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# Neuropathic pain: From actual pharmacological treatments to new therapeutic horizons

Maxime Thouaye<sup>a</sup>, Ipek Yalcin<sup>a, b, \*</sup>

<sup>a</sup> Centre National de la Recherche Scientifique, Université de Strasbourg, Institut des Neurosciences Cellulaires et Intégratives, Strasbourg, France

<sup>b</sup> Department of Psychiatry and Neuroscience, Université Laval, Québec, QC G1V 0A6, Canada

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## ABSTRACT

Neuropathic pain, caused by a lesion or disease affecting the somatosensory system, affects between 3 and 17% of the general population. The treatment of neuropathic pain is challenging due to its heterogeneous etiologies, lack of objective diagnostic tools and resistance to classical analgesic drugs. First-line treatments recommended by the Special Interest Group on Neuropathic Pain (NeuPSIG) and European Federation of Neurological Societies (EFNS) include gabapentinoids, tricyclic antidepressants (TCAs) and selective serotonin noradrenaline reuptake inhibitors (SNRIs). Nevertheless these treatments have modest efficacy or dose limiting side effects. There is therefore a growing number of preclinical and clinical studies aim at developing new treatment strategies to treat neuropathic pain with better efficacy, selectivity, and less side effects. In this review, after a brief description of the mechanisms of action, efficacy, and limitations of current therapeutic drugs, we reviewed new preclinical and clinical targets currently under investigation, as well as promising non-pharmacological alternatives and their potential co-use with pharmacological treatments.

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## 1. Introduction

Chronic pain is defined as any type of pain that persists more than three months following the initial triggering event (Scholz et al., 2019). Around 20% of the population worldwide is affected by this condition, and multiple disorders are associated with chronic pain, including mood disorders such as anxiety and major depressive disorders that affect 50% of patients with chronic pain. Chronic pain and its comorbidities are thus one of the most important causes of disability and impaired quality of life, with a societal cost that can reach \$700 billion in the United States, and over €340 billion in the European Union annually (Barham, 2012; Institute of Medicine (U.S.), 2011). Among its seven diagnostic categories defined by the 11th revised International Classification of Diseases and related health problems (ICD-11), neuropathic pain is one of the most prevalent pain conditions, affecting one in ten adults worldwide (Scholz et al., 2019).

Neuropathic pain is defined as a pain caused by a lesion or disease affecting the somatosensory system (Jensen et al., 2011; Treede et al., 2008). It can originate peripherally (nerves, plexus, etc.) or centrally (spinal cord and brain). Neuropathic pain can result from trauma (spinal cord injury, carpal tunnel syndrome, etc.), metabolic disorders

(peripheral diabetic polyneuropathy), viral infections (postherpetic neuralgia, Human Immunodeficiency Viruses-1 (HIV)), autoimmune disorders (multiple sclerosis) and chemotherapeutics affecting the nervous system (for review see (Baron et al., 2010)). Due to its diverse etiology, neuropathic pain remains difficult to diagnose clinically, especially when comorbid with other pathological conditions. As there is no generalizable classification allowing a clear diagnosis, a grading system, proposed by International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG), is often used (Finnerup et al., 2016). However, this grading system only determines the level of certainty for the presence of a neuropathic pain (possible, probable or definite) based on the patient's history, tests confirming lesions or diseases affecting the nervous system, and the neuroanatomical distribution of pain and its association with sensory signs. Symptoms of neuropathic pain include the presence of (i) paroxysmal or spontaneous pain, (ii) evoked pain, (iii) abnormal sensations, and/or (iv) sensory deficits (Bennett et al., 2007; Rasmussen et al., 2004). Paroxysmal pain corresponds to episodic pain that can occur several times a day and is described as a sensation of electrical shocks or stabbing, while spontaneous pain is a constant dull pain that can be described as sensation of cold, burning or itching associated with pins and needles. On the other

**Abbreviations:** ICD-11, 11th revised International Classification of Diseases and related health problems;  $\alpha$ 2A-Ars,  $\alpha$ 2A-adrenoceptors; ALA,  $\alpha$ -Lipoic Acid; AAV, Adeno-Associated Virus; ATP, Adenosine Triphosphate; AT2Rs, Angiotensin II Type 2 Receptors; ACC, Anterior Cingulate Cortex; AD, Antidepressant Drugs;  $\beta$ 2-ARs,  $\beta$ 2-adrenoceptors; BMI, Body Mass Index; BoNT/A, Botulinum Toxin type A; BDNF, Brain-Derived Neurotrophic Factor; CGRP, Calcitonin Gene Related Protein; CREB, cAMP-Response Element-Binding protein; CBD, Cannabidiol; CB1R, Cannabinoid Receptor type 1; CB2R, Cannabinoid Receptor type 2; CSF1-R, Colony-Stimulating Factor 1 Receptor; cAMP, cyclic Adenosine Monophosphate; DOR,  $\delta$ -Opioid Receptor; THC,  $\Delta$ 9-Tetrahydrocannabinol; DRGs, Dorsal Root Ganglia; DLPFC, Dorsolateral Prefrontal Cortex; EFNS, European Federation of Neurological Societies; EMEA, European Medicines Agency; FLT3, FMS-Like Receptor Tyrosine Kinase 3; FSTL1, Follistatin-like 1; FDA, Food and Drug Administration; GABA,  $\gamma$ -Aminobutyric Acid; GLA,  $\gamma$ -Linolenic Acid; GIRKS, G protein-coupled Inwardly-Rectifying Potassium channels; GPCRs, G Protein-coupled Receptors; GFLs, GDNF Family Ligands; GDNF, Glial cell line-Derived Neurotrophic Factor; HVACC, High-Voltage-Activated Calcium Channel; HIV, Human Immunodeficiency Viruses-1; IL-1 $\beta$ , Interleukin-1 $\beta$ ; IASP, International Association for the Study of Pain; KOR,  $\kappa$ -Opioid Receptor; LTD, Long-Term Depression; LTP, Long-Term Potentiation; MMP2, Matrix Metalloprotease 2; MKP-1,

Mitogen-Activated Protein Kinase Phosphatase 1; MAPK/ERK, Mitogen-Activated Protein Kinase/ Extracellular signal-Regulated Kinase; MOR,  $\mu$ -Opioid Receptor; NGF, Nerve Growth Factor; NPD1/PD1, Neuroprotectin D1/Protectin D1; NT3, Neurotrophin 3; NO, Nitric Oxide; NMDAR, N-Methyl-D-Aspartate Receptor; NOR, Nociceptin Opioid Receptor; N/OFQ, Nociceptin/Orphanin FQ; NSAID, Non-Steroidal Anti-Inflammatory Drugs; NNH, Number Needed to Harm; NNTs, Number-Needed-To-Treat; PAG, Periaqueductal Gray; PGE2, Prostaglandin E2; PKC, Protein Kinases C; P2XRs, Purinergic receptors; RTKs, Receptors Tyrosine Kinase; rTMS, repetitive Transcranial Magnetic Stimulation; RMT, Resting Motor Threshold; RVM, Rostral Ventral Medulla; SSRIs, Selective Serotonin Reuptake Inhibitors; SNRIs, Serotonin Noradrenaline Reuptake Inhibitors; Na<sup>+</sup>/K<sup>+</sup>-ATPase, Sodium potassium pump; NeuPSIG, Special Interest Group on Neuropathic Pain; SCS, Spinal Cord Stimulations; SNAP-25, Synaptosomal-Associated Protein, 25 kDa; tDCS, transcranial Direct Current Stimulations; TENS, Transcutaneous Electrical Nerve Stimulation; TRPA1, Transient Receptor Potential Ankyrin 1; TRPM8, Transient Receptor Potential Melastatin-8; TRPV1, Transient Receptor Potential Vanilloid member 1; TCAs, Tricyclic Antidepressants; Trk, Tropomyosin receptor kinase; TNF- $\alpha$ , Tumor Necrosis Factor  $\alpha$ ; Nav, Voltage-Gated sodium channels; VGCCs, Voltage-Gated Calcium Channels; VGPCs, Voltage-Gated Potassium Channels; VSCCs, Voltage-Sensitive Calcium Channels

\* Corresponding author at: INCI CNRS, 8 allée du Général Rouvillois, 67000 Strasbourg, France.

*E-mail address:* [yalcin@inci-cnrs.unistra.fr](mailto:yalcin@inci-cnrs.unistra.fr) (I. Yalcin).

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hand, symptoms of evoked pain include allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (increased pain from a stimulus that normally provokes pain), and hyperpathia (abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold). Abnormal sensations include paresthesia and dysesthesia, corresponding to stinging or tingling sensations that can be spontaneous or evoked. Finally, sensory deficits include partial or total loss of sensation of cold, warm or touch (hypoesthesia) in the painful area.

Treatment of neuropathic pain is challenging due to its heterogenic etiologies, lack of objective diagnosis tools and its resistance to classical analgesic drugs. As a result, neuropathic pain management strategies focus primarily on treating symptoms. According to NeuPSIG, subclasses of classical antidepressant drugs and anticonvulsants remain among the first-line treatments for many neuropathic pain conditions (Attal et al., 2010). Lidocaine, capsaicin, tramadol and tapentadol are recommended as second-line treatment while third-line treatments for neuropathic pain include strong opioids and Botulinum Toxin type A (BoNT/A) (Colloca et al., 2017; Dworkin et al., 2007) (Table 1). Besides these drugs, non-pharmacological alternatives such as neuromuscular and neuronal stimulations are used especially when none of the classical drugs is efficient, or as adjuvant therapy (Fig. 2). Finally, several clinical trials (Table 2) and preclinical studies (Table 3) have been con-

ducted to develop therapeutic targets that are more specific, more potent and/or with less side effects.

In this review, we will first describe the mechanisms of action, limitations and side effects of the current pharmacological treatments recommended for neuropathic pain. We will then focus on promising recently developed clinical and preclinical targets and their mechanism of action (Fig. 1). Finally, we will discuss the existing alternative non-pharmacological approaches, with their known mechanisms (Fig. 2), efficacy and limitations, and their prospective application to potentiate pharmacological treatments.

## 2. Pharmacological treatments

### 2.1. First line treatments

#### 2.1.1. Anticonvulsants

**2.1.1.1. Gabapentinoids.** Gabapentinoid drugs, initially described as anticonvulsants, include pregabalin (300–600 mg/day, twice a day) and gabapentin (1200–3600 mg/day, three times a day). Over the last two decades, they became the first-choice treatment and have been approved by the Food and Drug Administration (FDA) to treat neuropathic pain associated with diabetic peripheral neuropathy, spinal cord injury and postherpetic neuralgia (Attal et al., 2010; Colloca et

**Table 1**  
Current pharmacological treatments for neuropathic pain.

	Drugs	Dose range	Main mechanisms	Main side effects
<b>First-line Treatments</b>				
Anticonvulsants	Gabapentinoids	Pregabalin (300–600 mg/day)	- Inhibition of VSCCs through the binding of $\alpha_2\delta-1$ subunit	Dizziness, somnolence, peripheral oedema, and gait disturbance
		Gabapentin (1200–3600 mg/day)	- Increase of noradrenaline level	
	Others	Oxcarbazepine (900 mg/day)	- Block of Nav	Dizziness, drowsiness
		Carbamazepine (800 mg/day)	- Inhibition of spontaneous ectopic activity	
Antidepressants	TCAs	Amitriptyline (10–150 mg/day)	- Inhibition of the reuptake of noradrenaline and serotonin	Sedation, dizziness, dry mouth, constipation, urinary retention and headaches
	SNRIs	Duloxetine (60–120 mg/day)	- Activation of the endogenous opioid system (MOR & DOR)	Sedation or insomnia, headache, and/or decreased appetite or libido
	Venlafaxine (120–255 mg/day)	- Inhibition of microglia activation		
<b>Second-line Treatments</b>				
Topical agents	Lidocaine	- 5% patch - 8% spray	- Suppression of ectopic discharges in injured peripheral nerves by inactivating Nav1.7 and Nav1.8 - Blocking of VGPCs and VGCCs - Modulation of GPCRs (acetylcholine, glutamate, opioid and serotonin receptors)	Itching and erythema
	Capsaicin	- 0.025% cream - 0.075% cream - 0.075% oil - 8% patches	- Desensitization of TRPV1 - Mitochondrial dysfunction	
Weak opioids	Tramadol	100–400 mg/day	- Activation of the endogenous opioid system (MOR)	Nausea, vomiting, constipation, dizziness, somnolence, and a risk of abuse
	Tapentadol	50–600 mg/day	- Inhibition of the reuptake of serotonin and noradrenaline	
<b>Third-line Treatments</b>				
Strong opioids	Morphine	10–120 mg/day	- Activation of the endogenous opioid system (MOR > DOR > KOR)	Nausea, vomiting, constipation, dizziness, somnolence, respiratory depression and a risk of abuse
	Methadone	10–80 mg/day		
	Oxycodone	10–120 mg/day		
	Buprenorphine	0.2–0.6 mg		
	Fentanyl	12.5–50 $\mu$ g/h		
Neurotoxic proteins	BoNT/A	5–100 U	- Inhibition of release of pro-nociceptive neurotransmitters and neuropeptides - Inhibition of microglial activation - Inhibition of the upregulation of Nav1.7	Pain at the injection site

Abbreviations: Botulinum Toxin type A (BoNT/A);  $\delta$ -Opioid Receptor (DOR); G Protein-coupled Receptors (GPCRs);  $\kappa$ -Opioid Receptor (KOR);  $\mu$ -Opioid Receptor (MOR); Serotonin Noradrenaline Reuptake Inhibitors (SNRIs); Transient Receptor Potential Vanilloid member 1 (TRPV1); Tricyclic Antidepressants (TCAs); Voltage gated sodium channels (Nav); Voltage-Gated Calcium Channels (VGCCs); Voltage-Gated Potassium Channels (VGPCs); Voltage-Sensitive Calcium Channels (VSCCs).

**Table 2**

Non exhaustive list of new clinical targets for the treatment of neuropathic pain.

	Drug	Pharmacology	Dose range	Type of pain	Clinical phase
New clinical drugs					
Sodium channels blockers	Voxotrigine	Nav1.7 blockers	400 mg twice daily	Small fiber neuropathy	Phase II
	PF-05089771 BIIB095		150 mg twice daily Not provided	Diabetic neuropathy Healthy volunteers and diabetic neuropathy	Phase II Phase I
	GDC-0276		15–540 mg twice daily	Healthy volunteers	Phase I (discontinued)
P2XRs blockers	VX 150	Nav1.8 blocker	1250 mg/day	Small fiber neuropathy	Phase II
	Gefapixant	P2X3 antagonist	50–300 mg/day	Pain associated with interstitial cystitis	Phase II
NMDA blockers	NC-2600	P2X4 antagonist	Not provided	Not provided	Phase I
	Ketamine	NMDA antagonist	Intravenously infusions – subanesthetic dose	Chronic pain (not specified)	Observational study
TRPA1 blockers	GRC 17356	TRPA1 antagonist	Not provided	Diabetic neuropathy	Phase II (discontinued)
RTK modulators	Tanezumab	Anti-NGF monoclonal antibodies	20 mg every 8 weeks	Diabetic neuropathy	Phase II
NOR modulator	Cebrenopadol	NOR agonist	100–600 µg/day	Diabetic neuropathy	Phase II
AT2Rs blocker	EMA401	AT2Rs antagonist	Not provided	Diabetic neuropathy	Phase II
Antidepressants	Mirogabalin	Gabapentinoid	10–30 mg/day	Diabetic neuropathy & postherpetic neuralgia	Phase III
Cannabinoids	Dronabinol	THC	10 mg/day	Diabetic neuropathy	Phase II
	Epidolex	CBD	800 mg/day		
	Nabiximols	THC + CBD	10.8 mg/day THC + 10 mg/day CBD		

Abbreviations: Angiotensin II Type 2 Receptors (AT2Rs); Cannabidiol (CBD); Nerve Growth Factor (NGF); N-Methyl-D-Aspartate Receptor (NMDAR); Nociceptin Opioid Receptor (NOR); Purinergic receptors (P2XRs); Receptors Tyrosine Kinase (RTKs); Transient Receptor Potential Ankyrin 1 (TRPA1); Voltage gated sodium channels (Nav);  $\Delta$ 9-Tetrahydrocannabinol (THC).

al., 2017; Finnerup et al., 2015). The use of gabapentinoids has been shown effective mainly for two different types of neuropathic pain, postherpetic neuralgia (with pain reduction of at least 50% observed in 41% of patients for pregabalin and 32% of patients for gabapentin), and diabetic peripheral neuropathic pain (with pain reduction of at least 50% of observed in 41% of patients for pregabalin and 38% of patients for gabapentin) (Moore et al., 2009, 2014). Other studies showed a moderate effect of gabapentinoids on neuropathic pain induced by spinal cord injury, and contradictory effects on central neuropathic pain and on HIV-induced neuropathic pain (La Spina et al., 2001; Moore et al., 2009; Tong et al., 2021). However, there are few studies on their efficacy in other neuropathic pain conditions. Finally, Cochrane Data Base Analyses demonstrated that at least one adverse event has been reported in 62% of patients using gabapentin, and 11% discontinued due to an adverse event (19% suffer dizziness, 14% somnolence, 7% peripheral oedema, and 9% gait disturbance). However, only 3% of serious adverse effects were detected (Moore et al., 2014). The same results were obtained with pregabalin (Derry et al., 2019).

Both gabapentin and pregabalin bind to the  $\alpha_2\delta$  subunits of the Voltage-Sensitive Calcium Channels (VSCCs). The  $\alpha_2\delta$ -1 subunit is their primary target, as gabapentinoids-induced analgesia in neuropathic pain is lost in  $\alpha_2\delta$ -1 knock out mice (Field et al., 2006). This subunit is densely expressed in Dorsal Root Ganglia (DRGs), spinal cord and in supraspinal structures such as the anterior cingulate cortex (ACC), the periaqueductal gray (PAG), the amygdala and the insular cortex that are involved in the nociceptive and/or emotional aspects of chronic pain. The  $\alpha_2\delta$ -1 subunit has been shown to be upregulated in the DRG and/or in the dorsal horn of the spinal cord in different animal models of neuropathic pain (Luo et al., 2002, 2001; Narita et al., 2007; Xiao et al., 2007), while chronic administration of gabapentinoids normalizes this overexpression (Bauer et al., 2009; Morimoto et al., 2012; Xiao et al., 2007). Binding to  $\alpha_2\delta$ -1 triggers inhibition of cellular calcium influx and transmission of different neurotransmitters (including glutamate, noradrenaline and substance P). Even though the primary target of gabapentinoids is  $\alpha_2\delta$ -1 subunits, they recruit the descending noradrenergic pathway by activating the locus coeruleus and increase extracellular noradrenaline levels in the spinal cord (Hayashida et al., 2008; Suto et al., 2014). Gabapentinoids indirectly block the  $\gamma$ -Aminobutyric Acid

(GABA) transmission and increase spinal GABA release in neuropathic pain models. In addition to neurons, they also affect glial cells, especially microglia as well as the balance between anti- vs pro-inflammatory cytokine (Lee et al., 2013).

New gabapentinoid molecules continue to be developed, although classical gabapentinoids are already efficiently used for the treatment of neuropathic pain. For instance, Mirogabalin, a novel gabapentinoid with a better binding affinity for  $\alpha_2\delta$ -1 and  $\alpha_2\delta$ -2 subunits than pregabalin (Kato et al., 2021), showed more potent and longer-lasting analgesic effects than classical gabapentinoids in rat models of nerve injury, spinal cord injury, or diabetic neuropathy (Domon et al., 2018; Murasawa et al., 2020). Various clinical trials, including Phase III trials, also showed strong efficacy against diabetic neuropathic pain and postherpetic neuralgia (Baba et al., 2019; Javed et al., 2018). However, same side effects as classical gabapentinoids are observed, with a similar -if not higher- rate of treatment discontinuation due to somnolence side effect.

**2.1.1.2. Besides gabapentinoids.** Oxcarbazepine and carbamazepine are also considered effective against neuropathic pain, although they are currently considered a first-line treatment only for trigeminal neuralgia (with pain reduction of at least 30% observed in 88.3% of patients for carbamazepine and 90.9% of patients for oxcarbazepine (Di Stefano et al., 2021; Gambeta et al., 2020)), with drowsiness and dizziness being the main side effects. They are voltage-gated sodium channel (Nav) blockers and have been shown to inhibit spontaneous ectopic activity induced by nerve injuries (Burchiel, 1988; Chapman et al., 1998). This inhibition could depend of Nav1.1, selectively upregulated in trigeminal nerves but not somatic nerves, which could explain their greater efficacy in treating trigeminal neuropathic pain compared to other conditions (Pineda-Farias et al., 2021). Besides trigeminal pain, clinical studies demonstrated analgesic effect of oxcarbazepine against diabetic neuropathy, neuropathic pain induced by radiculopathy (pinching of a nerve root in the spinal cord) and mixed neuropathies (Zhou et al., 2017). However, the use of carbamazepine to treat other types of neuropathic pain than trigeminal neuralgia has not yet been demonstrated (Wiffen et al., 2014).

**Table 3**

Non exhaustive list of new pre-clinical targets for the treatment of neuropathic pain.

	Drug	Pharmacology	Animal model(s) used	Species	
New pre-clinical drugs					
Sodium channels blockers	Nav1.7	Narirutin	Flavonoid active constituent	SNI	Rat
		VY-NAV01	AAV	Nerve injury	Rodents
		Nav1.7-CRS		Oxaliplatin	Primates
Nav1.8	Dexpramipexole	Benzothiazole-like compound	CCI	Not provided	Mice
			Oxaliplatin	STZ-Induced	Diabetic neuropathic pain
Na <sup>+</sup> /K <sup>+</sup> -ATPase modulators	FXDY2-LASO-Gapmer	AAV	SNL		Rat
TRPM8 modulators	IGM5	TRPM8 agonist	CCI		Mice
	IGM-18	TRPM8 antagonist			
TRPA1 modulators	HC-030031	TRPA1 antagonist	Oxaliplatin		Rat
P2XRs blockers	Dexmedetomidine	α2 adrenergic receptor agonist with P2X7 inhibition properties	CCI		Rat
	IgG#191-Bbbt0626	Anti-P2X4 monoclonal antibody	PSNL		Mice
	NP-1815-PX	P2X4 antagonist	Postherpetic neuralgia		Mice
RTKs modulators	BT44	Ret agonist	SNL		Rat
			STZ-Induced		Diabetic neuropathic pain
	Democycline	Tetracyclines inhibiting the EphB1 receptor	Tissue injury by formalin		Mice
NOR modulators	Chlortetracycline				
	BDT001	FLT3 negative allosteric modulator	CCI		Mice
		SNL			
	Ro64-6198	Selective NOR agonist	SNI		Rat
	BU08028	Partial agonist of NOR and MOR	CCI		Mice
	SR16435				

Abbreviations: Chronic Constriction Injury of the sciatic nerve (CCI); FMS-Like Receptor Tyrosine Kinase 3 (FLT3); μ-Opioid Peptide receptor (MOR); Nociceptin Opioid Receptor (NOR); Purinergic receptors (P2XRs); Receptors Tyrosine Kinase (RTKs); Spared Nerve Injury; Spinal Nerve Ligation (SNL); Sodium potassium pump (Na<sup>+</sup>/K<sup>+</sup>-ATPase); Streptozotocin (STZ); The Partial Sciatic Nerve Ligation (PSNL); Transient Receptor Potential Ankyrin 1 (TRPA1); Transient Receptor Potential Melastatin-8 (TRPM8); Voltage gated sodium channels (Nav).

### 2.1.2. Antidepressants

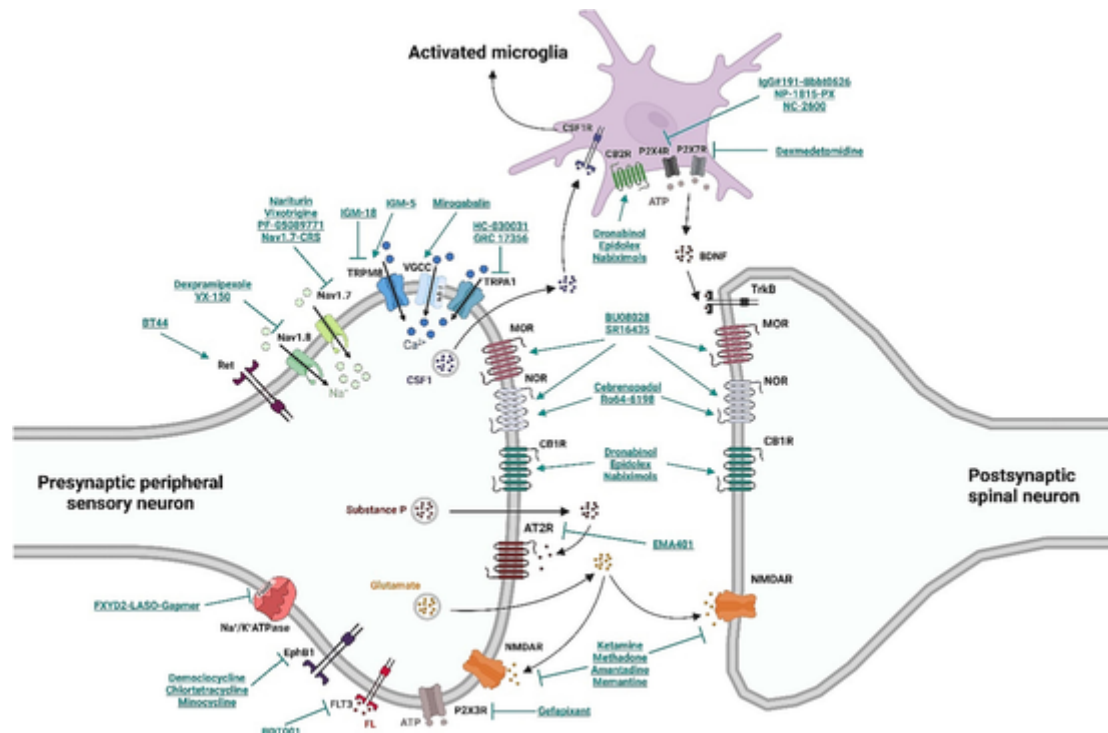
Along with anticonvulsants, antidepressants -and especially the Tricyclic Antidepressants (TCAs) and the selective Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)- are the most prescribed treatments against neuropathic pain (for review see (Kremer et al., 2016)). For TCAs, the Number-Needed-To-Treat (NNTs) is 3.6 to achieve at least moderate pain relief compared to placebo, the Number-Needed-To-Harm (NNH) for major adverse effects leading to withdrawal is 28 and for minor adverse effects (sedation, dizziness, dry mouth, constipation, urinary retention and headaches) is 6 (Saarto & Wiffen, 2007). SNRIs have a NNT of 6.4 for 50% pain relief as primary

endpoint, and NNH (sedation or insomnia, headache, and/or decreased appetite or libido) of 11.8 (Finnerup et al., 2015). The effect of antidepressants on neuropathic pain is independent of the patient's emotional state and involves mechanisms different from their antidepressant effect (Perahia et al., 2006). Indeed, lower therapeutic doses are sufficient to treat neuropathic pain than their use in major depressive disorders, and with a shorter duration of action (Onghena & Van Houdenhove, 1992). Among TCAs, amitriptyline (10–150 mg/day, at bedtime) is the most prescribed to treat postherpetic neuralgia, diabetic polyneuropathic pain and central neuropathic pain (Saarto & Wiffen, 2007). Among SNRIs, duloxetine (60–120 mg/day) and venlafaxine (120–255 mg/day) are mainly used for diabetic polyneuropathy and recommended by the European Federation of Neurological Societies (EFNS) and NeuPSIG as first line treatment for neuropathic pain. In addition, duloxetine is the only drug approved by the FDA and the European Medicines Agency (EMA) for painful diabetic polyneuropathy. Since both TCAs and SNRIs inhibit the reuptake of the noradrenalin and serotonin, most of the preclinical and clinical studies have focused on these two systems to understand their mechanisms of action in neuropathic pain. While several studies showed that the antinociceptive effect of chronic antidepressant administration is mediated by both noradrenergic and serotonergic systems, other studies suggest that the noradrenergic system is the primary target of their effects on neuropathic pain. Indeed, most preclinical and clinical studies showed that Selective Serotonin Reuptake Inhibitors (SSRIs) are ineffective or poorly effective in the treatment of neuropathic pain when administered alone (Attal et al., 2010; Otto et al., 2008). Concerning noradrenergic system, supraspinal structures, and in particular the locus coeruleus activating noradrenergic descending pathway, spinal cord and peripheral sites including dorsal root ganglia, are involved in the mechanisms of action of antidepressants (Obata, 2017). Besides monoamine component, complex interactions with ion channels, and especially Nav, in peripheral neurons have also been reported with TCAs (Cardoso et al., 2022). Since the effect of chronic antidepressants can be blocked by opioid antagonists such as naloxone and are lost in δ-Opioid Receptor (DOR)-deficient mice, the involvement of the opioid system in the effect of the antidepressants on neuropathic pain has been suggested. Interestingly, the adrenergic and opioid receptors recruited for the antiallodynic effect of antidepressants can differ between acute and chronic administration. Indeed, it has been shown that two distinct mechanisms exist by which antidepressants relieve neuropathic allodynia: one is observed after acute administration requiring central nervous system, descending noradrenergic inhibitory controls and α2A-Adrenoceptors (α2A-Ars), as well as the μ-Opioid Peptide receptor (MOR) and DOR. The second one is delayed, peripheral and requires noradrenaline from peripheral sympathetic endings and β2-Adrenoceptors (β2-Ars), as well as DOR from small peptidergic sensory neurons (Ceredig et al., 2018; Kremer et al., 2020, 2018).

Finally, antidepressants could also regulate the activation of microglial cells and proinflammatory actors in the spinal cord, involved in the maintenance of neuropathic pain. For example, it has been demonstrated in a rat model of diabetic neuropathic pain that duloxetine and atomoxetine, another SNRI, are able to reduce the microglial activation and the level of proinflammatory cytokines Tumor Necrosis Factor α (TNF-α) and Interleukin-1β (IL-1β) in the spinal cord, through the inhibition of the p-p38 and p-JNK pathways (Zhang et al., 2018). Another study showed that recruitment of noradrenaline in the peripheral nervous system leads to the stimulation of β2-Ars in the DRG and a decrease in the level of the proinflammatory cytokines TNF-α (Bohren et al., 2013).

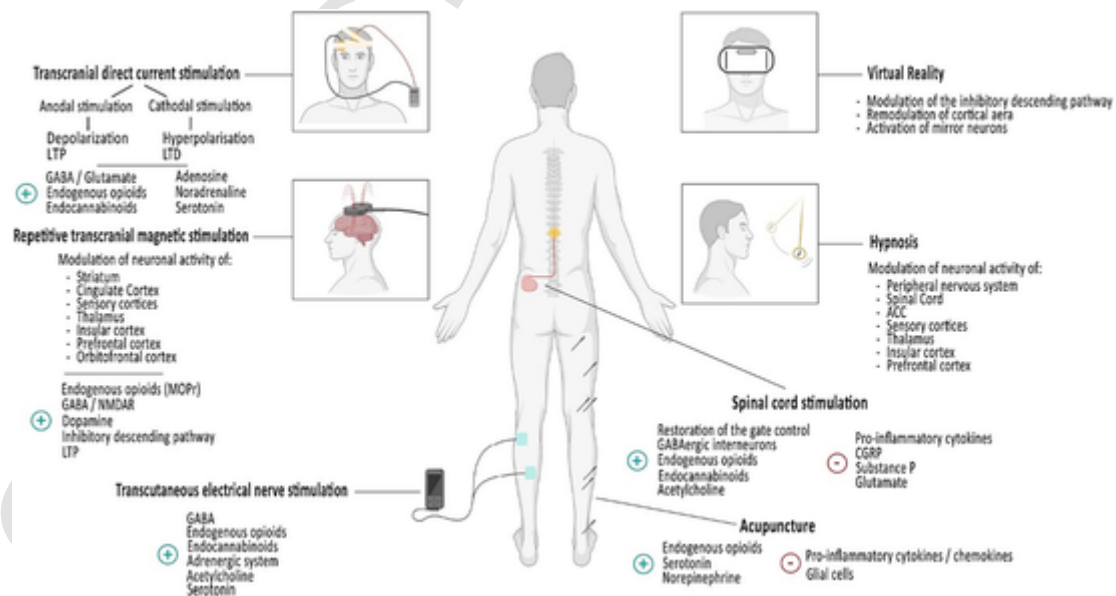
### 2.2. Second line treatments

Second line treatments include topical agents such as lidocaine and capsaicin, as well as tramadol.



**Fig. 1.** Possible mechanisms of action of new preclinical and clinical molecules against neuropathic pain.

New pharmacological molecules target in majority receptors and ion channels localized in the synapse between primary sensory neurons and spinal interneurons or projecting neurons, by activating inhibitory GPCRs (MOR, NOR, CB1R, CB2R), or inhibiting pronociceptive actors (P2XRs, ion channels, NMDARs, RTKs). Abbreviations: Angiotensin II Type 2 Receptors (AT2Rs); Adenosine Triphosphate (ATP); Brain-Derived Neurotrophic Factor (BDNF); Cannabinoid Receptor type 1 (CB1R); Cannabinoid Receptor type 2 (CB2R); Colony-Stimulating Factor 1 Receptor (CSF1-R); FMS-Like Receptor Tyrosine Kinase 3 (FLT3);  $\mu$ -Opioid Receptor (MOR); N-Methyl-D-Aspartate; Receptor (NMDAR); Nociceptin Opioid Receptor (NOR); Purinergic receptors (P2XRs); Sodium potassium pump ( $\text{Na}^+/\text{K}^+$ -ATPase); Transient Receptor Potential Ankyrin 1 (TRPA1); Transient Receptor Potential Melastatin-8 (TRPM8); Tropomyosin receptor kinase (Trk); Voltage gated sodium channels (Nav); Voltage-Gated Calcium Channels (VGCCs).



**Fig. 2.** Alternative non-pharmacological treatments for neuropathic pain and their possible mechanisms.

Abbreviations:  $\gamma$ -Aminobutyric Acid (GABA); Long-Term Depression (LTD); Long-Term Potentiation (LTP);  $\mu$ -Opioid Peptide receptor (MOR); N-Methyl-D-Aspartate Receptor (NMDAR).

Lidocaine is an amino amide used as local anesthetic, applied to the skin as 5% patch, cream, gel or 8% spray to treat neuropathic pain. Formulations of 5% patch corresponding to 700 mg of lidocaine have been developed since the 1990s, originally to treat postherpetic neuralgia

(Binder et al., 2009). In addition to this type of neuropathic pain, moderate effects have been observed against diabetic neuropathic pain, carpal tunnel syndrome and nerve injuries induced by surgery (Baron et al., 2009; Nalamachu et al., 2006; Voute et al., 2021). Pain relief (typi-

cally at least 50% reduction in pain intensity) is modest, generally 10 to 25% more than placebo and with NNT of 4–10. A maximum of 3 patches can be applied simultaneously each day for 12 h. Due to its local application, lidocaine patches have very few side effects, including itching and erythema at the application site. More recently, the efficacy of intravenous lidocaine infusions has been studied against spinal cord injury, peripheral nerve injury, diabetic polyneuropathy, or postherpetic neuralgia. However, the results remain inconclusive as there is considerable heterogeneity and variation between studies, or between patients within each study (Lee et al., 2022). It has been demonstrated in xenopus oocytes expressing Nav1.7 or Nav1.8, that lidocaine can suppress ectopic discharges in injured peripheral nerves by inactivating Nav1.7- or Nav1.8- dependent Na<sup>+</sup> currents (Chevrier et al., 2004). Moreover, lidocaine can induce a frequency-dependent blockade, meaning that the higher the frequency of action potential firing (as it is the case during neuropathic pain), the greater the efficacy of lidocaine. In addition to Na<sup>+</sup> channels, lidocaine is also able to block the Voltage-Gated Potassium Channels (VGPCs), Voltage-Gated Calcium Channels (VGCCs) and modulate different G Protein-coupled Receptors (GPCRs), including acetylcholine, glutamate, opioid, or serotonin receptors (Hermanns et al., 2019; Lirk et al., 2018; Tanelian & MacIver, 1991).

Another second-line treatment is capsaicin, a member of the vanilloid receptors family, that binds to the Transient Receptor Potential Vanilloid member 1 (TRPV1) expressed in peripheral sensory neurons. Prolonged activation of TRPV1 by capsaicin induces increased permeability of the receptor to calcium, followed by an increase in intracellular calcium in peripheral neurons. As a result of the calcium influx, calcium-dependent enzymes such as the calcineurin are then activated, leading to the dephosphorylation and desensitization of TRPV1. In addition to TRPV1, the High-Voltage-Activated Calcium Channel (HVACC) is also at the origin of the analgesic effects of capsaicin (Arora et al., 2021; Fattori et al., 2016; Holzer, 1991). At high doses, capsaicin can induce mitochondrial dysfunction leading to neuronal degeneration that could participate in impaired nociceptors function (Arora et al., 2021; Chiang et al., 2015). Various formulations have been developed for the local administration of capsaicin. Low doses of capsaicin gels (0.025%), creams (0.075%) or oil (0.075%) have been shown to be effective against diabetic and non-diabetic polyneuropathies, HIV-induced neuropathy or postherpetic neuralgia when treated for two to three months (Derry & Moore, 2012; Watson et al., 1993). For higher doses, conflicting results have been reported depending on the dose used, but a single application of 8% capsaicin patches showed an analgesic effect for up to 12 weeks after application, especially when used against diabetic neuropathy (Backonja et al., 2008; Vinik et al., 2016). Similar to lidocaine, capsaicin has very few side effects due to its local application which mainly consist of skin reaction such as itching, redness or pain at the time of the application. When 8% capsaicin patches are used, a local anesthetic is applied beforehand to avoid an intense burning sensation after application (Simpson et al., 2010).

Finally, tramadol (100–400 mg/day) and tapentadol (50–600 mg/day) are also used as second line treatment against neuropathic pain. They are weak opioid agonists with low affinity only for MOR (Hennies et al., 1988). However, the activation of opioid receptors can partially explain analgesic effect of tramadol and tapentadol since blocking the opioid system cannot fully block the effects of tramadol (Ide et al., 2006). Indeed, tramadol and tapentadol also inhibit the reuptake of serotonin and noradrenaline both involved in inhibitory descending pathway of pain (Garrido et al., 2000). With regard to tramadol, it has been showed that its main metabolite, M1 *O*-desmethyltramadol, more potent than the parent drug for producing analgesia, has better affinity for MOR, and is therefore considered as the main actor in the analgesic effects of tramadol (Gong et al., 2014). These analgesic effects of M1 are largely abolished in MOR knock-out mice, suggesting that the effect of tramadol on MOR are dependent on M1 (Ide et al., 2006). Even

though they share similar mechanisms of action and display moderate efficacy against diabetic or non-diabetic peripheral neuropathy (Bates et al., 2019), tapentadol has been shown to be two to three times more potent than tramadol (Mu et al., 2017). However, both have multiple side effects limiting their use, including nausea, vomiting, constipation, dizziness, somnolence, and a risk of abuse, although this risk is present to a lesser extent than with strong opioids.

### 2.3. Third line treatments

Due to the opioid crisis currently occurring especially in North America, strong opioids are only used as third-line treatment when first- and second-line treatments are inefficient for neuropathic pain. While the efficacy of morphine (10–120 mg/day), methadone (10–80 mg/day) and oxycodone (10–120 mg/day) has been clearly demonstrated in neuropathic pain, especially in postherpetic neuralgia or peripheral neuropathic pain (Sommer et al., 2020), results are contradictory for buprenorphine (0.2–0.6 mg, two to three times a day) or fentanyl (one day patch, 12.5–50 µg/h) (Derry et al., 2016; Wiffen et al., 2015). The effective dose of these different opioids is generally higher than their doses used in acute or non-neuropathic chronic pain. In addition to the classical side effects already described for tramadol, strong opioids can induce respiratory depression, and more importantly, a high risk of substance abuse and overdose mortality, which are the main reason of their use as a third choice and limitation of their long-term use (Benyamin et al., 2008). Clinically used opioids bind to MOR and, to a lesser extent, to the DOR and the κ-Opioid Receptor (KOR). These receptors, expressed throughout the somatosensory system, are coupled to the Gi/o protein. They inhibit the adenylyl cyclase pathway, activate G protein-coupled Inwardly-Rectifying Potassium channels (GIRKs), and block the VGCCs which in turn lead to neuronal inhibition (Corder et al., 2018).

BoNT/A, a neurotoxic protein, is also used as a third-line treatment against neuropathic pain when patients are resistant to other treatments. Single or repeated subcutaneous administration of BoNT/A is used to treat postherpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, and intractable neuropathic pain such as poststroke pain and spinal cord injury (Park & Park, 2017). Apart from pain at the injection side, BoNT/A induces no side effects. BoNT/A inhibits acetylcholine release at neuromuscular junctions, causing muscular paralysis at high doses and a muscle relaxant effect at low doses that is used to treat autonomic and movement disorders (Saffarian & Fooladi, 2018). For a long time, the analgesic effect of BoNT/A was considered to be due to its muscle relaxation effect but recent studies using BoNT/A animal models of neuropathic pain demonstrated that it has an analgesic effect independent of muscle relaxation. Indeed, BoNT/A has been shown to be able to cleave Synaptosome-associated Protein, 25 kDa (SNAP-25) in peripheral sensory neurons, thereby blocking the formation of a functional SNARE complex and inhibiting the release of pronociceptive neurotransmitters and neuropeptides such as substance P, glutamate and Calcitonin Gene Related Protein (CGRP) from nerve endings and DRG (Durham et al., 2004; Pantano & Montecucco, 2014; Rapp et al., 2006). Furthermore, intraplantar injection of BoNT/A in a rat model of nerve injury reduced microglia activation and release of the pro-inflammatory cytokines IL-1β and IL-18, and increased the release of anti-nociceptive cytokines (IL-10 and IL-1RA) (Zychowska et al., 2016). Finally, it has been shown in a rat model of trigeminal neuropathic pain that BoNT/A is able to inhibit the upregulation of Nav1.7, known to be involved in neuropathic pain mechanisms (Black et al., 2008; Hameed, 2019), which could participate in its analgesic effects (Yang, Shan, et al., 2022).



## 2.4. New pharmacological strategies

Treating neuropathic pain remains a challenge since 30–50% of patients are resistant to current treatment strategies, and side effects threaten patients' compliance. There is thus an urgent need to identify new mechanisms and thus targets to refuel the pharmaceutical pipeline with more efficient and better tolerated drugs. In the next section, we will focus on preclinical targets as well as drugs currently in clinical trials (Tables 2 and 3; Fig. 1). Finally, we will present alternative pharmacological treatments such as dietary supplements or traditional medicinal plants that could potentially help to complement neuropathic pain treatment.

### 2.4.1. New pharmacological target

#### 2.4.1.1. Ion channels.

A growing number of preclinical and clinical studies have been focusing on ion channels whose involvement in the development and maintenance of neuropathic pain has been demonstrated. It is well known that in neuropathic pain, the expression and function of Nav channels contributing to the generation and propagation of action potentials are increased in peripheral sensory neurons, leading to increased excitability (Laedermann et al., 2013; Li et al., 2018). In addition, dysregulation of sodium channels, especially the Nav1.7, Nav1.8 and Nav1.9 subtypes, plays an important role in the central nervous system sensitization responsible for the maintenance of neuropathic pain. Genetic studies revealed that mutation of Nav1.7 in humans is responsible for the congenital insensitivity to pain. Likewise, inactivation of Nav1.7 in mice results in a global insensitivity to acute or chronic pain, as well as to mechanical, thermal, or chemical stimuli (Gingras et al., 2014). At the mechanistic level, the endogenous opioid system, in particular enkephalin, has been shown to be upregulated in Nav1.7 deficient mice (Minett et al., 2015). Several Nav1.7-specific blockers have already been tested in various clinical trials, such as vixotrigine (phase II), PF-05089771 (phase II), BIIB095 (phase I), or GDC-0276 (Phase I) (for a review, see (Alsalousm et al., 2020)). Unfortunately, so far, none of them succeeded to show pain relief in trigeminal and postherpetic neuralgia, even though they significantly improve the proportion of responders (50% pain relief) as secondary outcomes without demonstrating any side effects (Price et al., 2017). Accordingly, Nav1.7 still remains an interesting target and new strategies, such as gene therapy with an Adeno-Associated Virus (AAV) targeting Nav1.7 (VY-NAV01) or Nav1.7-targeting monoclonal antibodies, are in preclinical development. Moreover, targeting a specific Nav1.7 domain through an AAV (Nav1.7-CRS) recently showed good results to downregulate Nav1.7 in rodents and primates, and prevented the establishment of neuropathic pain in preclinical model of nerve injury and chemotherapy-induced neuropathic pain, without altering physiological sensations (Gomez et al., 2023). Very recently, a preclinical study showed that a new natural compound isolated from the *Citrus unshiu*, Narirutin, has antinociceptive effects in neuropathic pain in a model of spare nerve injury in rats, which is mediated by the blocking of Nav1.7 (Yang, Shan, et al., 2022; Yang, Zhang, et al., 2022). Concerning the Nav1.8, new compounds have been identified to inhibit it specifically for the treatment of neuropathic pain. In particular, Dextrampipexole, a benzothiazole-like compound, was shown to induce analgesia in a mouse model of sciatic nerve constriction, chemotherapy-induced and diabetic neuropathic pain, without altering physiological functions of the sodium channel. A clinical study strengthened these results by reporting analgesic effect of a selective Nav1.8 inhibitor, VX 150 (Phase I), in neuropathic pain (Hijma et al., 2021).

Another possible preclinical target is the Transient Receptor Potential Melastatin-8 (TRPM8), a non-selective cation channel activated by cold (McKemy et al., 2002). However, its involvement in neuropathic pain is ambiguous as both activation and inhibition of TRPM8 by local

application of a high-dose of an agonist (IGM-5) and systemic or local application of an antagonist (IGM-18) respectively, induced analgesic effect in neuropathic condition (De Caro et al., 2019, 2018; Proudfoot et al., 2006). These contrary effects could be explained by extracellular  $\text{Ca}^{2+}$ -dependent desensitization observed after enhanced activation, leading to receptor inactivation, similarly to antagonist-induced effects (Rohács et al., 2005).

Transient Receptor Potential Ankyrin 1 (TRPA1) is another non-selective cation channel, activated by chemical irritants, but also by noxious thermal and mechanic stimuli (Kwan et al., 2006; Laursen et al., 2014; Wang et al., 2019). In the sciatic nerve ligation (SNL) model of neuropathic pain, higher expression of TRPA1 was observed (Katsura et al., 2006), while various preclinical studies have shown that inhibition of TRPA1 by antisense oligodeoxynucleotide, antagonists (HC-030031), or by TRPA1 knock out mice could alleviate neuropathic pain symptoms, and in particular cold and mechanical hyperalgesia, without altering normal sensitivity in models of chemotherapy-induced neuropathic pain and SNL (Bautista et al., 2006; Kwan et al., 2006; Nassini et al., 2011; Obata, 2005). A TRPA1 antagonist (GRC 17356) also showed promising results in a clinical trial (phase II) to treat diabetic peripheral neuropathy (Koivisto et al., 2022).

Over the past decade, a large number of studies have shown the involvement of purinergic receptors (P2XRs) in the development of neuropathic pain, and therapeutic effect of purinergic receptor blockade. P2XRs are Adenosine Triphosphate (ATP)-dependent ion channel receptors expressed through the entire nervous system, in particular in the spinal cord and in the peripheral neurons. Various studies have demonstrated that activation of P2X2R, P2X3R and heteromeric P2X2/3R mediating the ATP-response in the DRGs participates in neuropathic pain mechanisms, especially by increasing intracellular  $\text{Ca}^{2+}$  (Chen et al., 2005; Cockayne et al., 2000; Rae et al., 1998). CGRP release has been shown to sensitize P2X3R in cultured sensory neurons, through increased phosphorylation of cyclic Adenosine Monophosphate (cAMP)-Response Element-Binding protein (CREB). This increase of CREB phosphorylation results in an increase in P2X3R transcription that could participate in P2X3R-mediated nerve sensitization (Simonetti et al., 2008). P2X4R and P2X7R, expressed in spinal cord microglial cells, are also involved in neuropathic pain mechanisms by regulating microglia activation, and Brain-Derived Neurotrophic Factor (BDNF) release in the spinal cord. P2X3Rs and P2X4R antagonists showed antinociceptive effects in different animal models of neuropathic pain (Hasegawa et al., 2009; Jacobson et al., 2020; Sharp et al., 2006; Tsuda et al., 2003; Ulmann et al., 2008). It has also recently been shown that antinociceptive effect of dexmedetomidine, an adrenergic receptor agonist, in a rat model of nerve constriction is mediated by the inhibition of P2X7 (Lin et al., 2018). In addition to preclinical studies, diverse P2X receptor antagonists have been or are being tested clinically against various neuropathic pain conditions. For example, Gefapixant (AF-219), a P2X3 receptor antagonist, has currently been tested for endometriosis-related pain, and P2X4 receptor antagonist such as NP-1815-PX or NC-2600 have been under clinical trials for neuropathic pain. Finally, like Nav receptors, antibodies directed against P2X receptors, including IgG#191-Bbbt0626 for P2X4 receptor that showed antinociceptive effects against mechanical hypersensitivity in a mouse model of nerve injury are under clinical investigation (Williams et al., 2019).

#### 2.4.1.2. Sodium potassium pump.

The sodium potassium pump ( $\text{Na}^+/\text{K}^+$ -ATPase) is involved in maintaining the resting membrane potential through the exchange of 3 sodium ions outside the cell and 2 potassium ions inside the cells (Hamada et al., 2003). Reduced  $\text{Na}^+/\text{K}^+$ -ATPase activity in small diameter sensory neurons has been suggested to be involved in changes in neuronal excitability in patients with diabetic neuropathy (Krishnan & Kiernan, 2005), and genetic deletion of a  $\text{Na}^+/\text{K}^+$ -ATPase activator, the Follistatin-like 1 (FSTL1), expressed in the DRGs of small diameter sensory neurons in

mice, was sufficient to induce hypersensitivity (Li et al., 2011). Recently, it has been shown that blocking Fxyd2, a Na<sup>+</sup>/K<sup>+</sup>-ATPase modulator also expressed specifically in small diameter peripheral sensory neurons, prevents the induction of neuropathic pain in rat model of nerve injury, and a FXYD2 antisense oligonucleotide (FXYD2-LASO-Gapmer) has been proposed as a potential therapeutic for patients (Derre et al., 2023; Ventéo et al., 2016).

**2.4.1.3. Receptors tyrosine kinase (RTKs).** Initially known for their role in cellular differentiation, proliferation, and migration, RTKs and their ligands are also present in peripheral sensory neurons and spinal cord, and play an important role in neuropathic pain. Depending on their structures, ligands and functions, RTKs are divided in 20 classes. The involvement of several RTKs has been demonstrated in neuropathic pain, which make them promising preclinical and clinical targets (Ségaly et al., 2015).

In class III, all receptors are known for their role in different types of chronic pain, and among them the Colony-Stimulating Factor 1 Receptor (CSF1-R) and FMS-Like Receptor Tyrosine Kinase 3 (FLT3) have been strongly associated with neuropathic pain. CSF1-R is expressed in spinal microglia and participates in microglial activation through its ligand CSF1, released by peripheral sensory neurons (Guan et al., 2016; Lim et al., 2017; Okubo et al., 2016; Yang et al., 2018; Yu et al., 2021). Inhibition of CSF1R by a specific antagonist had an antinociceptive effect against mechanical hypersensitivity in a rat model of nerve injury when administered only at the early stage of neuropathic pain, suggesting an important role of CSF1R in the initiation of neuropathic pain (Yu et al., 2020). FLT3 has also recently been shown to contribute to the maintenance of neuropathic pain, and novel negative allosteric modulator (BDT001) targeting FLT3 has antiallodynic effects in different mice models of nerve injury such as spared nerve injury, the SNL, or chronic constriction injury of the sciatic nerve (Rivat et al., 2018). In order to develop new compounds with similar properties but better selectivity than BDT001, screening studies are in progress (Hany et al., 2022).

Class VII RTKs, composed of the Tropomyosin receptor kinase (Trk) TrkA, TrkB and TrkC, and their respective ligands Nerve Growth Factor (NGF), BDNF and Neurotrophin 3 (NT3) have been associated with neuropathic pain. Indeed, TrkB and BDNF are well described for their involvement in the mechanisms of spinal plasticity and pain sensitization leading to neuropathic pain. Higher levels of BDNF have been detected in the spinal cord, in a rat model of nerve injury (Miletic & Miletic, 2002) while BDNF heterozygous (+/-) knockout mice do not develop neuropathic pain (Boakye et al., 2021; Yajima et al., 2005). Besides, monoclonal antibodies such as the tanezumab targeting NGF are under development, as blocking these ligands showed a beneficial effect against neuropathic pain (Bannwarth & Kostine, 2017; Watson et al., 2008).

Three tetracyclines (demeclocycline, chlortetracycline, and minocycline) inhibiting the EphB1 receptor belonging to the class IX of RTKs in the DRG, spinal cord and brain of mice have also been proposed as treatment against neuropathic pain. However, further studies in chronic neuropathic pain models are needed, as preclinical studies have so far focused mainly on acute pain associated with nerve injuries (Ahmed et al., 2021).

Finally, Ret receptor and its ligands, the Glial cell line-Derived Neurotrophic Factor (GDNF) Family Ligands (GFLs) that compose the class XIV of RTKs, could also be of interest. A preclinical study showed that BT44, an agonist of Ret receptor, alleviates mechanical hypersensitivity in a rat model of diabetic neuropathic pain, and could be a promising therapeutic compound (Giraud et al., 2021; Mantyh et al., 2011; Viisanen et al., 2020).

**2.4.1.4. Glutamatergic receptors.** N-Methyl-D-Aspartate Receptor (NMDAR), a member of glutamate receptor family, is an ion-channel recep-

tor, present at most excitatory synapses. The alterations of its activity are strongly involved in the dysregulation of synaptic transmission and maladaptive plasticity occurring in the spinal cord (Zhou et al., 2011). Since its critical role in the pain sensitization is well known, different antagonists targeting NMDAR such as ketamine, amantadine and memantine have been clinically tested against neuropathic pain, and promising effects have been reported in diabetic neuropathic pain and nerve injuries, but not in postherpetic neuralgia (Huge et al., 2010; Nelson et al., 1997; Zhou et al., 2011). It has also been suggested that part of the efficacy of methadone compared with other opioids could be explained by its inhibitory effect on NMDAR (Aiyer et al., 2018; Schembri, 2019). A recent meta-analysis of randomized controlled trials involving ketamine showed that intravenous injection induced a significant reduction in pain intensity but also a significant increase in discomfort, and psychedelic effects one week after the end of treatment which persisted up to 30 days (Guimarães Pereira et al., 2022). However, there is no clinical evidence of its efficacy in any other mode of administration. Preclinical studies dissecting the mechanism action of ketamine in neuropathic pain revealed that a single dose induces a prolonged suppression of cortical hyperactivity associated with a reduction in aversive response to noxious stimuli in rodent models (Zhou et al., 2018). Interestingly, it has been shown, using neuropathic rodent models, that the antiallodynic effect of ketamine is transient while its effect on the emotional component of pain persists up to 72 h (Humo et al., 2020). Molecular studies deciphering its action demonstrated that ketamine recruits Mitogen-Activated Protein Kinase/ Extracellular signal-Regulated Kinase (MAPK/ERK) pathway by altering levels of Mitogen-Activated Protein Kinase Phosphatase 1 (MKP-1), pERK, pCREB and BDNF in the anterior cingulate cortex (Humo et al., 2020; Zhou et al., 2018). While growing number of studies focus on the action of ketamine in neuropathic pain, only a few studies showed the efficacy of methadone, amantadine and memantine in neuropathic pain.

**2.4.1.5. Opioid receptors.** The Nociceptin Opioid Receptor (NOR), also known as the Nociceptin/Orphanin FQ (N/OFQ) receptor, a member of the opioid GPCR subfamily, is also a promising therapeutic target to treat neuropathic pain. Indeed, its activation through intrathecal injection of its ligand N/OFQ or by agonists such as Ro64-6198, has antinociceptive effects in rat models of nerve injury (Obara et al., 2005; Yamamoto et al., 2000). In addition, its co-activation with MOR by partial agonists such as BU08028 or SR16435 elicits better analgesic effects with less side effects than MOR agonists alone in rodent models of nerve injury (Chao et al., 2020; Kiguchi et al., 2022; Sukhtankar et al., 2013). Clinical studies using Cebrenopadol, a mixed agonist of all opioid receptors with the highest affinity for NOR and then MOR (and lower affinity for DOR and KOR), seem to confirm this idea. Indeed, clinical trials have demonstrated that Cebrenopadol had analgesic effects when administered at lower doses than morphine (200–1600 µg once a day) against cancer-related neuropathic pain and diabetic neuropathy, with very few reports of withdrawal symptoms at the end of the treatment (Christoph et al., 2017; Eerdeken et al., 2019; Göhler et al., 2019). These studies thus confirm what has been observed in preclinical studies, in which intraperitoneal or intravenous administration had analgesic effects in mouse model of diabetic neuropathy and rat model of nerve injury, with less tolerance than morphine (Linz et al., 2014).

**2.4.1.6. Angiotensin II type 2 receptors.** Angiotensin II Type 2 Receptors (AT2Rs) are GPCRs coupled with Gi proteins that bind to the angiotensin II. Their activation leads to activation of the delayed rectifier K<sup>+</sup> channel involved in membrane repolarization after a depolarization and production of Nitric Oxide (NO) which blocks phosphorylation and activation of Erk1/2 (Kaschina et al., 2018; Pulakat & Summers, 2020). AT2Rs are expressed in small-diameter DRG neurons and partially co-localized with TRPV1 and TRPA1 receptors that are

important potential therapeutic target for neuropathic pain as mentioned before (Anand et al., 2013; Pulakat & Sumners, 2020). Pronociceptive actors such as the substance P, TNF $\alpha$  or Prostaglandin E2 (PGE<sub>2</sub>) have shown to activate AT2Rs, and increase the level of its ligand, angiotensin II, in a rat model of nerve injury (Smith, Woodruff, et al., 2013; Smith, Wyse, & Edwards, 2013). In addition, preclinical studies have demonstrated the analgesic effects of AT2Rs antagonists in mice and rat models of nerve injury, or rat models of HIV-induced neuropathic pain (Balogh et al., 2021; Khan et al., 2017; Shepherd et al., 2018; Shepherd & Mohapatra, 2019). This analgesic effect seems to be mediated by the p38 MAPK and p44/p42 MAPK pathways. A clinical study also supports these findings showing an analgesic effect of an AT2R antagonist, EMA401, in postherpetic neuralgia (Rice et al., 2014). However, other results from preclinical studies also showed beneficial results of AT2Rs agonists. These conflicting results could be explained by the different pathways regulated by AT2Rs, certain being pronociceptive and others antinociceptive (Pulakat & Sumners, 2020).

#### 2.4.2. Pharmacological alternatives

**2.4.2.1. Dietary supplements.** Dietary modifications have shown encouraging results in reducing neuropathic pain. Adhering recommended daily intakes of fruits, vegetables, and fibers has shown to have anti-neuroinflammatory, neuroprotective and antioxidant effects that help to treat neuropathic pain symptoms. Mediterranean diets, based on olive or seed oils and vegetables, can then be recommended to the patient. As a complement, restriction of other types of food, such as gluten- and sugar-based diet foods, also seems to help reduce neuroinflammation (Dragan et al., 2020; Kaushik et al., 2020).

The use of supplements of different fatty acids has also shown to be effective in alleviating neuropathic pain symptoms. Preclinical studies showed that  $\alpha$ -Lipoic Acid (ALA, also called thioctic acid), an antioxidant with neuroprotective effect, reduces symptoms in rodent models of neuropathic pain by inhibiting TRPV1 receptors, apoptosis and oxidative stress (Yazgan et al., 2023). Various clinical studies have also reported a positive effect of ALA on diabetic polyneuropathy, and chemotherapy-induced neuropathy.  $\Gamma$ -Linolenic Acid (GLA), found in seed oils, also induced pain relief in diabetic neuropathy in a clinical study. Supplementation with  $\omega$ -3 fatty acids reduced the risk of developing chemotherapy-induced neuropathy by 70% in patients treated with paclitaxel (Ghoreishi et al., 2012). The neuroprotective effect of  $\omega$ -3 fatty acids is due to anti-inflammatory properties of resolvins, lipid mediators derived from  $\omega$ -3 fatty acids supplementation. High levels of resolvins, such as Neuroprotectin D1/Protectin D1 (NPD1/PD1), have been demonstrated to prevent the sensitization of neuropathic pain in rat or mice model of nerve injury (Park et al., 2011; Serhan et al., 2015; Unda et al., 2020; Xu et al., 2013).

Finally, vitamins also play an important role in neuropathic pain, as deficiencies in thiamine (Vitamin B1), pyridoxine (Vitamin B6), folate (Vitamin B9), cobalamin (Vitamin B12), or/and Vitamin D have been observed in patients with neuropathic pain. Aforementioned vitamins play important role in neuroprotection, metabolism and immunity (Bilir et al., 2016; Depeint et al., 2006). More specifically, vitamin B1 (600mg/day) supplementation showed beneficial effects on diabetic neuropathy, and possibly against alcoholic neuropathy while vitamin B12 (500 mg 3 times a day) improved some of symptoms associated with diabetic neuropathy, especially weakness, numbness and fatigue. Preclinical data have also shown that folate supplementation increases axonal repair and alleviates neuropathic pain, probably by reducing the expression of Matrix Metalloprotease 2 (MMP2) which plays a role in the induction of neuropathic pain, as demonstrated in a rat model of spinal cord injury (Miranpuri et al., 2017). A cocktail of Vitamins B1, B6 and B12 also reduced mechanical allodynia in a rat model of diabetic neuropathy (Jolivald et al., 2009), while a combination of Vitamins B9 and B12 alleviated symptoms of peripheral neuropathy in a clinical study (Negrão et al., 2014). Finally, vitamin D replenishment

was shown to be effective in treating diabetic neuropathy in a clinical trial (Lee, 2008).

**2.4.2.2. Medicinal plants.** Patients suffering from neuropathic pain seek for alternative treatment strategies such as medicinal plants due to their limited side effects.

Extensive research is currently being conducted for the efficacy of two of *Cannabis Sativa's* main constituents, A9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD), to treat neuropathic pain. They act on the Cannabinoid Receptor type 1 (CB1R) and 2 (CB2R) expressed mainly in neurons and immune cells, respectively. These GPCRs modulate the transmission of nociceptive information at peripheral, spinal, and supraspinal levels by inhibiting transmitter release at presynaptic terminals (Azad et al., 2008; Freund et al., 2003; Matsuda et al., 1990; Romero-Sandoval et al., 2009). Conditional deletion of CB1Rs in the peripheral neurons or constitutive deletion of CB2R enhanced neuropathic pain symptoms in mouse model of nerve injury-induced neuropathic pain, while constitutive deletion of CB1 also aggravated anxiodepressive-like behavior, demonstrating their important role in the mechanisms of neuropathic pain (Agarwal et al., 2007; Racz et al., 2008; Rácz et al., 2015). Mixed agonists of CB1R and CB2R have been studied in animal models of diabetic neuropathy, neuropathic pain induced by nerve injury, postherpetic neuralgia, cancer-induced neuropathy or HIV-induced neuropathy. In virtually all these models, agonists reduced at least mechanical sensitivity, as well as thermal hypersensitivity for some of them (for review, see (Maldonado et al., 2016)). Even though some countries have already approved their use as an effective treatment, clinical trials are still ongoing, with contradictory results in neuropathic pain (Fitzcharles & Eisenberg, 2018). Promising results have been observed with THC/CBD oromucosal spray (nabiximols, also called Sativex) against HIV-induced neuropathic pain, chemotherapy-induced neuropathic pain, and diabetic neuropathy in recent studies, with no sign of tolerance (Überall, 2020). Phase II clinical trials are ongoing in order to compare THC alone (Dronabinol), CBD alone (Epidolex) or THC/CBD (nabiximols) against diabetic neuropathic pain. However, other studies have reported that these beneficial effects are only present in small percentage of patients, for a short period of time, or that they have important side effects diminishing patient compliance. Different formulations and doses are currently being tested clinically, which will provide further information on the benefits of medical cannabis to treat neuropathic pain.

Various studies showed the efficacy of curcumin, a spice derived from turmeric root, in reducing neuropathic pain, probably through its anti-inflammatory and antioxidant effects (Shishodia, 2005; Zhao et al., 2012). In preclinical models of chemotherapy-induced, alcoholic or diabetic neuropathy, or nerve injuries, curcumin reduced mechanical and thermal hypersensitivity, had neuroprotective effects (especially against chemotherapy drugs induced neuronal degeneration), reduced neuroinflammation, and/or improved nerve conduction velocity (Zanjani et al., 2014). In clinical studies, supplementation with curcumin-loaded nanocapsules (72% curcumin, 80 mg) improved symptoms of diabetic neuropathy (Basu et al., 2021). When co-administered with Non-Steroidal Anti-Inflammatory Drugs (NSAID) to treat peripheral neuropathy, a lower dose of NSAID could be used to achieve the same analgesic effect.

Saffron, another spice, and its active constituent, crocin, showed analgesic effects on mechanical and thermal hyperalgesia in preclinical models of neuropathic pain (Forouzanfar & Hosseinzadeh, 2018). Again, these effects seem to be due to anti-inflammatory effects, as a decrease in several pronociceptive cytokines was detected in the presence of saffron in a model of nerve injury in rats (Safakhah et al., 2016). In a clinical trial of chemotherapy-induced peripheral neuropathy, saffron (30 mg/day, for 8 weeks) considerably decreased symptoms of neuropathic pain, with low toxicity and no adverse side effects (Bozorgi et al., 2021).

Finally, several plants used in traditional Chinese, Indian, South-America, or Middle-Eastern medicine for centuries have also shown beneficial effects which are currently the subject of further studies. For example, DA-9801, an extract of the *Dioscorea* species found in Asia, had positive effects on models of diabetic neuropathy by improving nerve conduction velocity and preventing nerve degeneration. Several extracts from other plants such as *Pterodon pubescens* tree found in Brazil, *Ocimum Sanctum* in India, or *Elaeagnus angustifolia* used in Iranian medicine, have all showed anti-inflammatory and/or antioxidant effects that reduced symptoms in preclinical models (Forouzanfar & Hosseinzadeh, 2018). Several bioactive alkaloids of Chinese herbal medicine have also been isolated and are promising for developing new pharmacological drugs (Zhu et al., 2020). In preclinical models of diabetic peripheral neuropathy and different types of sciatic nerve injury, these alkaloids (including bullatine A, lappaconidine, berberine, koumine, and others) all induced a reduction in mechanical allodynia, thermal hyperalgesia, and even anxiodepressive-like behavior for some of them. These effects are suggested to be due to augmentation of GABAergic receptors activity, anti-inflammatory and antioxidant properties, downregulation of NMDA receptors and increased dynorphin production, especially in the DRG and spinal cord (Jiang et al., 2022). *Hypericum perforatum* L., also known as St. John's wort, a plant native from Asia, is also well known for its different properties, including antidepressant and anti-inflammatory effects (Barnes et al., 2001; Raso et al., 2002; Sosa et al., 2007). Preclinical studies in mouse model of HIV-induced neuropathy, and chemotherapy-induced neuropathy, or rat model of neuropathic pain induced by nerve injury or chemotherapy-induced neuropathy, reported antinociceptive effects of St. John's wort, due to one of its main active component, the hypericin (Galeotti et al., 2010; Sanna et al., 2016). The action of hypericin has been shown to be due to an inhibition of the Protein Kinases C (PKC)  $\gamma$  and  $\epsilon$ , known to be involved in neuropathic pain mechanisms. Duhuo Jisheng decoction (DHJSD), another formula widely used in traditional Chinese medicine, also showed efficacy against neuropathic pain in a preclinical model of sciatic nerve constriction (Gao et al., 2023). Among the 252 molecular and cellular targets of DHJSD identified, neuroinflammatory markers in particular seem to be modulated, including pro-inflammatory cytokines such as IL-17, and microglia. These studies identifying new active components with analgesic effects from traditional plant medicine could lead to new effective treatments against neuropathic pain.

### 3. Non-pharmacological and new alternative treatments

Besides the development of new pharmacological targets and drugs, non-pharmacological treatments have emerged since a few years to treat neuropathic pain (Fig. 2).

#### 3.1. Neuronal stimulation

Electrostimulations of the nervous system have been expanded to treat neuropathic pain as alternative treatment approaches based on different types of stimulation paradigms, such as Spinal Cord Stimulations (SCS), transcranial Direct Current Stimulations (tDCS), repetitive Transcranial Magnetic Stimulation (rTMS), and Transcutaneous Electrical Nerve Stimulation (TENS). All these different types of neuronal stimulation elicit promising results against neuropathic pain.

SCS consists of implanting electrodes bound to a pulse generator in the epidural space of the spinal cord to stimulate neurons of the dorsal horn (Knotkova et al., 2021). Different parameters have been used in preclinical and clinical studies, such as conventional stimulations (with a frequency of 30-80 Hz), low-frequency stimulations (5 Hz), or high-frequency stimulations (500 Hz-10 kHz). All have shown positive results against either mechanical allodynia or thermal hyperalgesia (Moisset et al., 2020). In clinical studies, conventional (85 Hz) or high-frequency stimulations (10 kHz) for 6 or 12 months elicited significant

pain relief against different types of peripheral neuropathy, diabetic neuropathy or postherpetic neuralgia. These analgesic effects seem to be due to a restoration of the gate control with an activation of GABAergic interneurons of the spinal cord, the endogenous opioid system and the endocannabinoid system, as well as the release of acetylcholine, and the inhibition of pronociceptive actors such as proinflammatory cytokines, CGRP, substance P, and glutamate (Sato et al., 2013; Stiller et al., 1995; Sun et al., 2021, 2017). Side effects of this technique include risks of infection as it is an invasive technique, or a malfunction of the device.

tDCS is a non-invasive technique consisting of applying at least two electrodes (one being an anode or a cathode, the other one a reference electrode) to the scalp, delivering constant low-voltage current to the brain to modulate the excitability of cortical neurons (Mori et al., 2010). Classical parameters of tDCS to treat neuropathic pain are anodal stimulation at the level of the primary motor cortex with intensity of 1-2 mA and sessions lasting between 5 and 20 min according to the study. Incremental pain relief through sessions has been observed in some studies in patients with neuropathic pain due to spinal cord injury or stroke (Moisset et al., 2020). However, large variability between the results from different studies, showing no effect versus 50% efficacy, is one of the drawbacks of this approach. Underlying mechanisms for the analgesic effects of tDCS are still under investigation. It has been shown so far that anodal stimulation activates neurons in the brain while cathodal stimulation inhibits them, which in turn lead to depolarization or hyperpolarization of neuronal functions, and facilitates Long-Term Potentiation (LTP) or Long-Term Depression (LTD) respectively (Lefaucheur, 2008; Monte-Silva et al., 2013; Souza et al., 2018). Mechanisms of action might then include an interruption of nociceptive integration through the hyperpolarization of brain structures involved. It has for example been shown that cathodal stimulation during tDCS is capable of disrupting tactile sensation several minutes after the end of the stimulation in healthy patients (Rogalewski et al., 2004). Preclinical study using tDCS on a mice model of nerve injury demonstrated that several neurotransmitter systems including the opioidergic, cannabinoid, adenosinergic, glutamatergic and GABAergic could be involved in its analgesic effects (Souza et al., 2018). Another recent preclinical study completed these studies by showing its reducing effect on neuroinflammation and oxidative stress (Akçay et al., 2023). Beside transient skin reactions such as itching and erythema, tDCS is shown to be very safe.

rTMS, another non-invasive technique, involves a coil placed on the skull triggering an electromagnetic field that modulates the excitability of the brain. Various parameters have been tried in diverse studies: (i) low (< 1 Hz) to high (> 5 Hz) frequencies, (ii) different intensities (1500 to 3000 pulses at 80 or 90% of the Resting Motor Threshold (RMT)), (iii) different duration and number of sessions (3 to 10 sessions of 6 to 40 min), (iv) different neuroanatomical locations (M1 cortex, secondary somatosensory cortex, insular cortex...) and (v) shapes of the coil (figure-of-8 or H1) (Lefaucheur et al., 2020; Moisset et al., 2020). Among all these different parameters, high frequency (10 Hz) rTMS at the primary motor cortex showed the most promising effect for postherpetic neuralgia, diabetic neuropathy or spinal cord injury, both after single or multiple sessions of stimulations. On the contrary, it seems that stimulations of the Dorsolateral Prefrontal Cortex (DLPFC) isn't efficient, as a clinical study comparing DLPFC and motor cortex stimulations using neuronavigated rTMS to treat peripheral neuropathic pain observed no difference between DLPFC stimulations and sham stimulations while pain intensity significantly reduced after motor cortex stimulations (Attal et al., 2021). As for almost all brain stimulation methods, its analgesic property is due to its effect on central modulatory system, in particular on the activation of the pain inhibitory descending pathway, but also through the activation of NMDAR inducing plasticity in the brain, release of anti-inflammatory cytokines (IL-10) as well as

dopamine and GABA release (Yang, Shan, et al., 2022; Yang, Zhang, et al., 2022).

Finally, TENS, consisting of delivering electrical pulses to the surface of the skin, by using electrodes placed near the painful area, is another non-pharmacological approach frequently used in neuropathic pain. Similar to previous stimulation techniques described here, different stimulation parameters such as intensities and frequencies are used in order to target different subpopulations of sensory neurons. It has been shown that low intensity stimulations (which are not painful) with high frequency (> 10 Hz) target mechanoreceptive A $\beta$  neurons, while high intensity stimulations (reaching the pain threshold) with either low (2-4 Hz) or high (10-200 Hz) frequency stimulate small diameter nociceptive and thermal sensory neurons, in particular A $\delta$  neurons (Moisset et al., 2020). Even though some of the studies have been done in a very small group of patients, different protocols alleviated diabetic neuropathic pain, chemotherapy-induced neuropathy, postherpetic neuralgia, and spinal cord injury. In the central nervous system, a recruitment of the inhibitory descending pathway has also been observed, with the release of endogenous opioids at the PAG and Rostral Ventral Medulla (RVM), as well as in the spinal cord, as antagonists of the opioid system inhibits TENS analgesia (Sluka et al., 1999, 2005). Other neurotransmitters are also involved, as blocking the CB1R or the  $\alpha$ -2 adrenergic receptor in the peripheral system (de Oliveira et al., 2020; King et al., 2005; Nam et al., 2001) or GABA, serotonergic and muscarinic receptors in the spinal cord (Maeda et al., 2007; Radhakrishnan et al., 2003; Radhakrishnan & Sluka, 2003) prevents the analgesic effect of TENS.

### 3.2. Exercise

Exercise has proved to be effective to reduce symptoms of different types of neuropathic pain, especially diabetic neuropathy, peripheral neuropathy, and chemotherapy-induced neuropathy (Leitzelar & Koltyn, 2021; Zhang et al., 2021). It has been demonstrated that it has benefic effects on the peripheral nervous system by preventing neuronal degeneration, increasing neurotrophic factors, and by its antioxidant and anti-inflammatory effects (Luo et al., 2022). In the central nervous system, exercise has also been shown to have anti-inflammatory and antioxidant effects and to induce neurotransmitters and neuropeptides release in the spinal cord (especially  $\beta$ -endorphin, met-enkephalin) and in the brainstem (serotonin) (Bobinski et al., 2015; Stagg et al., 2011). However, benefits of exercise depend on different factors such as sex, age, Body Mass Index (BMI), and fitness status (active or sedentary). More precisely, exercise proved more effective for younger, active, with lower BMI, and/or male patients. For chemotherapy-induced neuropathy, the type of chemotherapy seems to also be important, as exercise was more beneficial in case of radiotherapy or chemotherapy, as well as the type of cancer, being more beneficial for patients with breast cancer (Brett Whalen et al., 2022).

### 3.3. Acupuncture

Acupuncture consists of inserting various needles into the body, and is classically used in Chinese traditional medicine. If its legitimacy still remains debated in the scientific community, different technics of acupuncture showed positive results in clinical trials for neuropathic pain. Among these technics, normal-, warm-, fire- or electrical-needling, or moxibustion 2 to 7 times a week, showed higher analgesic effects when compared in different clinical trials to classical pharmacological treatments such as anticonvulsants, and NSAIDs (though the latter aren't recommended against neuropathic pain) (Zhao et al., 2022). Other studies have demonstrated at least 20% pain reduction with these techniques that present the advantage of being cost-effective, and with limited side effects. However, as for the majority of existing treatments, variability exists between studies, some having found no beneficial ef-

fects of acupuncture. It has been suggested that acupuncture may modulate the activation and/or liberation of actors of the neuroinflammatory system (including pronociceptive chemokines and cytokines, and glial cells), as well as restore the inhibitory pathway of pain by activating serotonin, opioid, and noradrenaline release in the spinal cord and the brain (Kim et al., 2005; Park et al., 2010; Sun et al., 2004; Zhang et al., 2014). Recently, it has also been demonstrated in a preclinical model of nerve injury that electroacupuncture can alleviate pain-induced anxiety by activating the dopamine D1 receptor and inhibiting the D2 receptor in the basolateral amygdala (Wu et al., 2022). Electroacupuncture also appears to modulate the formation of abnormal dendritic spines in the spinal cord, which may be involved in central sensitization during neuropathic pain (Wu et al., 2023). It is currently unknown if other types of acupuncture may have similar effects.

### 3.4. Other emerging therapeutics

New alternatives have been studied and used these last years to treat neuropathic pain, including hypnosis and virtual reality. However, if studies showed them effective against certain types of neuropathic pain, biological mechanisms involved for their analgesic effects remain predominantly unknown.

Hypnosis is defined by the Society of Psychological Hypnosis as "one person guided by another to respond to suggestions for changes in subjective experience, alterations in perception, sensation, emotion, thought or behavior" (Green et al., 2005). Hypnosis has been used for several years now to treat different types of pain, and recently, moderate to strong effects have been demonstrated for the treatment of neuropathic pain, and especially in case of spinal cord injury (Langlois et al., 2022). Studies with more than 8 sessions of hypnosis in particular showed interesting outcomes, accompanied or not with self-hypnosis sessions, where the patient is trained and encouraged to practice alone to enter a hypnotic-state (Jensen et al., 2009; Langlois et al., 2022). It is generally recommended to be used in complement to pharmacological treatments to increase the efficacy. However, more studies are required to conclude on its effect in other type of neuropathic pain than spinal cord injury, and to determine the mechanisms involved. For the latter, we only know that hypnosis induces alterations in the neuronal activity of the pain matrix including the ACC, the insular cortex, the somatosensory cortex, and the thalamus, through unknown mechanisms (Derbyshire et al., 2004; Dillworth et al., 2012; Faymonville et al., 2003).

Virtual reality consists of a computer-generated partial or total immersion in 3D images, with which one can interact. Due to its non-invasive properties with its lack of important side effects (that include motion sickness and physical fatigue) and adaptability to patient need, the use of virtual reality in clinic has started to increase recently. For neuropathic pain, it has been used especially for patients with spinal cord injury to help patients regaining mobility in the lower body with less pain. But clinical trials are in progress to test its efficacy for other types of neuropathic pain like neuralgia (Chi et al., 2019). The most used method is somatic virtual reality where the affecting limbs are represented virtually while stretching and doing mobility exercises, which could help dissociating the pain with the movement of the limb (Moseley, 2007; Soler et al., 2010). Using different methods of virtual training, a reduction of 15 to 80% of pain has been observed. Similar to hypnosis the underlying mechanisms involved in virtual reality therapy remain unclear. It has been suggested that it could be responsible for a readjustment of maladaptive reorganization of cortical areas such as the somatosensory and motor cortex, and/or to be due to a training of mirror neurons that would start being activated by virtual reality, without activating pain pathways (Chi et al., 2019; Eick & Richardson, 2015; Ramachandran & Altschuler, 2009).

### 3.5. Co-use of pharmacological and non-pharmacological treatments

In general, non-pharmacological treatments are only used when patients are resistant or intolerant to pharmacological strategies. While they offer promising analgesic effects with few side-effects, their long-term efficacy remains debated and inconsistent from study to study. However, a growing body of evidence suggests that combining non-pharmacological treatments with conventional drugs may potentiate their respective effects, thus allowing longer efficacy of treatments, with lower doses of drugs required. For instance, clinical studies have shown that combining DBS with conventional pharmacological treatments had better effects on pain relief and improving patients' quality of life than pharmacological treatments alone (Kumar et al., 2018; Shinu et al., 2022). Interestingly, 3 months of co-treatment was able to decrease the dose of medication (Goudman et al., 2023). Combining TENS with carbamazepine also showed better results in a clinical trial to treat refractory patients for trigeminal neuralgia, compared with carbamazepine alone (Millan-Guerrero et al., 2019; Motwani et al., 2023). A case report very recently suggested the potential use of pregabalin with TENS to treat neuropathic pain (Xia et al., 2021). Preliminary results also suggest improved efficacy of antidepressants when used with rTMS, to treat patients with neuropathic pain refractory to conventional treatments (Holm et al., 2023). Recently, a pre-clinical study showed a potentiated effect of TENS and CBD when combined in a mouse model of nerve constriction, with specific activation of the anti-inflammatory cytokine IL-10 only when administrated together (Malta, Netto, dos Santos, Veras, & Galdino, 2023). Finally, electroacupuncture combined with low-dose gabapentin also showed strong analgesic effects in a mouse model of chemotherapy-induced neuropathic pain (Kim et al., 2017). All these data suggest synergic effects of non-pharmacological and pharmacological treatments when administrated together. However, large-scale studies are now needed to confirm these results.

### 4. Conclusion

Treating neuropathic pain remains a challenge, and there is an unmet need to find new therapeutic approaches due to the lack of efficacy or side effects affecting patient compliance. Indeed, currently recommended treatments have significant adverse effects, ranging from dizziness, somnolence or nausea to substance abuse, overdose or respiratory depression. Another drawback of these treatments base on the fact that the efficacy varies according to the different types of neuropathic pain suggesting the involvement of different cellular and molecular mechanisms depending on the origin of the neuropathic pain, and underlining the need for personalized medicine.

Recent advances in our understanding of the peripheral and central mechanisms involved in different types of neuropathic pain have paved the way for discovery of several new preclinical and clinical targets such, as RTKs, TRPM8, sodium ion channels, CBRs or P2XRs. These new targets are of particular interest either due to their ability to better modulate afferent neurons involved in the transmission of the nociceptive information without affecting supraspinal regions, or because of their increased affinity for specific pharmacological targets, which can lead to increased potency and lower effective doses with a longer duration of action which can improve significantly efficacy but also the side effect profile of treatments. Examples include mirogabalin, which has greater affinity for  $\alpha_2\delta$ -1 and  $\alpha_2\delta$ -2 subunits than previous gabapentinoids, monoclonal antibodies specifically targeting P2XRs, or negative allosteric modulators targeting FLT3.

In addition to the development of more potent and selective drugs, new non-pharmacological treatment strategies such as noninvasive brain stimulations, including rTMS and tDCS, are also showing promising results in neuropathic pain. In addition, multimodal approaches combining therapeutic drugs with alternatives, which include changes

of lifestyle (better diet, dietary supplements, and more exercise), neural stimulation, acupuncture, hypnosis and/or virtual reality may enable better management of neuropathic pain. Large scale multicenter studies are now needed to further validate the use of new pharmacological and non-pharmacological treatment strategies.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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