadays HF10 therapy level 1 evidence for leg and chronic pain, with better results in terms of pain relief when compared to traditional SCS [40].

Burst Stimulation

One of the recent advances in stimulus delivering while using SCS is the concept of burst stimulation (BS). It represents a different mechanism of stimulation. While in traditional SCS regular stimulus, so-called tonic stimulation is being used. BS was designed to try to simulate another pattern by which neurons conduct pain signals, through packets of high-frequency pulses also known as bursts, which again, exert its effects without causing any paresthesia [41].

Some of the indications for burst stimulation are the same as the traditional SCS, such as back and leg pain and CRPS. However, lack of enough evidence to justify its use for the majority of other pain conditions is still a major concern. A double-blind randomized placebo-controlled trial has been conducted by N. Kriek and colleagues comparing tonic spinal cord stimulation; high-frequency and burst stimulation in patients with complex regional pain syndrome is currently being conducted [42].

In another randomized placebo-controlled trial performed by Schu S. and colleagues; the role of BS in failed back syndrome has been studied. Twenty patients were enrolled to receive burst, tonic, or sham stimulation. Assessing improvement by using a numerical pain scale (NRS) and Short-Form McGill Pain Questionnaire (SFMPQ), the burst stimulation resulted in lower mean NRS and SFMPQ compared to tonic stimulation. The authors concluded that burst stimulation showed better pain relief compared with tonic stimulation and placebo stimulation, being preferred by the majority of patients by not causing paresthesias [41].

DRG Stimulation

Another relatively new target to treat NP is the dorsal root ganglion (DRG), a pseudo-unipolar body cell that works like a "gatekeeper", transducing the primary sensitivity information from the periphery to CNS. Direct electrical stimulation of DRG is supposed to modulate peripheral NP [43].

A prospective multicenter trial published by Liem et al. compared the pain status in 32 subjects with NP from varying etiologies before and after a DRG stimulation system implantation. They found a 58 % decrease in pain from baseline at 6 months follow-up, and once the system was turned-off for a week, pain level became near the baseline. Hence, the authors suggest DRG as a valuable tool for the treatment of chronic pain, with a more selective stimulation of painful areas and reducing the side effects that are seen in standard SCS [35].

A prospective study of DRG stimulation for chronic pain enrolling ten patients and using VAS as primary endpoint found a 70 % reduction in pain after DRG stimulation implant (p=0.0007), and in seven patients, reduction in pain medication was achieved. As the conclusion, the authors suggest that DRG stimulation might be an efficient tool in patients with chronic pain, allowing the same benefits as SCS does, although it may overcome some anatomic difficulties present in SCS. DRG stimulation can be used, for example, in patients with phantom limb pain, complex regional pain syndrome, or post-herpetic neuralgia. An advantage of DRG stimulation is its precisely located stimulation, such as distal extremities for example (where conventional SCS is less efficient compared to its effectiveness in other painful areas) [44–47].

Peripheral Nerve Stimulation

Although insufficient evidence for peripheral nerve stimulation (PNS) efficacy is available, its use as a reasonable option in the treatment of NP associated with peripheral nerve injuries has emerged. PNS is a minimally invasive and relatively straightforward procedure, which can replace available neuroablative procedures [48]. Stimulating the nerve itself in a focal way and delivering electrical currents to the superficial dorsal horn, PNS is believed to produce analgesia based on the gate-control theory [49–51].

PNS is indicated to provide focal neuromodulation in severe chronic pain in a single nerve distribution, which has not responded to other treatments. Some of the indications are post-herpetic neuralgias (PHN), post-traumatic neuralgias, complex craniofacial neuralgias, occipital neuralgia, inguinal neuralgias, etc. Some studies have demonstrated the efficacy of PNS in reducing chronic pain. A prospective, randomized, controlled study found a 50 % reduction in pain with adequate stimulation in patients with chronic pain (p=0.003). In spite of some good results published so far, better-randomized controlled studies are necessary to define the role of procedure for each condition accurately [49–51].

Sacral Neuromodulation

Sacral neuromodulation (SCNM) is considered a palliative and alternative method to treat pelvic pain syndromes, as well as urologic disturbances. Some of the indications for SCNM are pudendal neuralgia and many others pain syndromes of this region.

In a single-center study by Donon et al., 93 patients underwent various sacral nerve stimulation indications. In a subgroup of 11 patients with chronic pelvic pain, 58 % pain relief was achieved during a follow-up of 8 years. However, the small level of evidence (level 4) is still not strong enough to support SCNM use in all patients who suffer neuropathic or other forms of chronic pelvic pain syndromes [52].

Deep Brain Stimulation

Deep brain stimulation (DBS) has been used to treat NP, especially when it affects large body regions. DBS is regarded the last resource of treatment of NP. The targeted areas of stimulation include the periventricular/periaqueductal gray area, ventral posterior medial and lateral thalamic nuclei and lateral rostral anterior cingulate cortex [53].

No major studies evaluating the use of DBS in different groups of patients have been published thus far. Several small studies have indicated varying rates of success in controlling pain, pointing out that the selection of candidates for the procedure is a major predictor of success, though multicenter research is mandatory to assess these variables. In a single-center case series published by Boccard et al., 85 patients underwent DBS surgery for NP from different etiologies. Using a mean follow-up of 19.6 months, they related 66 % of pain relief and significant improvement in the quality of life. The best results were achieved in the treatment of pain after amputation, brachial plexus injury, stroke, and headache. Despite these benefits of DBS therapy, clinical trials are still required [53–55].

Repetitive Transcranial Magnetic Stimulation (rTms)

rTMS is a relatively new technique; composed of coils that connect to a pulse generator, which deliver electrical stimulus on the scalp with the focus on the motor area, in a process called electromagnetic induction. This in turn, through pyramidal neurons, modulates sensitive neurons, evoking pain relief. This non-invasive method has been used to treat NP and major depression. For NP, the evidence of rTMS is relatively good (level B), although its analgesic effect lasts just 1 week, demanding multiple visits in order to perform the treatment

[56]. In addition, rTMS seems to be more useful for central rather than peripheral pain conditions [56]. Although there is some controversy regarding the use of rTMS use as a marker for identifying candidates for motor cortical stimulation (MCS) in the treatment of NP, it is routinely used for that purpose [33, 34].

Transcranial Direct Current Stimulation (tDCS)

Aiming to minimize to the frequent returning visits needed for the utilization of rTMS, tDCS has emerged as a possible solution since it might be applied at home. By a similar mechanism to the rTMS, tDCS delivers electric currents on the scalp, which in turn change membrane potentials, altering the excitability of these cells [57, 58].

Although with inconsistent results, some papers have addressed tDCS in NP treatment. In a sham-controlled trial of tDCS for central pain following traumatic spinal cord injury, Fregni et al. showed pain improvement after anodal stimulation compared to the sham treatment. Additionally, no adverse effects were noticed; particularly, no neuropsychological effects were revealed [59]. Similarly, Antal et al. used tDCS for treating patients with different types of chronic pain, and on a short-term basis (5 days usage), they demonstrated improvement in VAS up to 4 weeks after the treatment [60].

In a Cochrane systematic review with meta-analyses of non-invasive brain stimulation techniques for chronic pain, O'Connell NE and colleagues found five studies related to tDCS. However, they showed heterogeneity among studies, and no significant statistical differences between active and sham stimulation were found. Despite the little chances of side effects due to tDCS use, other studies are necessary to prove the real benefit of the utilization of this therapy [61].

Aiming to resolve this issue, O'Neill et al. are performing a randomized controlled trial, sham-controlled, double-blinded crossover study in patients with NP. The safety and efficacy outcomes of this study are pending [58].

Motor Cortex Stimulation

First described as a valuable alternative tool to treat NP from the central origin, MCS has been used since the 1990s. Its mechanism of analgesia seems to be related to the reduction of activation of a hyperactive thalamus, which is typically present in central pain. The procedure itself consists of an implant of epidural electrodes over the central gyrus, under general anesthesia or sedation plus local anesthesia. There are several studies correlating MCS and NP improvement, mainly in central post-stroke pain (CPSP), with good results, although no meta-analysis exists so far. For this reason, MCS is regard as level C in patients with neuropathic facial pain and central post-stroke pain [33, 62, 63]. A randomized, controlled, crossover trial aiming to evaluate 16 patients with NP after peripheral nerve lesion found no significant difference between groups in terms of pain relief, although MSC was considered right or satisfactory in 60 % of patients in the open phase of the study [64, 65].

Intrathecal Medications

Regarded an alternative treatment for patients who failed to experience pain relief with usual medications, intrathecal therapy (IT) is a well-established tool to treat cancer pain and possibly other forms of intractable pain, causing less adverse events than oral medications. Intrathecal morphine, the principle IT drug, has been used to treat NP. Other drugs have been used in clinical practice, particularly ziconotide and local anesthetics. Nociceptin/orphanin FQ peptide receptor (NOP) agonists are subject of some publications [66–68].

Despite less adverse events, IT using opioids may cause tolerance. In order to overcome this problem, Ziconotide has emerged as an alternative drug to treat cancer and non-cancer pain. Regarded as a non-opioid analgesic treatment option for patients with refractory neuropathic pain, its mechanism of action is blocking specific and selective N-type voltage-sensitive calcium channels in a reversible way, which in turn decreases neurotransmitters liberation from nociceptive afferents [67, 69].

A systematic review performed by Rauck et al. about IT ziconotide found some information about double-blind, placebo-controlled trials, which indicated that patients with NP related a mean improvement rate in pain score with monotherapy, ranging from 15.7 to 31.6 %. Additionally, this drug showed a safety profile when used with care, despite the possibility of nausea and/or vomiting, somnolence, confusion, dizziness, and urinary retention as adverse effects [67].

Although not yet available for clinical use, intrathecal administration of NOP agonists might lead to an antinociceptive effect by its ligation in receptors situated in the spinal cord. Doing so, NOP agonists might be potentially used as an effective treatment for NP when utilized in intrathecal drug delivery systems [68, 70, 71].

Also, the usage of dual NOP/MOP (μ-opioid receptor) ligands might be practical and even more potent than the selective NOP or MOP agonists. In relation to this, Sukhtankar et al. published an interesting study demonstrating this mechanism and its efficacy in mice. Besides, they showed good cost-effectiveness, with low rates of tolerance. However, additional studies in humans are necessary to prove any beneficial effect in NP, and to the best of our knowledge, no clinical trial addressing these drugs exists so far [68].

Optogenetics

One limitation of the neuromodulation used currently is related to the way the electrical current is delivered within the

CNS. In other words, the principle behind both the DBS and SCS systems is of a general stimulation in which neurons are stimulated in a non-specific way. Hence, all types of neurons are stimulated, including those not involved in the pathophysiology of the particular pain condition. Resultantly, non-desirable sites are also stimulated, creating side effects.

As a more precise technique, optogenetics emerges in to fill this blank of the classical neuromodulation. Called opsins, *Chlamydomonas reinhardtii Channelrhodopsin-2* (ChR2) and *Natronomonas pharaonis halorhodopsin* (NpHR) are two microbial proteins which have opposing effects. One of them may cause membrane cell depolarization, and another one might lead to hyperpolarization in those cells [72, 73].

They consist of light-sensitive membrane-bound G protein-coupled receptors, which by stereotactical surgery may be inserted into the brain and thus become a light receptor in neurons. This might be accomplished by the insertion of viral vectors that carry genes responsible for encoding ChR2 or NpHR. As a result, such viral vectors are assimilated by the genome of the target cell, and permanent gene expression may occur [72, 73].

Once stimulated by blue light with a spectrum of 470 nm, ChR2 activation occurs, and as a consequence, Na+influxes into the cells, deflagrating an action potential. On the contrary, NpHr is a Cl pump that is activated by yellow light (580 nm). Its mechanism is based on neuron hyperpolarization, leading to its suppression. The whole process is dependent upon the usage of a fiber optic device, which delivers light to the brain. Notably, this process might be achieved by the insertion of a micro cannula, which photostimulates specifically some groups of neurons intended. Finally, stimulation or inhibition, depending on which approach was previously chosen, may be obtained [72, 73].

Therefore, this innovative neuromodulation technique might be used in the near future as a valuable tool to treat chronic pain, causing a specific inhibition of pain fibers through NpHR function and, in theory, provoking its effects without evoking stimulus in other types of fibers. Moreover, through the stimulus of ChR2, the endogenous analgesic system is stimulated, which in turn might potentially cause pain relief [72, 73].

Aiming to show the role of the prefrontal cortex (PFC) in the analgesic system, Lee M and colleagues demonstrated that optogenetic activation of the PFC could lead to antinociceptive effects in a rat model of persistent NP. In this paper, these authors hypothesized the role of corticostriatal circuitry in pain regulation since the optogenetic activation of the prefrontal cortex led to corticostriatal stimulation and, as a consequence, pain suppression [74]. In another interesting work done by Iyer S.M. and colleagues, they performed intra-sciatic nerve injection of adenoviruses carrying an inhibitory opsin. Posteriorly, the light was delivered transdermally, which in turn enabled light-inducible inhibition of acute pain perception improving allodynia and hyperalgesia. Doing that, these authors have contributed to new insights in pain research, since new opsins could be tested [75].

Future Directives

In addition to the optogenetics as mentioned above and some neuromodulation modalities and drugs, one concept that has emerged is about the epigenetic regulation of NP. Conceptually, after tissue injury and acute pain, adaptation to this condition in some brain regions may develop. These regions could modulate themselves after neuroinflammation and chronic pain as a result of DNA methylation and histone modifications. Hence, epigenetics could drive change in gene expression from nociceptive cells after an environmental exposure, being responsible for maintenance of persistent pain or even play a role in transforming acute pain to chronic pain [76, 77].

That having been said, one medication or device that would be able to influence this process, changing the way in which the epigenetic regulation happens, could be potentially helpful in avoiding central sensitization. By doing so, the induction of chronic pain syndromes could be minimized or prevented [76, 78].

Conclusion

Many clinical and surgical therapies to treat NP have emerged over the last decade. With the wide acceptance of their use, new neuromodulation techniques and drugs and optogenetics might become, in near future, a part of the routine treatment of NP. Despite a lack of convincing RCTs addressing the efficacy of some of these new therapies for NP and the need for further studies, the progress achieved so far is valuable, accounting for significant improvement in the quality of life of many patients.

Indeed, there are no definitive treatments for NP. However, with advancing knowledge on the pathophysiology of pain, new methods might be proposed, ensuring greater effectiveness of different therapies, with a lower percentage of patients with refractory pain. Doing so, a new paradigm for the treatment of chronic pain will result.

Compliance with Ethical Standards

Conflict of Interest Bruno L. Pessoa, Gabriel Escudeiro, and Osvaldo JM Nascimento declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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