

REVIEW ARTICLE

Emerging pharmacological strategies for neuropathic pain: Mechanism-based targeting and precision medicine

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Abstract

Neuropathic pain (NP) is a type of chronic pain syndrome due to structural or functional alterations in the somatosensory nervous system after injury, including long-lasting painful sensations and allodynia and hyperalgesia. Due to its intricate pathophysiology and significant interindividual variation in therapeutic response, the current pharmacological approaches are constrained by suboptimal efficacy and potential adverse effects. Recent evidence emphasizes maladaptive neuronal plasticity, neuroinflammatory and neurotransmitter system abnormalities as the main components mediating NP initiation and maintenance, with glial activation, ion channel dysfunction, and neuroimmune interactions being critical for central sensitization and pain maintenance. There have been advances in molecular understanding leading to new therapeutic targets with the emergence of inflammatory signalling pathways, ion channels, and neurotrophic factor-related networks. At the same time, emerging therapeutic strategies, including molecularly targeted agents, biologics, regenerative approaches and experimental nanodelivery platforms, are expanding precision approaches to NP. However, successful clinical translation remains challenging due to limitations in disease modelling, target specificity and patient heterogeneity. The merging of pharmacogenomics and multi-omics data is even unlocking further individualized analgesic strategies, which, alongside neuromodulation techniques and multidisciplinary care models, are promising new routes for long-term pain management. This Review outlines the major pathogenic mechanisms of NP, summarizes conventional and emerging pharmacological strategies, critically evaluates translational barriers that have limited clinical success, and discusses future directions for biomarker-guided personalized analgesic therapy.

Keywords: Neuropathic pain, Neuroinflammation, Ion channels, Neuroimmune regulation, Targeted therapy, Pharmacogenomics, Personalized medicine

1 INTRODUCTION

Neuropathic pain (NP) is a common chronic pain condition caused by a lesion or disease affecting the somatosensory nervous system and is clinically characterized by ongoing or intermittent spontaneous pain, often accompanied by allodynia and hyperalgesia. It can arise from a wide range of conditions, including diabetic neuropathy, postherpetic neuralgia (PHN), spinal cord injury (SCI), and chemotherapy-induced neurotox-

icity, and is associated with substantial impairment in quality of life [1]. Epidemiological studies further highlight the considerable population-level burden of NP. In a survey of 24,925 individuals, 63.7% reported experiencing pain, and 15.7% (95% CI: 14.9%-16.5%) of those with pain met PainDETECT-based criteria for probable NP, corresponding to an estimated overall prevalence of approximately 10% (95% CI: 9.5%–10.5%) [2]. The prevalence of NP also appears to vary across racial and ethnic groups, with higher rates reported among



Black and Hispanic populations than among White populations. Despite this substantial clinical burden, current management remains largely symptom-oriented and commonly involves gabapentinoids and antidepressants as first-line therapies, with topical agents and opioid-based therapies used in selected or refractory cases [3].

NP differs from predominantly nociceptive or inflammatory pain in its tendency to persist after nervous system injury and in the marked interindividual variability in treatment response. Its development and maintenance involve complex interactions among maladaptive neuronal plasticity, neuroinflammatory activation, neurotransmitter dysregulation, and altered pain-processing networks [1]. For example, SCI has been reported to increase neuronal activity in several nociception-related regions, including the NTM/NPL regions (GrN and PBN), while increasing GAD67 expression in the periaqueductal gray (PAG), reducing serotonin levels in the raphe magnus nucleus (RMN), and suppressing NTR2-expressing fear-inhibitory neurons in the basolateral amygdala (BLA). SCI-induced alterations in hippocampal neurogenesis may further contribute to the persistence and amplification of maladaptive pain processing [4]. Collectively, these neuroplastic and neurochemical changes create a pathological environment that facilitates persistent nociceptive signalling and chronic pain. Advances in our understanding of NP pathophysiology have been accompanied by increasing efforts to identify novel pharmacological targets. In several rodent models of NP, compounds 50a and 56a have shown significant analgesic activity against oxaliplatin- and paclitaxel-induced neuropathy as well as streptozotocin-induced diabetic NP, with compound 56a exhibiting the strongest *in vivo* effects [5]. In addition, BDNF-mediated regulation of KCC2 expression in dorsal root ganglia (DRG) has been implicated in peripheral and central sensitization and may contribute to the attenuation of bisphenol A (BPA)-induced NP [6]. These findings illustrate how mechanistic studies can identify potential therapeutic targets and provide a rationale for the development of mechanism-based analgesic strategies.

Nevertheless, NP is still predominantly treated using conventional pharmacological and neuromodulatory agents, including gabapentinoids and antidepressants as first-line therapies, with topical agents and opioid-based therapies used in selected or refractory cases. Although these therapies can provide symptomatic relief, their overall efficacy is often modest, adverse effects remain common, and treatment responses vary substantially among patients [3]. Despite considerable progress in elucidating the molecular mechanisms underlying the development and persistence of NP, translating these discoveries into clinically effective therapies remains challenging. Numerous molecular targets have demonstrated promising analgesic effects in preclinical models, yet relatively few have achieved successful clinical translation. This translational gap likely reflects several factors, including the limited ability of experimental models to reproduce the phenotypic heterogeneity of

human NP, insufficient target specificity, the lack of validated predictive biomarkers, and substantial interpatient variability. As understanding of NP biology continues to evolve, therapeutic development is progressively shifting from symptom-oriented management toward mechanism-based interventions targeting neuroinflammation, ion-channel dysfunction, synaptic plasticity, and neuroimmune interactions. At the same time, advances in precision medicine and pharmacogenomics are creating new opportunities for individualized treatment selection and optimization. In this Review, we summarize the major biological mechanisms underlying NP, discuss conventional and emerging pharmacological approaches, critically examine the translational barriers limiting the clinical success of mechanism-based therapies, and highlight future opportunities for biomarker-guided and precision-oriented pain management.

2 BIOLOGICAL MECHANISMS OF NP

2.1 Neuronal plasticity and pain signal transduction

NP is a chronic pain condition caused by injury or dysfunction of the nervous system and can arise as a consequence of trauma, inflammation or peripheral nerve damage. NP is a multifactorial condition involving a complex network of pathological changes occurring in both the peripheral and central nervous systems. In this context, maladaptive neuronal plasticity and remodelling of pain-associated signalling processes emerge as essential factors in the establishment and maintenance of chronic pain. Trans-synaptic autophagy has been recently identified as an important regulatory process involved in chronic pain states [7]. In terms of synaptic organization and neuronal function, autophagic removal of damaged cellular components at local compartments modulates both processing and transmission of nociceptive signals [7]. Nevertheless, dysregulation or excessive activation of this process may lead to abnormal remodelling of neural circuits that enhance nociceptive signalling, resulting in heightened pain sensitivity and the persistence of pathological pain [8].

The spinal cord acts as a central regulatory hub both to initiate and maintain NP. In addition to serving as a relay for peripheral nociceptive signals, the spinal cord also plays an active role in central sensitization and the development of chronic pain states. Activation of spinal neurons and glial cells following peripheral nerve injury or intrinsic spinal stress signals leads to significant alterations in neuronal excitability and synaptic plasticity [9]. The coordinated interactions between neurons and glial cells in the spinal cord are crucial for developing and maintaining central sensitization. Microglia can also affect astrocytic activity and disturb synaptic glutamate clearance, resulting in the activation of extrasynaptic NMDARs, increased aberrant neuronal excitability, and enhanced aberrant synaptic transmission as well as neural network remodelling [10]. Meanwhile, miR-146a-5p regulates the balance of microglial autophagy and pyroptosis through TRAF6 targeting [11]. These

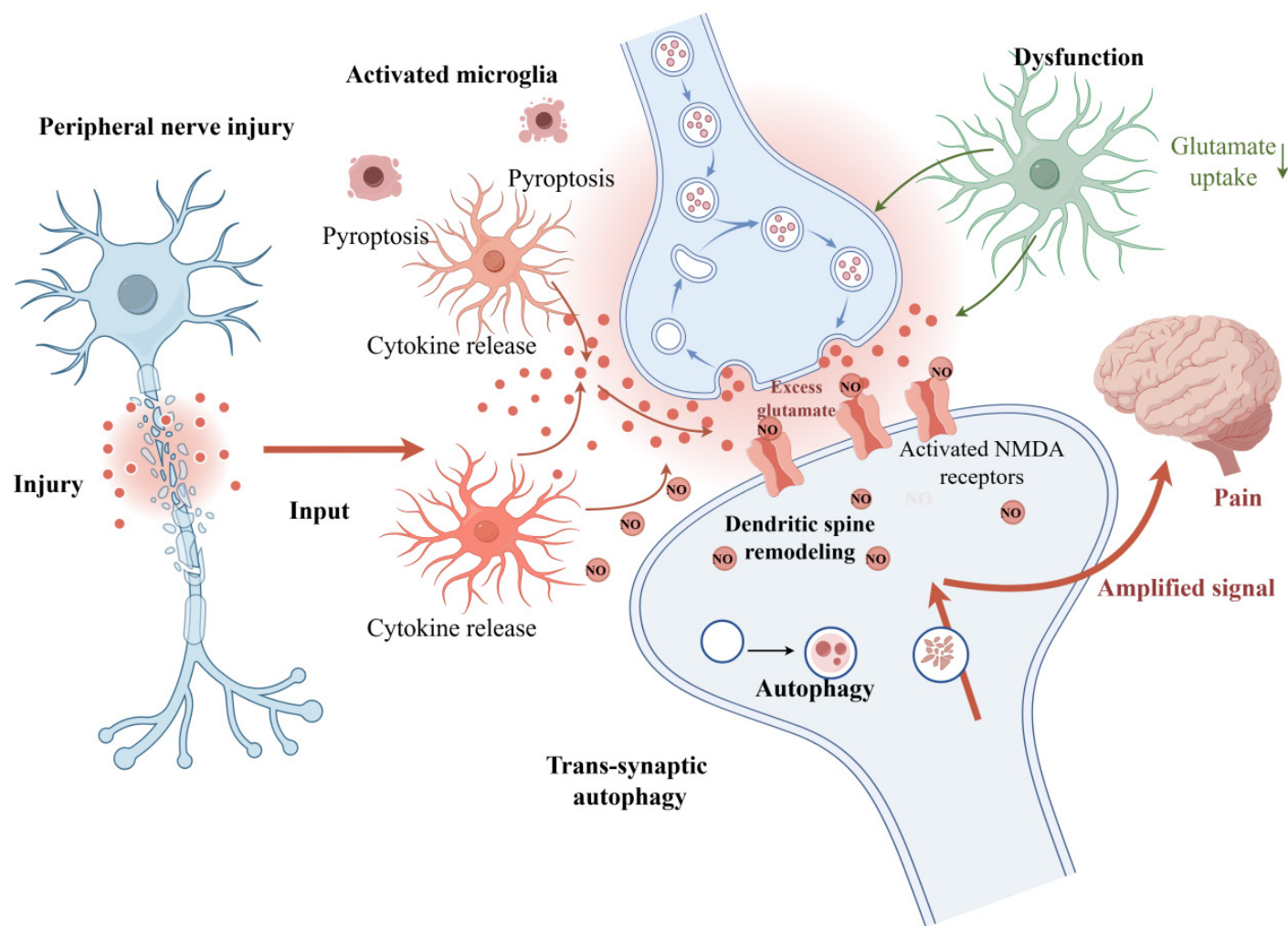


Figure 1. Trans-synaptic autophagy, glial activation, and NMDA receptor-mediated amplification of nociceptive signalling in NP. This schematic represents mechanisms of pain signal amplification in NP. After injury of peripheral nerves, abnormal sensory input is delivered to the spinal cord and induces the activation of microglia with pyroptosis and cytokine release. These processes induce remodelling of the synaptic microenvironment through neuroglial interactions. At the same time, astrocytic dysfunction reduces glutamate uptake, resulting in its accumulation within the synaptic cleft and a sustained activation of NMDARs and associated nitric oxide signalling pathways, which increases neuronal excitability. Autophagy mediates trans-synaptic turnover and dendritic spine remodelling, underlying aberrant synaptic transmission and central sensitization. Together, these convergent mechanisms maintain the amplification of nociceptive signals and drive NP initiation and persistence.

neuro–glial interactions play a pivotal role in synaptic dysfunction and the persistence of pain signalling.

Advances in mechanistic understanding have led to the identification of emerging molecular pathways and therapeutic targets. GRID1/GluD1-dependent trans-synaptic autophagy has been implicated in synaptic regulation associated with chronic pain, and its dysfunction induces abnormal pain phenotypes, underscoring its role in pain maintenance [7]. In addition, NMDA receptor-associated nitric oxide signalling is a key regulator of spinal nociceptive transmission. Eukaryotic elongation factor 2 kinase (eEF2K) modulates L-arginine utilization and participates in NMDA-dependent nitric oxide signalling, thereby influencing neuronal excitability and synaptic transmission [12]. Following peripheral nerve injury, microglial

activation and pyroptosis, impaired astrocytic glutamate uptake, dysregulated trans-synaptic autophagy and enhanced NMDA receptor signalling are functionally coupled, collectively driving spinal synaptic plasticity remodelling and sustained amplification of nociceptive signalling as shown in **Figure 1**. Targeting NMDA receptor-related signalling networks may therefore provide novel molecular strategies for therapeutic intervention.

Overall, NP is characterized by increased neuronal excitability, aberrant nociceptive signalling, and remodelling of spinal neural circuits. Trans-synaptic autophagy plays a critical role in regulating synaptic structure and neuronal activity during the development and maintenance of chronic pain, whereas excessive microglial activation exacerbates neuroinflammation.

tion and sustains pain signalling. These central plasticity mechanisms provide a foundation for further exploration of inflammation-driven pain processes.

2.2 Inflammation-driven mechanisms of NP

Neuroinflammation is a key driver of the development and persistence of NP. In particular, activation of microglia and astrocytes enhances nociceptive signalling through the release of pro-inflammatory cytokines and chemokines, thereby increasing pain sensitivity and promoting chronicity.

Metabolic reprogramming, especially enhanced glycolysis, plays a central role in sustaining neuroinflammatory responses in neuropathic pain. Activated microglia undergo metabolic reprogramming characterized by a shift from oxidative phosphorylation toward enhanced glycolysis, which promotes pro-inflammatory signalling, supports sustained neuroinflammatory responses, and contributes to pain sensitization and persistence [13]. Given the important role of glial cells and glycometabolism reprogramming in neuropathic pain, targeting glial cells and their metabolic regulation has emerged as a potential therapeutic strategy [13]. For instance, semaglutide (SEMA) has been reported to exert neuroprotective effects in diabetic NP by inhibiting astrocytic and microglial activation, thereby alleviating inflammation and oxidative stress [14]. Furthermore, PRMT6 interacts with HIF-1 α to promote the stabilization of glycolytic processes, subsequently enhancing neuroinflammation and facilitating pain progression, suggesting its potential as a therapeutic target [15].

Beyond glycolytic regulation, accumulating evidence indicates that additional molecular regulators participate in the control of neuroinflammatory responses. TRIM28 has been implicated in NP pathogenesis by modulating microglial function and regulating autophagy and ferroptosis, suggesting a previously unrecognized mechanistic link involved in pain development [16]. In addition, ozone has been reported to alleviate neuroinflammation through activation of the p-AMPK/Gas6/MeTK/SOCS3 signalling axis, thereby enhancing macrophage clearance, with preliminary findings indicating its potential clinical relevance [17]. Collectively, glial activation and the production of pro-inflammatory mediators represent key contributors to aberrant pain signalling, whereas glycolytic reprogramming and associated pathways not only support the metabolic requirements of inflammatory processes but also reveal potential therapeutic targets. Modulating these mechanisms may facilitate the development of more precise and individualized therapeutic strategies for NP and provide new opportunities for future drug discovery.

2.3 Neurotransmitter imbalance and pain perception

In addition to neuroinflammatory processes and glial cell-mediated regulation, disruption of neurotransmitter homeosta-

sis represents another fundamental mechanism contributing to NP development. Disruption of the balance between excitatory and inhibitory neurotransmission is considered an important contributor to abnormal pain processing in NP. This imbalance promotes neuronal hyperexcitability and leads to sustained amplification of nociceptive signalling. Among the major inhibitory neurotransmitter systems, γ -aminobutyric acid (GABA) and glycine are pivotal for ensuring efficient inhibitory circuits. Under physiological conditions, GABA prevents excessive neuronal activation via receptor-mediated signalling to reduce nociceptive transmission. However, impaired GABAergic function is common in NP. Following neuronal injury or circuit disruption, reduced GABA release and diminished receptor responsiveness may weaken inhibitory regulation, allowing sustained nociceptive signalling and persistent pain perception [18]. Simultaneously, maladaptive reorganization of local neural circuits (synaptic restructuring and upregulation or downregulation of pain-related pathways) contributes to the amplification of nociceptive inputs. Thus, perturbing excitatory–inhibitory balance not only increases local pain processing, but can also increase the spread of hypersensitivity across regions beyond the initial site of injury.

The spinal cord serves as a key integration centre for nociceptive information processing. After neural injury or pathological changes, spinal neurons can develop spontaneous hyperexcitability, generating persistent nociceptive activity. At the same time, neuroinflammatory responses promote the release of excitatory neurotransmitters and further increase neuronal responsiveness, thereby sustaining abnormal pain signalling. Multiple molecular pathways participate in this process. For example, the $\alpha 2\delta$ -1 subunit, metabotropic glutamate receptor 5 (mGluR5), and NMDA receptor signalling pathways have been implicated in spinal disinhibition and nociceptive hypersensitivity following injury. These molecular changes collectively contribute to the establishment of a dysregulated neurotransmitter network that supports NP development and maintenance. Given the central role of excitatory–inhibitory imbalance in NP, restoring inhibitory neurotransmission has become an important therapeutic direction. Strategies that enhance KCC2 function can help re-establish inhibitory control in the central nervous system (CNS), thereby correcting excitation–inhibition (E/I) imbalance and reducing pathological pain [19]. In addition, botulinum toxin A has been reported to relieve chronic sciatic pain through modulation of SNAP-25 expression [20]. Therapeutic approaches designed according to specific pathological mechanisms may provide additional opportunities to restore coordination between excitatory and inhibitory networks and achieve more effective pain control.

In summary, impaired inhibition and neurotransmitter imbalance are core mechanisms underlying NP pathogenesis. Sustained and inappropriate excitation/inhibition imbalance drives pain hypersensitivity, whereas keeping a proper equilibrium of excitatory vs inhibitory signalling is critical for nor-

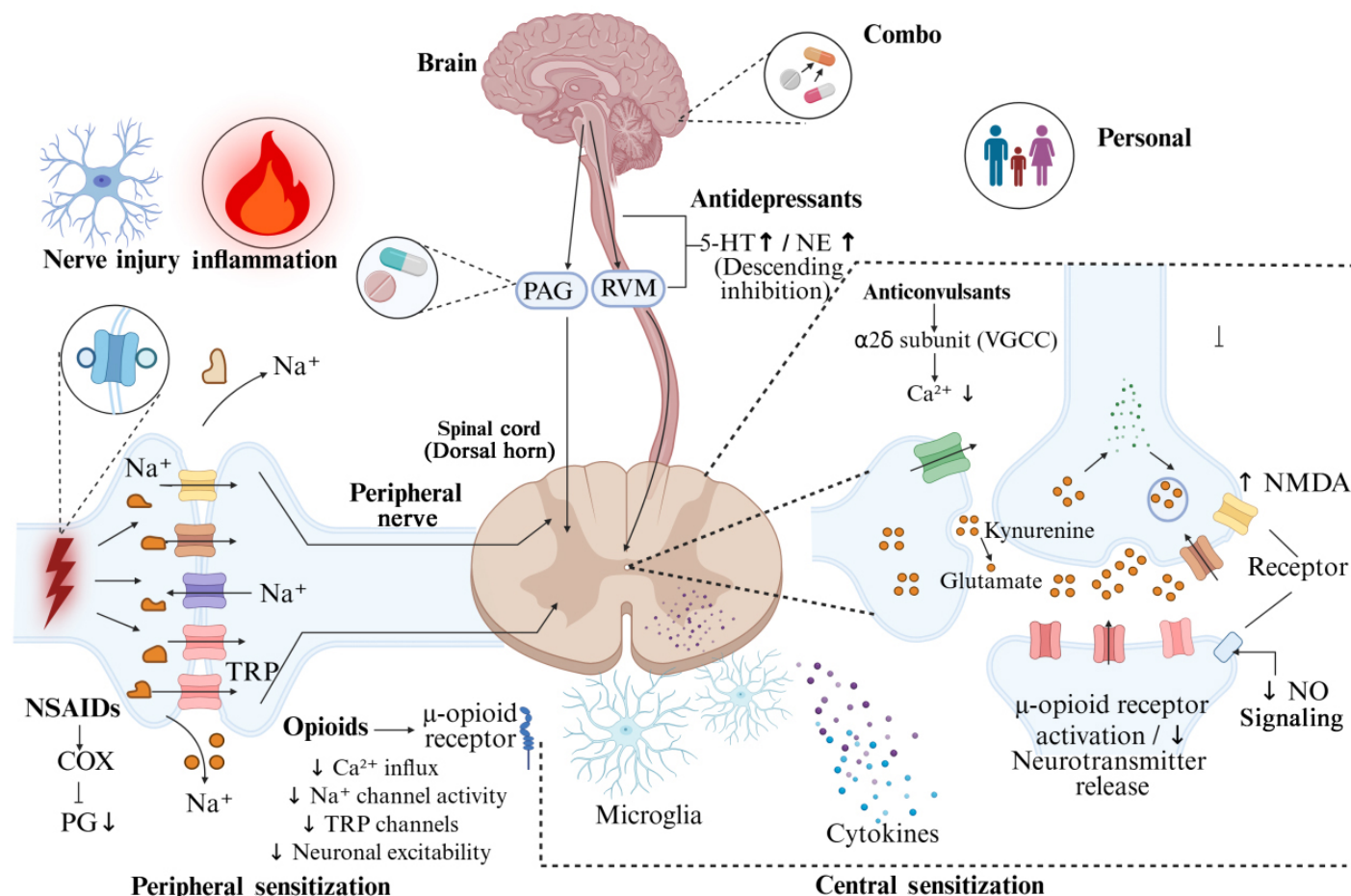


Figure 2. Mechanistic targets of conventional pharmacological therapies in NP. This schematic highlights the major targets and mechanisms of action for classical pharmacotherapy in NP, which mainly modulate peripheral or central sensitization, and descending inhibitory pathways. NSAIDs work by inhibiting COX activity and the subsequent synthesis of prostaglandins; this reduces inflammation as well as peripheral sensitization. Opioids produce analgesia via μ -opioid activation that inhibits Ca^{2+} channel influx and downregulates voltage-gated sodium channels, as well as TRP channels, to decrease neuronal excitability. Antiepileptic drugs mainly act on the $\alpha 2\delta$ subunit of voltage-gated calcium channels, reducing pathological excitatory neurotransmitter release. Moreover, these agents target glutamatergic transmission, NMDA receptor activity, and neuroinflammatory processes—all of which together affect the initiation and chronicity of NP.

mal pain processing. Better characterization of these mechanisms may enable the design of more mechanistically-principled and personalized strategies aimed at re-establishing E/I balance and enhancing NP management.

3 CONVENTIONAL PHARMACOLOGICAL APPROACHES

3.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs exert their analgesic and anti-inflammatory effects mainly through inhibition of cyclooxygenase (COX)-dependent prostaglandin synthesis. Although these agents are widely used in inflammation-related pain conditions, their effectiveness in NP is generally limited. Increasing evidence suggests that NSAIDs may also influence pain processing beyond classi-

cal suppression of inflammation through mechanisms involving lipid mediators and metabolic regulation. For instance, aspirin-triggered lipoxin A4 decreases NP-like behaviours and anxiety-related responses in diabetic rats, while simultaneous administration with cannabinoid receptor agonists produces greater analgesic effects than either treatment alone [21]. In addition, short-term treatment with diclofenac was found to reduce sensory dysfunction associated with NP, which may be mediated by modulation of the kynurenine pathway, including increases in KYNA levels and an increased KYNA/QA ratio. Such effects may be due to modulation of glutamatergic neurotransmission and pathways involved in excitotoxicity [22]. Consequently, NSAIDs may represent more than just inhibitors of inflammatory responses in NP, and may regulate peripheral sensitization, central sensitization, and descending pain inhibitory pathways (Figure 2).

NSAIDs have shown minimal but clinically relevant effects in many NP-related clinical conditions, especially in sciatica. Sciatica is a common condition caused by nerve root compression associated with local inflammatory responses triggered by intervertebral disc herniation or degenerative changes of the spine, manifesting as radiating pain along the sciatic nerve distribution. NSAIDs may partially attenuate nociceptive transmission and pain perception by reducing local inflammation and peripheral sensitization [23]. Yet, in a clinical context, patients with acute low back pain or sciatica treated with NSAIDs (either alone or in conjunction with other analgesic medications) do not show major improvements in functional recovery [24]. This observation indicates that the therapeutic effect of NSAIDs may be partly dependent on disease-related characteristics and patient-specific factors. Importantly, sciatica encompasses heterogeneous spine-related leg pain conditions with differing dominant pain characteristics, including nociceptive and neuropathic components, rather than representing a uniformly classical neuropathic pain condition [25, 26]. Thus, the clinical efficacy of NSAIDs in sciatica is primarily likely mediated by inhibition of peripheral inflammatory pathways rather than direct alteration of neuropathic mechanisms. This further highlights that the relatively modest effects of systemic anti-inflammatory agents in classical NP suggest that simple modulation of inflammation is insufficient to overcome the multiple redundant neuronal and neuroimmune alterations involved in chronic NP [1, 27].

NSAIDs have a long history of analgesic efficacy, but chronic use warrants safety concerns. Gastrointestinal complications (e.g., mucosal injury, ulcer development, and bleeding) are common but serious adverse events associated with prolonged exposure or high-dose use, especially in elderly individuals. NSAIDs may additionally adversely affect renal function and increase cardiovascular risk, especially among patients with existing disease states predisposing to these outcomes [28]. Consequently, NSAID treatment should be guided by individualized risk stratification that considers medication type, dosage, and duration of therapy. NSAIDs are often used in conjunction with other non-opioid analgesics or neuromodulatory agents (antidepressants and anticonvulsants) to overcome the limitations of NSAID monotherapy and increase analgesic efficacy. These multimodal strategies could act by modulating pain pathways regulated through different molecular targets, possibly improving analgesic efficacy and neuropathic symptoms [29]. However, in patients with moderate-to-severe NP or inadequate responses to NSAIDs, anti-inflammatory analgesia alone is often insufficient and may require treatment escalation to agents that act through different mechanistic pathways, such as opioids.

3.2 Opioids: Efficacy and risks

Opioids are still an important class of drugs for NP, especially in cases of moderate to severe pain or inadequate response to

first-line treatments. The majority of their analgesic effects are mediated through the activation of μ -opioid receptors, which suppress the transmission of nociceptive signals. In addition to central actions, peripheral μ -opioid receptor activation may further modulate pain processing through the regulation of transient receptor potential (TRP) channels and voltage-gated sodium channels, as well as decreasing nitric oxide-associated stress responses and neuroinflammatory activity. These interactions likely contribute to analgesic effects at the molecular level [30].

Various formulations of opioids have been investigated across multiple NP conditions. Tramadol-based combinations have shown favourable efficacy and tolerability in managing patients suffering from PHN; for example, extended-release tramadol combined with an immediate-release formulation has demonstrated efficacy in reducing pain intensity while improving quality of life [31]. Tapentadol has been investigated as a treatment option for patients with cancer-related NP who do not respond adequately to conventional opioid therapy, providing analgesic benefits with a relatively favourable safety profile [32]. Methadone has also been used as an adjunctive therapy in specific clinical scenarios, in which improvements in sleep quality and other functional outcomes may be achieved [33].

Recent developments in our knowledge of the mechanisms of NP have additionally encouraged increased opportunities for personalized pain treatment with opioids. For example, the combination of morphine and FLT3 inhibitors has been shown to retain analgesic efficacy while decreasing side effects related to opioid dosage escalation, highlighting the value of incorporating mechanism-based approaches in clinical practice [34]. These results provide further information on how opioid-based therapies may be optimized in clinical practice.

Although long-term opioid treatment has shown clinical utility, it is not without important drawbacks, notably tolerance, dependence, and a variety of other side effects. Individualized treatment decisions should incorporate consideration of both pain phenotype and underlying disease characteristics, as well as patient tolerance, in order to find the optimal balance between analgesia and safety. Combination strategies using neuromodulatory agents, specifically antidepressants and anticonvulsants, to improve long-term NP management have received increasing interest in this setting.

Another major concern during prolonged opioid therapy is opioid-induced hyperalgesia (OIH), which represents a paradoxical increase in pain sensitivity after exposure to opioids. Clinically, differentiation of OIH from disease progression, opioid tolerance, or inadequate pain control can be difficult. Signs of OIH include worsening pain despite escalating doses of opioids, increased sensitivity to pain (hyperalgesia), decreased analgesic effects from the same opioid dose, and relief after decreasing the opioid dose or rotating to another opioid

[35, 36]. The proposed mechanisms underlying OIH involve enhanced glutamatergic signalling, NMDA receptor activation, neuroinflammatory responses, and central sensitization, which collectively contribute to increased nociceptive processing [35, 37]. Several therapeutic strategies, including opioid dose adjustment, opioid rotation, NMDA receptor modulation using low-dose ketamine, and partial opioid receptor agonists, have been explored; however, their clinical effectiveness remains to be fully established [36, 37].

3.3 Antidepressants and antiepileptic drugs in pain management

NP is a chronic pain condition caused by injury or dysfunction of the nervous system and is characterized by persistent or intermittent pain, limited responsiveness to conventional analgesics, and frequent co-occurrence with affective disorders, including anxiety and depression. Its pathogenesis involves complex alterations in neuronal plasticity, neuroinflammatory regulation, and neurotransmitter homeostasis, among which monoaminergic signalling pathways play an important regulatory role. Descending inhibitory pathways mediated by serotonin and noradrenaline represent essential modulatory systems involved in the control of nociceptive processing. Accordingly, antidepressants may exert therapeutic benefits in NP through both mood-related and analgesic mechanisms. At the molecular level, these agents exert analgesic effects by strengthening descending inhibitory pathways and modulating neuroinflammatory responses. For example, paroxetine has been reported to attenuate chronic NP through the regulation of multiple pain-associated proteins [38]. In addition, low-dose esketamine has been shown to alleviate depression-like behaviours associated with NP, possibly through modulation of the Homer1a–mGluR5 signalling pathway [39].

In clinical practice, combining antidepressants with antiepileptic drugs has become an important therapeutic approach for NP management. Antiepileptic agents, particularly gabapentin and pregabalin, primarily reduce neuronal hyperexcitability by targeting voltage-gated calcium channel $\alpha 2\delta$ subunits or stabilizing neuronal membrane function, thereby limiting abnormal neuronal firing and reducing pain transmission. By contrast, antidepressants act mainly through inhibition of neurotransmitter reuptake, enhancing serotonergic and noradrenergic signalling and modulating multiple pain-related pathways. Clinical studies have indicated that fixed-dose combinations (FDCs) of low-dose pregabalin and duloxetine can achieve analgesic effects comparable to high-dose pregabalin monotherapy while maintaining an acceptable safety profile. Dizziness and somnolence remain the most commonly reported adverse events [40]. Furthermore, trazodone administered at doses of 50–100 mg has been reported to enhance the analgesic effects of gabapentin, providing additional support for low-dose combination strategies in NP treatment [41].

Recently, novel antidepressants have gained attention for their potential role in NP treatment. Venlafaxine exerts multimodal effects through the modulation of multiple neurotransmitter receptors and signalling pathways, including $\alpha 2$ -adrenergic receptors, 5-HT₃ and 5-HT_{1B/1D} receptors, cholinergic pathways, as well as CB1/CB2 cannabinoid and adenosine A1 receptors [42]. In preclinical models, venlafaxine has been shown to attenuate oxaliplatin-induced NP and mechanical allodynia, with $\alpha 2$ -adrenergic and 5-HT₃ receptors contributing to distinct pain modalities [42]. In addition, antidepressants have been shown to demonstrate analgesic effects in trigeminal neuralgia (TN), visceral pain and inflammatory pain models, with relatively mild adverse effects, including nausea, dry mouth and sleep disturbances [43].

Overall, antidepressants and antiepileptic drugs play a central role in the long-term management of NP by modulating neurotransmitter systems and neuronal excitability. However, conventional pharmacotherapy remains limited by interindividual variability in efficacy and adverse effects, with mechanisms largely confined to neurotransmitter regulation. With increasing recognition of the role of neuroinflammation in pain maintenance and amplification, therapeutic strategies targeting neuroinflammatory pathways are emerging as a major focus of research. A summary of representative agents, mechanisms of action and clinical applications of antidepressants and antiepileptic drugs in NP is provided in **Table 1**.

4 EMERGING PHARMACOLOGICAL STRATEGIES

4.1 Targeting neuroinflammation

Neuroinflammation is a central mechanism underlying the initiation and persistence of NP. Following peripheral nerve injury, activation of glial and immune cells leads to the release of pro-inflammatory mediators, including TNF- α , IL-1 β , and IL-6, which enhance neuronal excitability and amplify nociceptive signalling through neuroimmune interactions, thereby promoting central sensitization and pain chronicity. Consequently, targeting neuroinflammatory pathways has emerged as a major therapeutic strategy.

Within neuroinflammatory regulation, glial polarization states play a critical role in pain modulation. Emerging evidence indicates that active components of DHJSD may attenuate neuroinflammation by regulating microglial M1 polarization, potentially via Peroxisome proliferator-activated receptor- γ (PPARG)-dependent mechanisms [80]. In addition, the double-stranded RNA-induced Toll-like receptor 3 (dsRNA–TLR3) signalling pathway has been implicated in both neuroinflammation and the development of morphine tolerance, suggesting that targeting this pathway may provide a therapeutic approach to mitigate opioid tolerance [81]. Inter-glial immune signalling also represents a promising avenue for intervention. For example, intrathecal administration of the CD200R1 agonist

Table 1. Comparative roles of antidepressants and antiepileptic drugs in the management of NP

Drug class	Representative agents	Primary targets/mechanisms	Indications	Analgesic advantages	Adverse effects	References
Tricyclic antidepressants	Amitriptyline	Modulation of neurotransmission in pain pathways	Palliative care; lumbosacral radiculopathy	Pain improvement in 43.3% after 14 days or $\geq 30\%$ relief in a subset	Dizziness, dry mouth, constipation, urinary retention	[44, 45]
Antiepileptics	Gabapentin	Binds to the $\alpha 2\delta$ -1 subunit of voltage-gated calcium channels; injury-induced $\alpha 2\delta$ -1 upregulation is associated with gabapentin-sensitive allodynia	NP	Effective against neuropathic allodynia; early combination therapy may benefit patients with intense and deep pain	Generally well tolerated; reported adverse drug reactions are mostly mild and non-serious	[46, 47]
Antiepileptics	Pregabalin, gabapentin	$\alpha 2\delta$ -1 subunit targeting	PHN	Combination therapy enhances efficacy	No significant increase in risk with combination	[48, 49]
Antiepileptics	Carbamazepine, oxcarbazepine	Sodium channel blockade; selective inhibition of ectopic afferent activity	TN	First-line therapy with phenotype-specific targeting	Increased risk of ischaemic stroke (HR 1.78)	[50, 51]
Antidepressant–antiepileptic combination	Pregabalin + duloxetine	$\alpha 2\delta$ -1 targeting and monoamine reuptake inhibition	Painful diabetic peripheral neuropathy (DPNP)	Superior improvement in pain, sleep and mood versus pregabalin–nortriptyline	Higher incidence of mild adverse events (30% vs. 16.67%)	[52]
Antidepressants	Duloxetine	Inhibition of 5-HT and noradrenaline reuptake	Diabetic neuropathy	Improves objective neurological outcomes	Nausea (10.6%), dizziness (7.1%), somnolence (6.2%)	[53]
Antiepileptics	Pregabalin	Binding to voltage-gated Ca^{2+} channel $\alpha 2\delta$ subunit; reduces central sensitization	Radiotherapy-induced NP (head and neck cancer)	Superior pain relief and quality-of-life improvement vs placebo	Good tolerability; adverse events comparable to placebo	[54]
Antidepressants	LPM580098	Triple reuptake inhibition; modulation of NR2B/CaMKII α /GluR1 pathways	NP	No significant sedation or motor impairment	No marked central inhibitory effects	[55]
Antidepressants	Topical amitriptyline (10%)	Local inhibition of voltage-gated sodium channels in nociceptors	Chemotherapy-induced neuropathy; burning mouth syndrome	Effective analgesia with reduced systemic toxicity	Occasional mild somnolence and dry mouth	[56, 57]
Antiepileptics	Pregabalin	$\alpha 2\delta$ -1 subunit targeting; inhibition of Ca^{2+} currents	Post-traumatic NP	No superiority over placebo in large RCT (≤ 15 weeks)	Dizziness (14.6%), somnolence (9.9%)	[58, 59]
Antidepressants	Flupentixol + melitracen	Dopamine receptor antagonism + monoamine reuptake inhibition	Persistent idiopathic facial pain	High response rate (82%) with rapid onset	Mild somnolence, dry mouth	[60]
Antiepileptics	HSK16149	Modulation of GABAergic pathways	DPNP	Demonstrates superior efficacy vs placebo	Common dizziness and somnolence (mostly mild–moderate)	[61]
Antiepileptics	Mirogabalin	Selective binding to $\alpha 2\delta$ -1 subunit	Lumbar disc herniation–related NP	Enhances NSAID efficacy and improves sleep	Somnolence (31.1%), dizziness (18.9%)	[62]
Antiepileptics	Mirogabalin	Selective $\alpha 2\delta$ ligand	DPNP	Dose-dependent analgesia; 30 mg/day effective	Somnolence, dizziness, oedema, weight gain	[63]
Antiepileptics	Mirogabalin	$\alpha 2\delta$ -1 targeting	Cervical radiculopathy–related NP	Superior efficacy in combination with NSAIDs	Somnolence, dizziness	[64]
Antidepressants	Duloxetine, amitriptyline	Dual central–peripheral analgesic mechanisms	NP	Delayed analgesia associated with peripheral neuroimmune modulation	Somnolence (42.4%), dizziness (21.2%), dry mouth (21.2%)	[65, 66]

Antiepileptics	Gabapentinoids	LAT1-mediated BBB transport; influenced by genetic polymorphisms	NP	Highest efficacy and safety in GG genotype	Somnolence and dizziness (highest in GA genotype)	[67]
Antiepileptics	Lacosamide	Sodium channel blockade	Peripheral NP	Higher rates of $\geq 30\%$ and $\geq 50\%$ pain relief vs placebo	Good tolerability	[68]
Antiepileptics	Mirogabalin	Potent and selective $\alpha 2\delta$ ligand	DPNP	Cost-effective (ICER below willingness-to-pay threshold)	Somnolence (26.7%), dizziness (12.3%), oedema, weight gain	[69, 70]
Antiepileptics	Lacosamide	Sodium channel blockade	TN	Comparable efficacy to carbamazepine	Somnolence, dizziness, mood instability	[71]
Antiepileptics	HSK16149	Potent $\alpha 2\delta$ ligand; inhibits [^3H]gabapentin binding	DPNP	~23-fold greater potency than pregabalin; longer duration; improved CNS safety	Good tolerability; low incidence of severe adverse events	[72, 73]
Antiepileptics	Pregabalin	$\alpha 2\delta$ targeting	DPNP, PHN and other NP	Greater cost-effectiveness vs gabapentin	Sexual dysfunction (41.3%)	[74, 75]
Antiepileptics	Pregabalin	$\alpha 2\delta$ subunit modulation	PHN	Faster pain relief; improved sleep and mood	Dry mouth, somnolence, blurred vision, ataxia	[76]
Antidepressants	Duloxetine	5-HT/NE reuptake inhibition	DPNP, CIPN, refractory cancer-related NP	Effective in treatment-resistant cases	Nausea, constipation, somnolence, sexual dysfunction	[77, 78]
Antiepileptics	Pregabalin	$\alpha 2\delta 1$ targeting; inhibition of silent cold nociceptors	Oxaliplatin-induced neuropathy	Reduces cold allodynia by suppressing silent nociceptor activation	Dizziness, somnolence	[79]

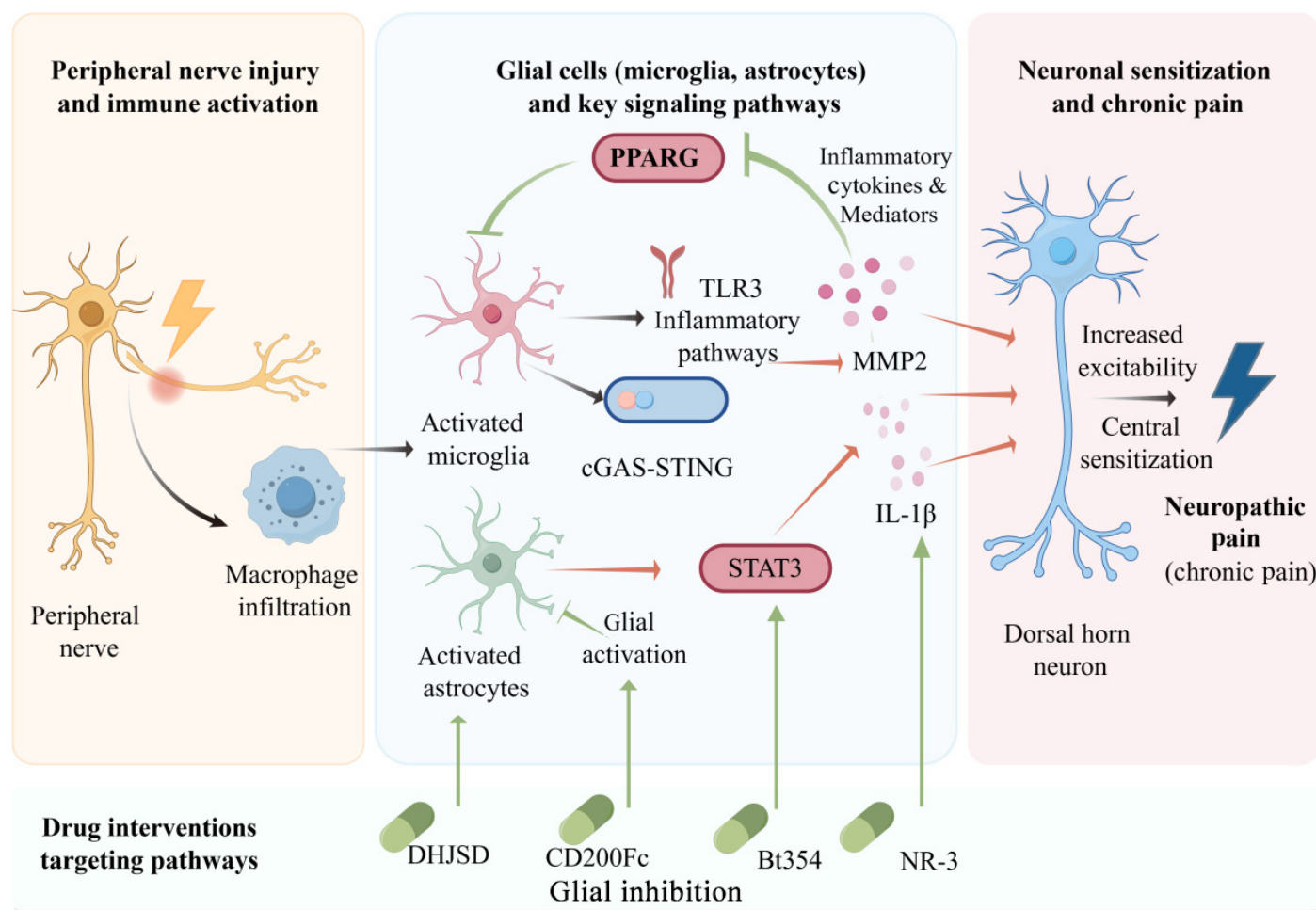


Figure 3. Neuroinflammatory signalling pathways and therapeutic targets in NP. This figure depicts the major mechanisms whereby neuroinflammation contributes to the development and persistence of NP after peripheral nerve injury. Nerve injury leads to immune activation and macrophage infiltration, subsequently triggering microglial and astrocyte activation in the central nervous system. Numerous signalling pathways and molecular regulators, including peroxisome proliferator-activated receptor gamma (PPARG), Toll-like receptor 3 (TLR3), the cGAS–STING axis, STAT3, and the MMP2/IL-1 β pathway, promote the amplification of neuroinflammatory responses. Such processes potentiate the release of inflammatory mediators, elevate neuronal excitability, and promote central sensitization, thus ultimately facilitating the transition to chronic NP. The schematic also summarizes representative therapeutic strategies including DHJSD, CD200Fc, Bt354, and NR-3, and highlights that targeting glial activation and inflammatory signalling networks represents a promising direction for NP therapy.

CD200Fc rapidly suppresses glia-associated neuroinflammatory responses and effectively alleviates NP, highlighting its potential as a novel therapeutic modality [82].

Advances in molecular biology have revealed a growing number of inflammatory signalling pathways that contribute to NP pathogenesis. Among these, the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) pathway, a critical component of innate immune sensing, has emerged as an important regulator of neuroinflammation and a potential therapeutic target for NP [83]. Similarly, signal transducer and activator of transcription 3 (STAT3) acts as a key molecular regulator in NP by influencing glial polarization and the expression of inflammatory mediators. Pharmacological inhibition of STAT3 signalling using Bt354 has been reported to suppress inflam-

matory responses and reduce pain behaviours, supporting its potential therapeutic value [84]. These findings highlight emerging molecular targets for the development of more precise anti-inflammatory analgesic approaches. Following peripheral nerve injury, the activation of neuroinflammatory cells and the disruption of multiple signalling networks interact to promote the initiation and persistence of NP. The major mechanisms and corresponding therapeutic targets are summarized in **Figure 3**.

In addition to upstream signalling pathways, therapeutic strategies targeting inflammatory mediators and downstream effectors have also attracted increasing attention. For example, NR-3 has been shown to increase mechanical and thermal pain thresholds in spinal nerve ligation (SNL) models without altering

baseline nociception in healthy animals, suggesting a favourable degree of therapeutic selectivity. Its analgesic effects are likely mediated through inhibition of the MMP2/IL-1 β signalling axis in the DRG and spinal astrocytes, thereby attenuating neuroinflammation and reducing persistent pain states [85]. Overall, continued advances in our understanding of neuroinflammation and neuroimmune interactions are accelerating the development of therapies targeting inflammatory mediators and related signalling pathways. These approaches provide important mechanistic insights into NP treatment and may contribute to the future development of more targeted and individualized therapeutic strategies.

4.2 Stem cell therapy and regenerative medicine

Stem cell-based therapies have attracted growing attention in NP research because of their potential immunomodulatory, neuroprotective, and regenerative effects. Among these approaches, mesenchymal stem cells (MSCs), including human umbilical cord-derived MSCs (HUC-MSCs), have shown analgesic potential in preclinical models. Their beneficial effects are thought to involve multiple mechanisms, including regulation of neuroinflammatory responses, modulation of glial activation, secretion of neurotrophic factors, and restoration of the injured neural microenvironment [86, 87]. In addition, transplantation of neural stem/progenitor cells has demonstrated therapeutic effects in experimental models of nerve injury and spinal cord injury (SCI), possibly through promoting neural repair processes and reducing pain sensitization [88, 89].

In addition to direct cellular transplantation, cell-free strategies based on extracellular vesicles, particularly MSC-derived exosomes, have enhanced the potential applications of regenerative therapies. Experimental studies suggest that exosomes can influence a range of pathological processes relevant to NP, including inflammatory regulation, synaptic plasticity, remyelination, and neuronal survival. Compared with cell-based therapies, exosome-based therapeutic approaches may offer some advantages, such as lower immunogenicity and improved biosafety profiles [90]. Despite encouraging evidence in preclinical studies, clinical translation of stem cell-based therapies for NP remains limited. The current evidence is mainly based on animal models of peripheral nerve injury or SCI, and high-quality randomized controlled trials in patients with NP are still lacking. Ultimately, a wide range of translational challenges need to be addressed, including variability in cell sources, manufacturing processes, administration routes, dosing regimens, quality control procedures, and long-term safety assessment [91-94]. Thus, stem cell-based therapies should currently be viewed as investigational rather than established NP treatment modalities. Future studies will need to focus on improving manufacturing standardization, identifying biomarker-defined patient populations most likely to respond, and conducting rigorously designed clinical trials using clinically meaningful outcomes.

4.3 Rational combination strategies and multi-target pharmacotherapy

Single-target therapeutic strategies in NP remain insufficient and are unlikely to fully address the heterogeneous mechanisms underlying disease, such as neuronal hyperexcitability, neuroinflammatory activation, and central sensitization. This has led to the development of combination approaches, where small molecules and biologic agents are administered together since such strategies may provide complementary benefits in terms of tissue penetration, onset of action, and target specificity, potentially allowing intervention at multiple pathological processes.

Biologic therapies directed at neuroinflammatory pathways represent one area of growing interest. Astrocyte senescence has been suggested to contribute significantly to neuroinflammatory responses after peripheral nerve injury, and targeting astrocytic activation states or related secreted molecules, such as clusterin (CLU), may represent a potential therapeutic strategy [95]. Similarly, nerve growth factor (NGF) is an important regulator of pain sensitivity and is involved in several pain-associated conditions. NGF silencing has been reported to influence nociceptive signalling pathways and may improve the efficacy of immunochemotherapy while supporting relatively low-toxicity delivery approaches [96]. Together, these findings suggest that selective regulation of inflammatory mediators and neurotrophic factors may provide opportunities to intervene in neuroinflammatory processes involved in NP.

Because of the potential complementary effects between different agents, a mechanistic aspect of combination therapies is that they may produce effects unattainable with single-agent treatment. Small molecules usually allow rapid modulation of neuronal activity, whereas biologic agents may have a more prolonged effect on the regulation of inflammatory and immune processes. For instance, ambroxol, a small-molecule ion channel modulator, inhibits Nav1.8 and can additionally influence TRPV1 and TRPA1 channels at higher concentrations, indicating a relatively wide modulatory profile [97]. Such features may support the rationale for combining ion channel modulators with anti-inflammatory biologics. Furthermore, data from immunomodulatory studies suggest that multi-pathway interventions may enhance analgesic responses through regulation of cytokine networks, including enhancement of IL-10 expression and suppression of chemokine signalling pathways [98, 99]. In clinical practice, combination therapy is usually used when monotherapy does not offer adequate analgesia or if dose escalation is limited due to adverse effects. However, the evidence for specific mechanism-based combinations remains limited. Current clinical recommendations remain focused on rational first-line drug selection, patient-tailored dose optimization and ongoing assessment of treatment efficacy and tolerability whilst minimising the risk of polypharmacy [100]. Combination approaches may provide advantages for selected

patient populations, yet few clinical trials have defined a standard regimen applicable to NP. These combinations will also need to be based on biological mechanisms, pain phenotypes, and individual patient characteristics as opposed to simply empirical drug combinations [100, 101].

The incorporation of nanodelivery platforms has further expanded the potential of combined small-molecule and biologic therapies. Different nanocarriers offer unique advantages in central nervous system targeting and the coordinated delivery of multiple therapeutic cargos. For instance, 46.1-Lipo liposomes markedly increase brain-specific accumulation of pralidoxime, achieving approximately a tenfold enhancement in targeting efficiency [102]. Similarly, liposomal co-delivery of donepezil, memantine, and BACE-1 siRNA has been shown to reduce β -amyloid levels and related gene expression while suppressing inflammatory responses, illustrating the potential of multi-target therapeutic regulation [103]. Furthermore, lipid nanoparticles enable mRNA transport across the blood-brain barrier into the central nervous system, whereas Tan IIA-based nanoparticles promote neuroprotection and regeneration by modulating neural stem cell differentiation and neuroimmune responses [104, 105]. Collectively, nanocarrier-mediated combination strategies enable coordinated intervention at molecular, cellular, and tissue levels, providing an integrated framework for future NP therapy. Meanwhile, increasing recognition of interindividual genetic differences in drug responses highlights the potential importance of pharmacogenomics in precision treatment strategies. Despite rapid progress in nanotechnology, no nanoparticle-based formulation has been approved specifically for NP treatment by the FDA or other major regulatory agencies to date. Currently available nanomedicines are primarily applied in oncology, infectious diseases, and nucleic acid delivery, including liposomal systems, polymeric nanoparticles, and lipid nanoparticle-based platforms [106, 107]. Therefore, nanocarrier applications in NP remain an emerging area of investigation rather than an established clinical approach. Major translational challenges include achieving selective targeting within the nervous system, accurately predicting in vivo biodistribution, establishing scalable manufacturing processes, defining regulatory requirements, and demonstrating long-term safety [100, 108].

5 PERSONALIZED THERAPY AND PHARMACOGENOMICS

5.1 Genetic determinants of drug response

In neuropathic and other chronic pain conditions, marked interindividual differences are observed in both analgesic efficacy and treatment-related adverse effects. Pharmacogenomic studies have shown that genetic variants of drug-metabolizing enzymes, key transporters involved in drug transport, and target proteins can influence clinical responses to therapy and

susceptibility to toxicity. Thus, elucidating the genetic factors underlying interindividual differences in analgesic responses has become an integral part of precision medicine for pain treatment. Importantly, beyond single loci, the genetic determinants of treatment response span multiple biological levels, including pain processing, pharmacokinetics, pharmacodynamics and clinical outcomes, resulting in individualized therapeutic strategies as depicted in **Figure 4**.

Genetic variation affecting analgesic response is an important factor contributing to interindividual differences in pain treatment outcomes. Although various genetic determinants can impact therapeutic responses and adverse effects, polymorphisms in drug-metabolizing enzymes are arguably the most studied mechanism. Analgesics are often subject to extensive enzymatic biotransformation, and genetic variants affecting these pathways may result in altered enzyme activity that affects drug exposure, therapeutic efficacy and the likelihood of adverse effects. Nonetheless, the clinical consequences of individual variants are highly context-dependent and depend on disease, treatment strategy, and patient characteristics. As an example, the CYP2D6*2 polymorphism was not associated with analgesic response in PHN patients treated with tramadol; thus, its predictive value may be limited to certain clinical contexts [109]. Besides affecting metabolic enzymes, variant alleles of drug transporters might affect pharmacological responses by changing the distribution and availability of drugs. The ABCB1 rs1045642 polymorphism has been associated with differential analgesic responses to a combined treatment of nortriptyline and morphine, with certain genotypes showing greater therapeutic benefit [110]. These results suggest that while drug metabolism and transport pathways differ due to genetic variation, their clinical application remains limited and requires further validation.

Single-nucleotide polymorphisms (SNPs) related to nociceptive signalling pathways and potential therapeutic targets may also modulate response to analgesic treatment. SNPs in genes involved in pain transmission and opioid signalling pathways may influence sensitivity to various opioid-based therapies. Such genetic variability may, in part, account for differences between patients with chronic low back pain (CLBP), such as greater analgesic benefit in some patients and limited responses in others despite similar treatment strategies [111]. These findings lend support to potential clinical utility of incorporating genetic information in chronic pain management. In addition, variations in candidate genes may contribute to the response and adverse effects of cannabinoid-based treatments, thus directly or indirectly affecting efficacy and tolerability, including future treatment discontinuation [112].

In addition to pharmacological effects, genetic variations drive differences in intrinsic pain processing, such as individual pain sensitivity and susceptibility to chronic pain states. It is likely

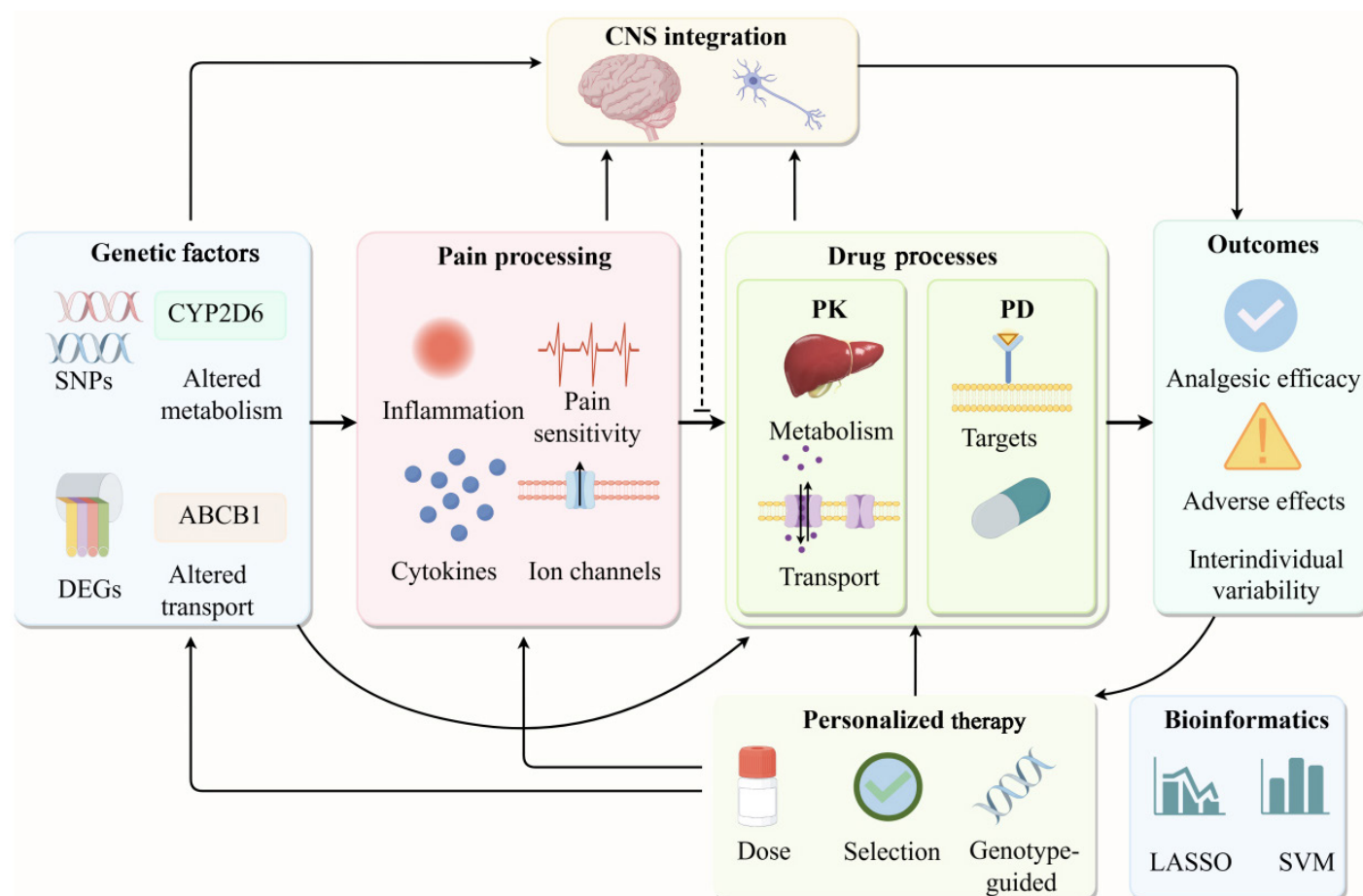


Figure 4. Genetic determinants of variability in analgesic response: An integrated mechanistic framework. This schematic depicts the genetic influences that lead to interindividual variation in analgesic responses via multi-level modulation of pathways involved in pain processing and drug action. Drug metabolism and transport, target sensitivity, as well as pain-related inflammatory responses and ion channel activity are influenced by genetic polymorphisms and DEGs. Together, these effects modify central integration of nociceptive signals and drug actions within the nervous system, resulting in differences in analgesic potency, side effects, and response. Based on this framework, integration of bioinformatic analyses with candidate gene identification may support genotype-guided drug selection, and dose optimization, thereby facilitating the transition towards personalized and precision-based pain management.

that genes affecting neurotransmitter regulation and pathways important in nociceptive signalling neural circuits modulate pain thresholds and contribute to the development of chronic pain phenotypes. Differentially expressed genes (DEGs) identified in patients with low back pain were found to be enriched in neuroinflammation-associated pathways, and key candidate genes KLRK1, LRRK2, NLRP3 and PLG were identified through LASSO regression and support vector machine (SVM) analyses [113]. In summary, genetic influences impact multiple aspects of neuropathic and chronic pain, including drug metabolism, treatment response, as well as the biological basis of pain susceptibility. This suggests that pharmacogenomic research, which is currently ongoing, may ultimately be incorporated into clinical decision-making to improve drug selection and optimize dosing strategies for more individualized analgesic therapy approaches.

5.2 Clinical implementation of personalized therapy

Precision dosing strategies have gained increasing utility in the individualization of NP management. Intrathecal drug delivery (ITDD) systems offer the potential for effective and localized administration of analgesic agents in chronic pain patients, particularly those with refractory NP. Clinical evidence has shown that ITDD pumps can maintain accurate dosing and consistent delivery performance when used with off-label medications or mixtures of drugs infused under different conditions [114]. The stability generated can help individualize treatment regimens according to pain severity, medication tolerance and therapeutic response for improving pain management. By increasing availability of the drug at the site of action and limiting systemic exposure with concomitant adverse effects, intrathecal delivery represents a therapeutic option for precision analgesia,

thus offering an attractive approach compared with systemic administration.

Contemporaneously with drug delivery advances, digital health technologies are offering new opportunities for tailored treatment decision-making. Tools like the systematic individualized benefit–risk evaluation tool (SIBRET) can help clinicians and patients systematically weigh the potential benefits and risks of different therapeutic options, thereby supporting more informed treatment decisions [115]. Moreover, SIBRET has provided proof-of-concept evidence for the analgesic efficacy of topical 10% phenytoin cream, further illustrating the potential role of local treatment strategies in precision pain management [115]. Integrating patient characteristics, clinical outcomes, and risk assessments into modeling platforms may lead to more rational selection and optimization of therapeutic interventions.

Novel neuromodulation modalities also broaden the arsenal of personalized treatment options for NP. The closed-loop spinal cord stimulation (CL-SCS) systems employing ECAP feedback can provide continuous monitoring of neural responses and dynamic adjustment of stimulation parameters, further stabilizing neural activation [116]. ECAP-modulated CL-SCS provides enhanced neuromodulation control in cervical and thoracic spinal applications. Compared with wider-targeted neuromodulation, the design may improve analgesic efficacy, while reducing stimulation levels that are greater or lower than optimal and enhancing control of cervical neural structures with a narrow therapeutic window.

Altogether, precision drug delivery, digital decision-support systems and closed-loop neuromodulation indicate a move toward more individualized and data-informed NP management. At the same time, these systems are still in clinical development and much additional research will need to be done to delineate their mechanisms, optimize their integration with current treatments, and construct robust predictive paradigms. **Table 2** highlights the key differences in mechanisms of action, delivery approaches and clinical applications between these personalized therapeutic modalities.

5.3 Future directions in personalized therapy

The trend of NP management is gradually changing from traditional empirical drug selection to more mechanism-informed and personalized therapy with the continued advancement of precision medicine. Multi-omics approaches in conjunction with other clinical characteristics lay an invaluable foundation for this transition. Integration of genomic, transcriptomic, proteomic and metabolomic analyses has advanced our understanding of the molecular networks involved in both initiation and maintenance of the pain state; this has enabled identifi-

cation of targets for potential therapeutic intervention. Among these molecular properties, functional gene expression profiles in nociceptive neurons have gained increasing attention, especially ion channel-related genes including SCN9A, SCN10A, TRPV1, and TRPA1 that govern neuronal excitability and mediate calcium-dependent responses to external stimuli (such as capsaicin) [140]. Neuron-derived S100A4 has also been shown to modulate neurotoxic astrocyte reactivity and is associated with neuroinflammation and persistent pain, suggesting that S100A4 may represent a potential therapeutic target for NP [141]. Thus, the integration of multi-omics datasets with bioinformatic analyses to define molecular subtypes could allow for biologically based patient stratification and precision therapy.

A more detailed understanding of neuroimmune mechanisms has further broadened the possibilities for personalized NP treatment. Chronic pain involves inflammatory alterations within the central nervous system accompanied by neurophysiological changes, which are associated with distinct clinical pain phenotypes, particularly the severity of nociplastic pain [142]. Systematic characterisation of neuroimmune signalling networks may open up a path to elucidate biological heterogeneity in patients and identify novel therapeutic targets for mechanism-based intervention. Molecularly, regulation of TGFβ1 and GP130 signalling pathways has been suggested to participate in pain modulation in preclinical studies, positioning these targets as potential candidates for further translational research.

Beyond molecular classification, directed modulation of specific nociceptive pathways is emerging as a novel strategy in NP personalized therapy. Ion channel disorders, neuroimmune interactions and inflammatory signalling are not independent phenomena but interconnected regulatory networks that together promote the onset and maintenance of NP. Post-translational modifications of NaV1.7 can influence neuronal excitability, P2X3 receptor signalling interacts with microglial activation, and NLRP3 inflammasome activity contributes to pain maintenance [143-145]. In the meantime, however, alternative therapeutic strategies are being investigated. Sustained analgesic activity, improved glycaemic control and reduced opioid consumption are observed with inhaled cannabis in patients with refractory diabetic neuropathy while maintaining an acceptable safety profile. Future studies integrating biomarkers, such as levels of endogenous cannabinoids, may further elucidate the mechanisms underlying this therapeutic effect and refine patient selection for treatment response [146]. In general, the field of NP management is converging on a molecularly informed classification, mechanism-based intervention, and data-driven treatment decisions. There are still major hurdles to overcome, yet bringing together biological signatures, clinical phenotypes and insights into mechanisms is likely to move the field closer to precision therapy.

Table 2. Emerging perspectives in pharmacological management of NP: Towards individualized therapy

Drug	Target	Mechanism	Clinical application	Inter-individual variability	Selection rationale	References
Pregabalin + α -lipoic acid	$\alpha 2\delta$ subunit; antioxidant	Combined calcium channel modulation and antioxidation	Peripheral NP	Comparable efficacy across sub-groups	RCT shows no superiority over pregabalin alone	[117]
Mirogabalin	$\alpha 2\delta$ -1 subunit	Voltage-gated calcium channel modulation	NP	Variable efficacy with co-medication or dosing	Response predictable based on combination regimens	[118]
Oxcarbazepine	Voltage-gated sodium channels	Sodium channel blockade	NP syndromes	Response to intravenous lidocaine	Lack of lidocaine response predicts poor efficacy	[119]
Ketamine	NMDA receptor	NMDA receptor antagonism	NP	White matter microstructure (internal capsule; default mode network)	Structural connectivity predicts analgesic response	[120]
Pregabalin	$\alpha 2\delta$ subunit	Reduction of central sensitization	NP	Early pain response (weeks 1–3)	Early improvement predicts long-term efficacy	[121]
Lidocaine spray	Voltage-gated sodium channels	Local sodium channel blockade	Acute TN	Nerve distribution and dosing	Response predicted by anatomical targeting	[122]
Capsaicin 8% patch	TRPV1 receptor	Functional defunctionalization of epidermal nerve endings	Traumatic peripheral NP	Cold allodynia; absence of penetrating pain	Baseline phenotype predicts response	[123]
Carbamazepine	Voltage-gated sodium channels	Suppression of neuronal hyperexcitability	TN	NVC ≤ 5 mm ³ and ≤ 3 mm distance	Predicts response to low-dose therapy	[124]
Oxcarbazepine vs pregabalin	Sodium channels vs $\alpha 2\delta$ subunit	Distinct mechanisms	Post-spinal cord injury NP	Pain phenotype	Drug selection guided by evoked pain characteristics	[125]
Carbamazepine	Voltage-gated sodium channels	Correction of mutant channel activation	Inherited erythromelalgia	Nav1.7-I234T mutation	Genotype predicts therapeutic response	[126]
ISC 17536	TRPA1 receptor	Peripheral nociceptive signal modulation	Painful diabetic neuropathy	Preserved small-fibre function	Greater efficacy in defined sensory phenotype	[127]
Multimodal analgesia	μ -opioid receptor, monoamine transporters, sodium channels	Combined mechanisms	Acute herpetic pain	Age ≥ 50 ; moderate–severe pain	Early treatment reduces PHN risk	[128]
Intravenous lidocaine	Voltage-gated sodium channels	Systemic sodium channel blockade	Multiple NP syndromes	High baseline pain; older age	Greater benefit in these populations	[129]
Esketamine	NMDA receptor	Analgesic and rapid antidepressant effects	PHN with depression/anxiety	Psychiatric comorbidity	Faster symptom relief vs sufentanil	[130]
Mirogabalin	$\alpha 2\delta$ -1 subunit	Selective calcium channel modulation	Central NP after spinal cord injury	Moderate renal impairment	Dose adjustment improves safety and efficacy	[131]
Capsaicin	TRPV1 receptor	Peripheral nociceptor defunctionalization	Localized NP	Pain catastrophizing; sensory thresholds; TRPV1 polymorphism	Multivariable prediction model guides therapy	[132]
Pregabalin	$\alpha 2\delta$ subunit	Central sensitization inhibition	Painful diabetic neuropathy	Demographics, BMI, disease duration, depression	ARMAX modelling predicts response	[133]
Carbamazepine	Voltage-gated sodium channels	Neuronal stabilization	TN	Diabetes and glycaemic control	Poor glycaemic control predicts reduced efficacy	[134]

Mirogabalin	$\alpha 2\delta$ -1 subunit	Selective calcium channel modulation	Taxane-induced neuropathy	Poor response to duloxetine	Alternative or add-on strategy	[135]
Pregabalin	$\alpha 2\delta$ subunit	Central sensitization inhibition	Painful diabetic neuropathy	4-week response trajectory	Early response guides continuation	[136]
Ketamine	NMDA receptor	NMDA receptor antagonism	NP	Descending inhibitory pathway connectivity	Functional connectivity predicts response	[137]
Nortriptyline + morphine	μ -opioid receptor; monoamine transporters	Dual analgesic mechanism	NP	ABCB1 rs1045642 polymorphism	Genotype predicts treatment efficacy	[110]
Topical lidocaine	Voltage-gated sodium channels	Peripheral nociceptor inhibition	Mono-/polyneuropathy	Increased C-nociceptor excitability	Predicts enhanced response	[138]
Lacosamide	Nav1.7 sodium channel	Enhancement of slow inactivation	Nav1.7-related small fibre neuropathy	Gain-of-function mutations	Electrophysiological response predicts efficacy	[139]

6 TRANSLATIONAL CHALLENGES OF MECHANISM-BASED THERAPIES: LESSONS FROM CLINICAL FAILURES

While mechanism-based research has greatly advanced our understanding of NP pathophysiology, translation of promising molecular findings into successful analgesic treatments remains an ongoing challenge. While many targets involved in neuronal excitability, neuroinflammation and neuroimmune regulation have shown analgesic potential in preclinical studies, only a small number of these targets have demonstrated effective clinical translation. This discrepancy between experimental success and clinical application mirrors the heterogeneity of human NP, which is a group of heterogeneous conditions rather than a single disease process. The differences in disease origin, lesion location, sensory phenotypes, molecular changes and personalized treatment responses still make it difficult to develop mechanism-guided therapies [1, 147]. Voltage-gated sodium channel Nav1.7 provides a representative example of the clinical challenges associated with translating genetically validated targets into analgesic therapies. Nav1.7 functions as a regulator of peripheral nociceptive signalling. Strong evidence supporting Nav1.7 as a potential analgesic target has been provided by human genetic studies, showing that gain-of-function mutations in SCN9A can cause inherited pain disorders including primary erythromelalgia and paroxysmal extreme pain disorder in humans, while loss-of-function mutations lead to congenital insensitivity to pain. These results stimulated the exploration of selective Nav1.7 inhibitors as potential therapeutic agents [1, 148]. Despite strong genetic support and promising data from experimental models, multiple Nav1.7 inhibitors have failed to achieve sufficient clinical efficacy. Possible explanations include incomplete target engagement in human tissues, compensatory effects of other sodium channel subtypes, discrepancies between preclinical models and human pain conditions, and the lack of robust biomarkers to identify patients whose pain will respond best. The Nav1.7 experience shows that successful translation requires a biologically attractive target, appropriate patient selection, adequate exposure to the drug tested and clinically meaningful outcome measures.

Similar translational challenges have been encountered with other mechanism-based targets. Nerve growth factor (NGF) signalling represents an attractive therapeutic target because NGF contributes to nociceptor sensitization, inflammatory responses, and pain amplification. Anti-NGF therapies have demonstrated substantial analgesic effects in preclinical studies and clinical trials of osteoarthritis-related pain; however, concerns regarding rapidly progressive osteoarthritis and joint safety have restricted their broader clinical application [149, 150]. These observations underscore that targeting a biologically relevant pathway alone does not necessarily ensure an adequate therapeutic window. Several factors contribute to the

limited translation of mechanism-based analgesics. Current animal models have greatly contributed to the understanding of NP mechanisms; however, they mainly capture specific components of pain-related behaviors, such as stimulus-evoked hypersensitivity, and may not fully reproduce complex human pain experiences, including ongoing spontaneous pain, affective dimensions, and disease heterogeneity. Therefore, improving the clinical relevance of behavioral assessments remains an important challenge for translational pain research [151, 152]. Many candidate targets are involved in physiological neuronal functions, creating difficulties in achieving sufficient analgesia while preserving normal sensory processing. The absence of clinically validated biomarkers limits patient stratification and may obscure therapeutic benefits in biologically defined responder populations [147, 153].

Therefore, future development of mechanism-based therapies should move beyond traditional target-centric approaches toward integrated precision strategies. Combining human-relevant disease models, multi-omics profiling, molecular biomarkers, and clinical phenotyping may facilitate identification of mechanistically distinct NP subgroups. In addition, rational multi-target interventions that simultaneously regulate neuronal excitability, neuroinflammation, and immune-synaptic interactions may provide a more effective approach than single-target inhibition. Such strategies may improve the likelihood of successful translation from experimental discoveries to individualized NP treatment [1].

7 ADJUNCTIVE THERAPEUTIC STRATEGIES

7.1 Integration of non-pharmacological interventions

In the comprehensive management of NP, pharmacotherapy alone is often insufficient to achieve sustained long-term efficacy, and non-pharmacological interventions are increasingly recognized as important adjunctive strategies. Approaches such as physical and exercise-based therapies, acupuncture and electroacupuncture, as well as neuromodulation techniques exert multi-level effects ranging from peripheral repair to central regulation. When combined with pharmacological treatment, these modalities provide complementary benefits and support a more integrated management framework.

Among physical and exercise-based interventions, photobiomodulation therapy (PBMT) and functional exercise demonstrate notable analgesic and rehabilitative potential. PBMT improves mitochondrial function, modulates inflammatory responses, and promotes neural regeneration through light stimulation at specific wavelengths, thereby reducing pain sensitivity. In parallel, aerobic exercise (for example, swimming) alleviates pain by regulating neuroimmune responses, and neural plasticity while preserving muscle function [154]. These findings support the value of multimodal non-pharmacological strategies in NP management.

Increasing evidence has elucidated the molecular and circuit-level mechanisms underlying acupuncture and electroacupuncture-mediated analgesia. Electroacupuncture modulates multiple stress-response and neuroprotective signalling pathways through stimulation of specific acupoints. For instance, it has been shown to inhibit ferroptosis via regulation of the SAT1/ALOX15 pathway, thereby alleviating NP and suggesting ferroptosis as a potential therapeutic target [155]. At acupoints such as Zusanli (ST36) and Baihui (GV20), electroacupuncture-induced analgesia may be associated with suppression of ferroptosis in spinal neurons, partially mediated by activation of the Nrf2 signalling pathway [156]. At the central level, electroacupuncture also modulates functional activity in pain-related brain regions. It has been reported to restore suppressed Tet1 expression in hippocampal neural stem cells (NSCs) and promote adult neurogenesis in the ventral dentate gyrus by alleviating Prox1 hypermethylation, thereby contributing to the long-term antidepressant effects of electroacupuncture in chronic neuropathic pain [157]. In addition, electroacupuncture attenuates NP by inhibiting endoplasmic reticulum stress mediated by BIP and IRE-1 α in the anterior cingulate cortex, highlighting the role of ER stress in pain pathophysiology [158]. Clinically, electroacupuncture has been shown to alleviate multiple NP symptoms, including burning pain, electric shock-like sensations, and mechanical allodynia, while improving psychosocial function and quality of life; however, larger-scale studies are still required to validate its efficacy and generalizability [159].

Electroacupuncture treatment has been shown to provide neuromodulatory effects, and recent advances in neuromodulation have led to increasing attention toward the combination of electroacupuncture with other neuromodulation modalities. Electroacupuncture produces significant antinociceptive effects in models of chronic sciatic nerve compression that are increased by combined stimulation of the infralimbic region of the medial prefrontal cortex (mPFC), suggesting that different neuromodulatory strategies may have synergistic effects [160].

In conclusion, physical and exercise-based treatments, acupuncture and electroacupuncture, and neuromodulation strategies all exert analgesic effects through coordinated regulation of inflammatory responses, cellular stress pathways, and central neural networks. Integration of these non-pharmacological strategies with pharmacotherapy may facilitate a more holistic and individualized treatment paradigm, which could improve pain control as well as affective and behavioural changes associated with chronic pain while also paving the way for integration with psychological and behavioural therapies.

7.2 Synergistic effects of psychological and behavioural interventions

In the comprehensive management of NP, pharmacological treatment alone is often insufficient to achieve satisfactory

symptom control, and the incorporation of non-pharmacological strategies has become an important component of multimodal care. Evidence indicates that, among patients with comorbid anxiety and depression, pharmacological therapies, including antiepileptic and antidepressant agents, remain fundamental treatment options, whereas early integration of non-pharmacological interventions focused on physical activity may provide additional benefits in pain management and recovery from pain-related disability [161]. Accordingly, behavioural interventions and lifestyle-oriented strategies have become important components of multidisciplinary pain management. Patients with NP frequently experience emotional distress, impaired sleep, and reduced physical activity, which may further reinforce pain persistence through complex neuropsychological mechanisms. Structured behavioural approaches, including cognitive-behavioural therapy, graded activity programmes, and pain coping skills training, aim to modify maladaptive pain-related perceptions, reduce catastrophizing, and improve emotional regulation and coping capacity.

Lifestyle interventions also play a meaningful role in the long-term management of chronic pain. Exercise, sleep hygiene, and psychological techniques may modulate pain processing through multiple biological and psychological pathways. Aerobic exercise has been shown to enhance neural plasticity and increase the amplitude of transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEPs), suggesting its involvement in regulating cortical excitability and supporting functional recovery. There is a strong association between sleep disruption and greater pain interference, whereas the relationship between sleep quality and pain severity seems to be bidirectional [162, 163]. Moreover, mindfulness-based interventions have been shown to decrease pain intensity and unpleasantness as well as reduce negative emotional responses to pain [164]. Collectively, these findings indicate that exercise, sleep regulation, and psychological interventions may influence both neural and subjective pain processing and serve as effective adjuncts to NP management.

The rapid development of digital health technologies for behavioural support and self-management of chronic pain has provided additional opportunities as well. Psycho-educational interventions based on combined disease-specific information and multidisciplinary self-management strategies, such as those developed for endometriosis, have been shown to reduce symptom burden, anxiety, depression and NP while improving disease-related knowledge and quality of life [165]. Digital interventions such as mobile applications, web-based learning platforms and remote monitoring systems enable ongoing delivery of pain education, psychosocial support and symptom monitoring, facilitating enhanced patient engagement and tailored management. Combining behavioural therapy, lifestyle modification, and digital interventions may provide additional benefits for long-term outcomes. Such approaches are characterized by a multidisciplinary practice involving medical, psy-

chological and rehabilitation perspectives; thus, their application requires effective collaboration among various health professionals. Patient-centred, team-based care models may ultimately offer a more integrated framework for optimizing NP management while facilitating the delivery of improved and personalized treatment strategies.

7.3 Role of multidisciplinary teams (MDTs) in pain management

The management of NP is inherently multifaceted, and one-discipline-based approaches are often insufficient due to the diverse clinical manifestations and long-term care needs. MDTs offer a more integrated structure by bringing together the expertise of specialists, which fosters comprehensive assessment, collaborative clinical decision-making and personalized treatment approaches. MDTs may enhance the quality of both therapeutic decision-making and the delivery of care for pain through this collaborative model.

Clinical pharmacists within multidisciplinary pain management programmes have become more involved in optimizing pharmacological treatment. Clinical pharmacists involved in interdisciplinary care models have been shown to significantly reduce the overall medication use over five or more follow-up visits for patients undergoing chronic opioid therapy (COT). In addition, pharmacist-led interventions can improve adherence to guideline-recommended prescribing practices, optimize prescriptions with and without an opioid component, and increase access to evidence-based care [166]. Likewise, current guidelines for trigeminal neuralgia (TN) indicate MDT-based methods for both acute and chronic management. These approaches place a greater emphasis on collaborative evaluation and evidence-based decision-making, and treatments can be adapted according to ongoing assessments of clinical outcomes [167].

MDT-based care helps maximize pharmacotherapy, but also has potential benefits for longer-term outcomes in people with chronic pain. Psychological factors are closely associated with changes in pain-related disability, and early assessment of the psychological domain may facilitate earlier and more individualized multidisciplinary interventions [168]. In clinical contexts, MDT approaches combine pharmacologic, psychological, and rehabilitative strategies to deliver integrated pain management. Patients receiving MDT interventions have shown better pain control and improvement in functional outcomes at follow-up compared with conventional care, including a significant reduction in movement-related pain scores at 3 months [169].

In summary, structured multidisciplinary collaboration is an important part of modern NP management. MDTs offer more patient-centered individualized care through a multidisciplinary approach, with expertise spanning clinical, psychologi-

cal, and rehabilitation domains. This model provides an important approach toward advancing more personalized pain management and improving treatment outcomes, although it may vary in its implementation within healthcare settings.

8 DISCUSSION

Recent evidence indicates that NP may be better understood as a complex pathological condition arising from dysregulation of neuro-immune-synaptic networks rather than simply as a consequence of peripheral nerve injury. Following nerve injury, microglia and astrocytes undergo rapid activation, releasing pro-inflammatory mediators while concurrently promoting synaptic plasticity and increasing the excitability of dorsal horn neurons. Enhanced neuronal activity further reinforces neuro-inflammatory signalling, resulting in the establishment of a sustained neuroimmune positive feedback loop. Within this regulatory framework, the Hv1 proton channel has emerged as an important modulatory component. Hv1 contributes to reactive oxygen species (ROS) generation in microglia following spinal nerve transection (SNT), facilitates astrocyte activation, and increases interferon- γ (IFN- γ) expression, ultimately promoting pain hypersensitivity [170]. These findings highlight the potential of targeting neuroimmune interactions and ion channel-mediated signalling pathways as therapeutic strategies for NP.

Despite the availability of multiple pharmacological interventions, the overall therapeutic efficacy of current treatments remains suboptimal. Existing analgesic approaches primarily focus on modulating neurotransmitter systems or reducing neuronal hyperexcitability. For example, the tricyclic antidepressant amitriptyline produces analgesic effects through inhibition of serotonin and noradrenaline reuptake; although approved by the US Food and Drug Administration (FDA) for depression treatment, it is widely used in clinical practice for NP management [171]. Similarly, calcium channel modulators, including gabapentin and pregabalin, are regarded as first-line treatments, with gabapentin demonstrating a favourable balance between analgesic efficacy and tolerability, thereby supporting long-term treatment adherence [172]. Meanwhile, novel ion channel-targeting agents continue to be explored. The voltage-gated sodium channel modulator vixotrigine has demonstrated good tolerability at single doses of up to 825 mg and repeated administration of 450 mg twice daily [173]. In addition, transient receptor potential (TRP) channels are important regulators of peripheral inflammatory pain. Increased TRPV1 expression and reduced TRPM8 activity contribute to enhanced nociceptive signalling, whereas TRPM8 activation can suppress TRPV1 function in DRG neurons, providing a potential mechanism underlying the analgesic effects of menthol [174]. Collectively, these findings suggest that although modulation of specific molecular pathways can provide partial relief in NP, the complex interactions among neuroinflammation, synaptic plasticity, and neural repair processes limit the efficacy of sin-

gle-target interventions. Therefore, therapeutic strategies capable of simultaneously addressing multiple pathological mechanisms may better reflect the biological complexity of NP.

With the advancement of precision medicine, therapeutic strategies for NP are gradually transitioning from empirical treatment toward individualized approaches. Nevertheless, personalized NP management remains at an early stage, largely owing to the limited availability of reliable predictive biomarkers and validated decision-making frameworks. Future studies should focus on integrating multi-omics datasets, clinical phenotypes, and real-world evidence to establish comprehensive patient stratification systems that can facilitate treatment optimization. Furthermore, integrated therapeutic approaches combining multi-target pharmacological interventions, neuroimmune modulation, and regenerative strategies may offer a more effective framework for precision analgesia. The shift from single-mechanism therapies toward network- and system-level regulation will be essential for developing mechanism-based and personalized treatment strategies for NP.

9 LIMITATIONS OF THIS REVIEW

As a narrative review rather than a systematic review or meta-analysis, this study may be subject to potential selection and interpretation bias, and quantitative estimates of therapeutic efficacy were not performed. Although systematic reviews and meta-analyses have generated important evidence regarding pharmacological interventions for NP, substantial heterogeneity remains across studies, including differences in disease etiology, diagnostic criteria, treatment duration, and outcome measurements, which limits direct comparisons among therapeutic strategies [1, 27]. The evidence summarized in this Review spans multiple stages of therapeutic development, from cellular and animal experiments to early clinical investigations and established treatment approaches. These distinct levels of evidence should be interpreted according to their respective translational contexts rather than being considered directly comparable.

Importantly, many mechanism-based targets that demonstrate efficacy in experimental models have failed to achieve successful clinical translation, largely due to discrepancies between preclinical models and human NP conditions, insufficient target specificity, and the absence of reliable biomarkers for identifying responsive patient populations [151, 175]. Several emerging therapeutic strategies, including stem cell-based therapies, exosome-derived products, nanomedicine, pharmacogenomics-guided interventions, and closed-loop neuromodulation, are currently being actively explored. Although these approaches have demonstrated encouraging biological effects in preclinical models and early-stage clinical studies, their widespread clinical implementation will require further evidence regarding long-term efficacy, safety profiles, manufacturing consistency, and cost-effectiveness. Nanomedicine, in

particular, has shown considerable potential for improving drug targeting and enhancing therapeutic bioavailability. However, challenges associated with *in vivo* distribution, large-scale manufacturing, regulatory approval, and long-term safety evaluation remain major barriers limiting clinical translation [107, 108]. Similarly, pharmacogenomic strategies designed to guide analgesic selection require additional prospective clinical validation before they can be routinely integrated into NP management [176]. NP represents a biologically diverse group of disorders caused by multiple etiologies, including peripheral nerve injury, diabetes, chemotherapy, infection, and SCI. The considerable variation in clinical manifestations, underlying molecular mechanisms, and treatment responsiveness suggests that mechanism-based therapies are unlikely to provide consistent benefits across all patients without reliable approaches for patient stratification [153]. Future studies combining detailed clinical phenotyping, molecular biomarker identification, multi-omics profiling, and prospective clinical validation will be critical for refining patient classification and advancing more individualized therapeutic strategies for NP.

10 CONCLUSION

NP is a biologically heterogeneous condition, arising from complex interactions among neuronal hyperexcitability, neuroimmune activation, glial dysfunction, synaptic plasticity and pain-processing network remodeling. While conventional pharmacological therapies still constitute the core of clinical management, their suboptimal efficacy and the unwanted side effects associated with treatment indicate a necessity for therapeutic approaches more closely tailored to the underlying disease processes. In this Review, we assess recent advances in pharmacological therapies and novel approaches to alleviate NP within a mechanism-to-translation framework. Instead of focusing on experimental effectiveness alone in appraising potential therapies, we use a broader framework that integrates biological plausibility, strength of evidence, clinical feasibility, and translational limitations. This viewpoint highlights that for the successful development of NP treatments, not only do promising molecular targets need to be discovered but responsive patient populations need to be precisely defined and predictive biomarkers need to be established, which requires a more concerted effort.

Although there has been great progress in understanding NP pathophysiology, translating mechanism-based discoveries into effective clinical therapies remains challenging. Numerous promising targets identified in preclinical studies have failed to translate into substantial clinical benefit, which likely highlights issues in disease modeling, target selectivity, and the significant inter-patient NP heterogeneity. Novel strategies such as stem cell therapies, nanomedicine approaches, pharmacogenomics-guided methods and closed-loop neuromodulation appear to offer exciting avenues for future therapy but need to be validated in well-designed studies prior to widespread clinical

cal application. The future management of NP will likely depend on the combination of mechanistic classification, molecular biomarkers, multi-omic approaches and detailed clinical phenotyping in order to provide a better basis for precision medicine. Adopting approaches that target mechanisms involved in neuropathic pain rather than relying on empirically driven interventions for the management of clinical symptoms may lead to enhanced outcomes and reduce the substantial burden associated with chronic NP.

ABBREVIATIONS

BLA, Basolateral amygdala; BPA, Bisphenol A; CLBP, Chronic low back pain; CL-SCS, Closed-loop spinal cord stimulation; CLU, Clusterin; COT, chronic opioid therapy; COX, Cyclooxygenase; DEGs, Differentially expressed genes; DRG, dorsal root ganglia; ECAP, Evoked compound action potential; eEF2K, Eukaryotic elongation factor 2 kinase; FDA, Food and Drug Administration; FDCs, Fixed-dose combinations; HUC-MSCs, Human umbilical cord-derived MSCs; IFN- γ , interferon- γ ; ITDD, Intrathecal drug delivery; KYNA, Kynurenic acid; MDTs, Multidisciplinary teams; MEPs, Motor evoked potentials; mGluR5, metabotropic glutamate receptor 5; mPFC, Medial prefrontal cortex; MSCs, Mesenchymal stem cells; NGF, Nerve growth factor; NMDARs, NMDA receptors; NP, Neuropathic pain; NSAIDs, Nonsteroidal anti-inflammatory drugs; PAG, Periaqueductal grey; PBMT, Photobiomodulation therapy; PHN, Postherpetic neuralgia; PPARG, Peroxisome proliferator-activated receptor- γ ; QA, Quinolinic acid; ROS, reactive oxygen species; SCI, Spinal cord injury; SNPs, Single-nucleotide polymorphisms; SNT, spinal nerve transection; STAT3, signal transducer and activator of transcription 3; SVM, Support vector machine; TMS, Transcranial magnetic stimulation; TN, trigeminal neuralgia; TRP, Transient receptor potential.

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Author contributions

Rui Zhao conceived the review topic, performed the literature search and analysis, drafted and revised the manuscript, prepared the figures, and approved the final version of the manuscript.

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Ethics approval and consent to participate

Not applicable. This manuscript does not contain any studies involving human participants or animals performed by any of the authors.

Consent for publication

Not applicable. This manuscript does not include details, images, or videos relating to an individual person.

Competing interests

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REFERENCES

- [1] Finnerup NB, Kuner R, Jensen TS. Neuropathic pain: From mechanisms to treatment. *Physiol Rev*. 2021 Jan 1;101(1):259-301. <https://doi.org/10.1152/physrev.00045.2019>
- [2] DiBonaventura MD, Sadosky A, Concialdi K, Hopps M, Kudel I, Parsons B, et al. The prevalence of probable neuropathic pain in the US: Results from a multimodal general-population health survey. *J Pain Res*. 2017 Nov 1;10:2525-2538. <https://doi.org/10.2147/JPR.S127014>
- [3] Kaye AD, Armistead G, Amedio LS, Manthei ME, Ahmadzadeh S, Bernhardt B, et al. Evolving treatment strategies for neuropathic pain: A narrative review. *Medicina (Kaunas)*. 2025 Jun 10;61(6):1063. <https://doi.org/10.3390/medicina61061063>
- [4] Wang L, Gunduz MA, Semeano AT, Yilmaz EC, Alanazi FAH, Imir OB, et al. Coexistence of chronic hyperalgesia and multilevel neuroinflammatory responses after experimental SCI: A systematic approach to profiling neuropathic pain. *J Neuroinflammation*. 2022 Oct 29;19(1):264. <https://doi.org/10.1186/s12974-022-02628-2>
- [5] Gryzlo B, Zareba P, Malawska K, Mazur G, Rapacz A, La Tka K, et al. Novel functionalized amino acids as inhibitors of GABA transporters with analgesic activity. *ACS Chem Neurosci*. 2021 Aug 18;12(16):3073-3100. <https://doi.org/10.1021/acscchemneuro.1c00351>
- [6] Xian H, Guo H, Liu Y, Ma S, Zhao R, Zhang J, et al. Nociceptor-localized KCC2 suppresses brachial plexus avulsion-induced neuropathic pain and related central sensitization. *Cell Biosci*. 2025 Jan 31;15(1):12. <https://doi.org/10.1186/s13578-025-01354-5>
- [7] Narasimhan KKS, Chettiar PB, Kiritoshi T, Ji G, Neugebauer V, Dravid SM. Trans-synaptic signaling through GRID1/glutamate receptor delta-1 and CBLN1/cerebellin-1 facilitates autophagic flux in central amygdala and prevents chronic pain. *Autophagy*. 2025 Dec;21(12):3216-3239. <https://doi.org/10.1080/15548627.2025.2574968>
- [8] Xiong W, Ping X, Ripsch MS, Chavez GSC, Hannon HE, Jiang K, et al. Enhancing excitatory activity of somatosensory cortex

- alleviates neuropathic pain through regulating homeostatic plasticity. *Sci Rep*. 2017 Oct 6;7(1):12743. <https://doi.org/10.1038/s41598-017-12972-6>
- [9] Chen S, Jin X, Pan H. Endogenous nitric oxide inhibits spinal NMDA receptor activity and pain hypersensitivity induced by nerve injury. *Neuropharmacology*. 2017 Oct;125:156-165. <https://doi.org/10.1016/j.neuropharm.2017.07.023>
- [10] Gu N, Makashova O, Laporte C, Chen C, Li B, Chevillard PM, et al. Microglia regulate neuronal activity via structural remodeling of astrocytes. *Neuron*. 2025 Oct 15;113(20):3408-3423. e5. <https://doi.org/10.1016/j.neuron.2025.07.024>
- [11] Hua T, Yang M, Song H, Kong E, Deng M, Li Y, et al. HucMSCs-derived exosomes attenuate inflammatory pain by regulating microglia pyroptosis and autophagy via the miR-146a-5p/TRAF6 axis. *J Nanobiotechnology*. 2022 Jul 14;20(1):324. <https://doi.org/10.1186/s12951-022-01522-6>
- [12] Gladulich LFH, Peixoto-Rodrigues MC, Campello-Costa P, Paes-de-Carvalho R, Cossenza M. NMDA-induced nitric oxide generation and CREB activation in central nervous system is dependent on eukaryotic elongation factor 2 kinase. *Biochim Biophys Acta Mol Cell Res*. 2020 Oct;1867(10):118783. <https://doi.org/10.1016/j.bbamer.2020.118783>
- [13] Kong E, Li Y, Deng M, Hua T, Yang M, Li J, et al. Glycometabolism reprogramming of glial cells in central nervous system: Novel target for neuropathic pain. *Front Immunol*. 2022 May 20;13:861290. <https://doi.org/10.3389/fimmu.2022.861290>
- [14] Lee SO, Kuthati Y, Huang WH, Wong CS. Semaglutide ameliorates diabetic neuropathic pain by inhibiting neuroinflammation in the spinal cord. *Cells*. 2024 Nov 8;13(22):1857. <https://doi.org/10.3390/cells13221857>
- [15] Hua T, Kong E, Zhang H, Lu J, Huang K, Ding R, et al. PRMT6 deficiency or inhibition alleviates neuropathic pain by decreasing glycolysis and inflammation in microglia. *Brain Behav Immun*. 2024 May;118:101-114. <https://doi.org/10.1016/j.bbi.2024.02.027>
- [16] Tang J, Chen Q, Xiang L, Tu T, Zhang Y, Ou C. TRIM28 fosters microglia ferroptosis via autophagy modulation to enhance neuropathic pain and neuroinflammation. *Mol Neurobiol*. 2024 Nov;61(11):9459-9477. <https://doi.org/10.1007/s12035-024-04133-4>
- [17] Ruan S, Jia R, Hu L, Liu Y, Tian Q, Jiang K, et al. Ozone promotes macrophage efferocytosis and alleviates neuropathic pain by activating the AMPK/Gas6-MerTK/SOCS3 signaling pathway. *Front Immunol*. 2024 Nov 19;15:1455771. <https://doi.org/10.3389/fimmu.2024.1455771>
- [18] Wang R, Yue C, Cong F, Lou Y, Liu Y, Xu C, et al. A sustained-release gel alleviates neuropathic pain in SNI mice by reversing Glu/GABA imbalance and chloride efflux disorders. *Int J Biol Macromol*. 2025 Jan;286:138501. <https://doi.org/10.1016/j.ijbiomac.2024.138501>
- [19] Kadam SD, Hegarty SV. Development of KCC2 therapeutics to treat neurological disorders. *Front Mol Neurosci*. 2024 Dec 10;17:1503070. <https://doi.org/10.3389/fnmol.2024.1503070>
- [20] Ding X, Wang W, Ding Z, Liu Y, Zhong J, Chen H. Impact of Botox-A SNAP-25 protein expression and the mechanism of inhibitory neurotransmitter imbalance in chronic sciatic nerve pain rat model. *Exp Ther Med*. 2017 Jun;13(6):2783-2786. <https://doi.org/10.3892/etm.2017.4351>
- [21] Ferreira MV, Jesus CHA, Bonfim da Costa JP, Oliveira G, Liebl B, Verri Junior W, et al. Aspirin-triggered lipoxin A4 reduces neuropathic pain and anxiety-like behaviours in male diabetic rats: Antinociceptive enhancement by cannabinoid receptor agonists. *Eur J Pharmacol*. 2025 Feb 15;989:177254. <https://doi.org/10.1016/j.ejphar.2025.177254>
- [22] Debbag S, Yalcinkaya A, Saricaoglu F. Nociceptive improvements and kynurenine pathway alterations with diclofenac treatment in a rat model of neuropathic pain created by partial sciatic nerve ligation. *Eur Rev Med Pharmacol Sci*. 2023 May;27(9):4239-4247. https://doi.org/10.26355/eurrev_202305_32334
- [23] Grovle L, Hasvik E, Holst R, Saetre A, Brox JI, Mathiassen S, et al. Efficacy of naproxen in patients with sciatica: Multicenter, randomized, double-blind, placebo-controlled trial. *Pain*. 2024 Nov 1;165(11):2606-2614. <https://doi.org/10.1097/j.pain.0000000000003280>
- [24] Hung KKC, Lam RPK, Lee HKH, Choi YF, Tenney J, Zuo Z, et al. Comparison of diclofenac with tramadol, tizanidine or placebo in the treatment of acute low back pain and sciatica: Multi-center randomized controlled trial. *Postgrad Med J*. 2024 Oct;100(1188):741-750. <https://doi.org/10.1093/postmj/qgae052>
- [25] Koes BW, van Tulder MW, Peul WC. Diagnosis and treatment of sciatica. *BMJ*. 2007 Jun 23;334(7607):1313-1317. <https://doi.org/10.1136/bmj.39223.428495.BE>
- [26] Schmid AB, Tampin B, Baron R, Finnerup NB, Hansson P, Hietaharju A, et al. Recommendations for terminology and the identification of neuropathic pain in people with spine-related leg pain. Outcomes from the NeuPSIG working group. *Pain*. 2023 Aug 1;164(8):1693-1704. <https://doi.org/10.1097/j.pain.0000000000002919>
- [27] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol*. 2015 Feb;14(2):162-173. [https://doi.org/10.1016/S1474-4422\(14\)70251-0](https://doi.org/10.1016/S1474-4422(14)70251-0)
- [28] Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev*. 2017 Aug 2;8(8):CD012537. <https://doi.org/10.1002/14651858.CD012537.pub2>
- [29] Derry S, Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T, et al. Topical analgesics for acute and chronic pain in adults - an overview of cochrane reviews. *Cochrane Database Syst Rev*. 2017 May 12;5(5):CD008609. <https://doi.org/10.1002/14651858.CD008609.pub2>
- [30] Gadepalli A, Ummadisetty O, Akhilesh, Chouhan D, Anmol, Tiwari V. Loperamide, a peripheral Mu-Opioid receptor agonist, attenuates chemotherapy-induced neuropathic pain in rats. *Int Immunopharmacol*. 2023 Nov;124(Pt B):110944. <https://doi.org/10.1016/j.intimp.2023.110944>

- [31] Kawai S, Hasegawa J, Ito H, Fukuuchi Y, Nakano H, Ohtani H, et al. Efficacy and safety of twice-daily tramadol hydrochloride bilayer sustained-release tablets with an immediate release component for postherpetic neuralgia: Results of a Phase III, randomized, double-blind, placebo-controlled, treatment-withdrawal study. *Pain Pract.* 2023 Mar;23(3):277-289. <https://doi.org/10.1111/papr.13190>
- [32] Sugiyama Y, Kataoka T, Tasaki Y, Kondo Y, Sato N, Naiki T, et al. Efficacy of tapentadol for first-line opioid-resistant neuropathic pain in Japan. *Jpn J Clin Oncol.* 2018 Apr 1;48(4):362-366. <https://doi.org/10.1093/jjco/hyy023>
- [33] Pentiado Junior JAM, Barbosa MM, Kubota GT, Martins PN, Moreira LI, Fernandes AM, et al. METHA-NeP: Effectiveness and safety of methadone for neuropathic pain: A controlled randomized trial. *Pain.* 2025 Mar 1;166(3):557-570. <https://doi.org/10.1097/j.pain.0000000000003413>
- [34] Jouvenel A, Tassou A, Thouaye M, Ruel J, Antri M, Leyris JP, et al. FLT3 signaling inhibition abrogates opioid tolerance and hyperalgesia while preserving analgesia. *Nat Commun.* 2024 Nov 7;15(1):9633. <https://doi.org/10.1038/s41467-024-54054-y>
- [35] Angst MS, Clark JD. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology.* 2006 Mar;104(3):570-587. <https://doi.org/10.1097/00000542-200603000-00025>
- [36] Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician.* 2011 Mar-Apr;14(2):145-161. <https://doi.org/10.36076/ppj.2011/14/145>
- [37] Roeckel LA, Le Coz GM, Gaveriaux-Ruff C, Simonin F. Opioid-induced hyperalgesia: Cellular and molecular mechanisms. *Neuroscience.* 2016 Dec 3;338:160-182. <https://doi.org/10.1016/j.neuroscience.2016.06.029>
- [38] Zarei M, Sabetkasaei M, Moini-Zanjani T. Effect of paroxetine on the neuropathic pain: A molecular study. *Iran Biomed J.* 2020 Sep;24(5):306-313. <https://doi.org/10.29252/ibj.24.5.301>
- [39] Wang L, Zhao S, Shao J, Su C. The effect and mechanism of low-dose esketamine in neuropathic pain-related depression-like behavior in rats. *Brain Res.* 2024 Nov 15;1843:149117. <https://doi.org/10.1016/j.brainres.2024.149117>
- [40] K K, Dutt S, Rattan P, Dadhania A, Gupta R, Joshi D, et al. Fixed dose combination of low dose pregabalin and duloxetine, or pregabalin monotherapy for neuropathic pain: A double-blind, randomized, parallel-group study. *F1000Res.* 2023 Mar 30;12:353. <https://doi.org/10.12688/f1000research.130345.1>
- [41] Oggianu L, Garrone B, Fiorentini F, Del Bene F, Rosignoli MT, Di Giorgio FP, et al. PK/PD analysis of trazodone and gabapentin in neuropathic pain rodent models: Translational PK-PD modeling from nonclinical to clinical development. *Clin Transl Sci.* 2023 Apr;16(4):606-617. <https://doi.org/10.1111/cts.13472>
- [42] Li D, Lee JH, Choi CW, Kim J, Kim SK, Kim W. The analgesic effect of venlafaxine and its mechanism on oxaliplatin-induced neuropathic pain in mice. *Int J Mol Sci.* 2019 Apr 3;20(7):1652. <https://doi.org/10.3390/ijms20071652>
- [43] Todorovic M, Micov A, Nastic K, Tomic M, Pecikoza U, Vukovic M, et al. Vortioxetine as an analgesic in preclinical inflammatory pain models: Mechanism of action. *Fundam Clin Pharmacol.* 2022 Apr;36(2):237-249. <https://doi.org/10.1111/fcp.12737>
- [44] Hussein A, Digges M, Chang S, Hunt J, Doogue M, Rowett D, et al. Pharmacovigilance in hospice/palliative care: Net effect of amitriptyline or nortriptyline on neuropathic pain: UTS/IMPACCT rapid programme international consecutive cohort. *Palliat Med.* 2022 Jun;36(6):938-944. <https://doi.org/10.1177/02692163221085855>
- [45] Royds J, Cassidy H, Conroy MJ, Dunne MR, Lysaght J, McCrory C. Examination and characterisation of the effect of amitriptyline therapy for chronic neuropathic pain on neuropeptide and proteomic constituents of human cerebrospinal fluid. *Brain Behav Immun Health.* 2020 Dec 7;10:100184. <https://doi.org/10.1016/j.bbih.2020.100184>
- [46] Nayak MK, Kapadia JD, Desai CK, Desai MK, Shah BJ. An evaluation of efficacy and safety of commonly prescribed drugs and effect of these drugs on quality of sleep in patients suffering from zoster-associated pain. *J Clin Pharmacol.* 2018 Nov;58(11):1406-1417. <https://doi.org/10.1002/jcph.1255>
- [47] Luo ZD, Calcutt NA, Higuera ES, Valder CR, Song YH, Svensson CI, et al. Injury type-specific calcium channel alpha 2 delta-1 subunit up-regulation in rat neuropathic pain models correlates with antiallodynic effects of gabapentin. *J Pharmacol Exp Ther.* 2002 Dec;303(3):1199-1205. <https://doi.org/10.1124/jpet.102.041574>
- [48] Tao L, Yin D, Xie J. Comparative effectiveness of gabapentin and pregabalin combination therapy in postherpetic neuralgia: A single-masked randomised controlled trial. *J Coll Physicians Surg Pak.* 2025 Sep;35(9):1122-1127. <https://doi.org/10.29271/jcpsp.2025.09.1122>
- [49] Zhou MH, Chen SR, Jin D, Huang Y, Chen H, Chen G, et al. Spinal $\alpha 2\delta$ -1 induces GluA3 degradation to regulate assembly of calcium-permeable AMPA receptors and pain hypersensitivity. *J Clin Invest.* 2025 Oct 23;136(1):e193349. <https://doi.org/10.1172/jci193349>
- [50] Patel R, Kucharczyk M, Montagut-Bordas C, Lockwood S, Dickenson AH. Neuropathy following spinal nerve injury shares features with the irritable nociceptor phenotype: A back-translational study of oxcarbazepine. *Eur J Pain.* 2019 Jan;23(1):183-197. <https://doi.org/10.1002/ejp.1300>
- [51] Worm J, Jorgensen IF, Davidsson OB, Hjalgrim H, Roder T, Ostrowski SR, et al. Trigeminal neuralgia and its comorbidities: A nationwide disease trajectory study. *Pain.* 2025 Apr 1;166(4):879-887. <https://doi.org/10.1097/j.pain.0000000000003428>
- [52] Dasari PC, Chandu A, Bodala M, Bandaru SP, Chundu UC, Nelluri PS, et al. Comparative cohort study of pregabalin nortriptyline and pregabalin duloxetine in the management of diabetic peripheral neuropathic pain. *Sci Rep.* 2025 Dec 17;15(1):43980. <https://doi.org/10.1038/s41598-025-27617-2>
- [53] Osama M, Javaid M, Shahid B, Heema, Jamali AG, Anwar B, et al. Efficacy of duloxetine in the management of diabetic neuropathy: A prospective observational cohort study. *Cureus.* 2025 Apr 16;17(4):e82382. <https://doi.org/10.7759/cureus.82382>
- [54] Jiang J, Li Y, Shen Q, Rong X, Huang X, Li H, et al. Effect of pregabalin on radiotherapy-related neuropathic pain in patients

- with head and neck cancer: A randomized controlled trial. *J Clin Oncol*. 2019 Jan 10;37(2):135-143. <https://doi.org/10.1200/JCO.18.00896>
- [55] Li N, Li C, Han R, Wang Y, Yang M, Wang H, et al. LPM580098, a novel triple reuptake inhibitor of serotonin, noradrenaline, and dopamine, attenuates neuropathic pain. *Front Pharmacol*. 2019 Feb 14;10:53. <https://doi.org/10.3389/fphar.2019.00053>
- [56] Genevois AL, Ruel J, Penalba V, Hatton S, Petitfils C, Ducrocq M, et al. Analgesic effects of topical amitriptyline in patients with chemotherapy-induced peripheral neuropathy: Mechanistic insights from studies in mice. *J Pain*. 2021 Apr;22(4):440-453. <https://doi.org/10.1016/j.jpain.2020.11.002>
- [57] Lebel A, Da Silva Vieira D, Boucher Y. Topical amitriptyline in burning mouth syndrome: A retrospective real-world evidence study. *Headache*. 2024 Oct;64(9):1167-1173. <https://doi.org/10.1111/head.14818>
- [58] Markman J, Resnick M, Greenberg S, Katz N, Yang R, Scavone J, et al. Efficacy of pregabalin in post-traumatic peripheral neuropathic pain: A randomized, double-blind, placebo-controlled phase 3 trial. *J Neurol*. 2018 Dec;265(12):2815-2824. <https://doi.org/10.1007/s00415-018-9063-9>
- [59] Kremer M, Yalcin I, Nexon L, Wurtz X, Ceredig RA, Daniel D, et al. The antiallodynic action of pregabalin in neuropathic pain is independent from the opioid system. *Mol Pain*. 2016 Mar 29;12:1744806916633477. <https://doi.org/10.1177/1744806916633477>
- [60] Wang Y, Shrestha N, Shen Y, Luo F. Effectiveness and safety of flupentixol and melitracen tablets for the treatment of patients with persistent idiopathic facial pain: A retrospective observational study. *Pain Physician*. 2024 May;27(4):263-272. <https://doi.org/10.36076/ppj.2024.7.263>
- [61] Guo X, Zhang T, Yuan G, Zeng W, Hu Q, Ma J, et al. GABA analogue HSK16149 in chinese patients with diabetic peripheral neuropathic pain: A phase 3 randomized clinical trial. *JAMA Netw Open*. 2024 Aug 1;7(8):e2425614. <https://doi.org/10.1001/jamanetworkopen.2024.25614>
- [62] Suzuki H, Kaito T, Nakashima H, Takahashi H, Yamamoto S, Tabata S, et al. Efficacy and safety of mirogabalin as an add-on to nonsteroidal anti-inflammatory drugs for neuropathic pain caused by lumbar disc herniation: A randomized controlled study (Miro-Hers). *Pain Ther*. 2025 Dec;14(6):1879-1898. <https://doi.org/10.1007/s40122-025-00776-w>
- [63] Baba M, Matsui N, Kuroha M, Wasaki Y, Ohwada S. Mirogabalin for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo-controlled phase iii study in Asian patients. *J Diabetes Investig*. 2019 Sep;10(5):1299-1306. <https://doi.org/10.1111/jdi.13013>
- [64] Hirai T, Okawa A, Takahashi H, Shiosakai K, Yoshii T; Miro-Cens investigators. Efficacy and safety of mirogabalin in patients with neuropathic pain due to cervical spondylotic radiculopathy: Miro-Cens, a randomized, controlled, interventional study. *Pain Ther*. 2025 Jun;14(3):1063-1079. <https://doi.org/10.1007/s40122-025-00722-w>
- [65] Kremer M, Yalcin I, Goumon Y, Wurtz X, Nexon L, Daniel D, et al. A dual noradrenergic mechanism for the relief of neuropathic allodynia by the antidepressant drugs duloxetine and amitriptyline. *J Neurosci*. 2018 Nov 14;38(46):9934-9954. <https://doi.org/10.1523/JNEUROSCI.1004-18.2018>
- [66] Nepal R, Bajracharya MR, Karki BB, Mall D, Shrestha PS, Wasti KP, et al. Amitriptyline, pregabalin and duloxetine for treatment of painful diabetic peripheral neuropathy. *J Nepal Health Res Counc*. 2024 Jun 22;22(1):185-191. <https://doi.org/10.33314/jnhrc.v22i01.5120>
- [67] Shaheen A, Alam SM, Azam F, Khan M, Ahmad Saleem S, Liaquat A, et al. Influence of single nucleotide polymorphism of LAT1 on therapeutic response to gabapentinoids in Pakistani patients with neuropathic pain. *Basic Clin Pharmacol Toxicol*. 2021 Mar;128(3):503-510. <https://doi.org/10.1111/bcpt.13534>
- [68] Carmlund ME, Kreutzfeldt MD, Holbech JV, Brask-Thomsen PK, Kroigard T, Hansen PN, et al. The effect of lacosamide in peripheral neuropathic pain: A randomized, double-blind, placebo-controlled, phenotype-stratified trial. *Eur J Pain*. 2024 Jan;28(1):105-119. <https://doi.org/10.1002/ejp.2165>
- [69] Gray E, Ye X, Wang Y, Wang S. Cost-effectiveness of mirogabalin for the treatment of diabetic peripheral neuropathic pain in Taiwan. *Value Health Reg Issues*. 2021 May;24:148-156. <https://doi.org/10.1016/j.vhri.2020.10.003>
- [70] Tetsunaga T, Tetsunaga T, Nishida K, Misawa H, Takigawa T, Yamane K, et al. Short-term outcomes of mirogabalin in patients with peripheral neuropathic pain: A retrospective study. *J Orthop Surg Res*. 2020 May 26;15(1):191. <https://doi.org/10.1186/s13018-020-01709-3>
- [71] Lappichetpaiboon P, Tiamkao S, Ruangsri S, Paphangkorakit J, Pitiphat W, Jorns TP. Efficacy and safety of lacosamide in patients with trigeminal neuralgia: An 8-week pilot dose-escalation study. *J Oral Facial Pain Headache*. 2025 Mar;39(1):119-127. <https://doi.org/10.22514/jofph.2025.011>
- [72] Pan T, Ma J, Li Y, Wang K, Jiang C, Zhang Y, et al. Rapid onset of pain relief with crisugabalin in patients with diabetic peripheral neuropathic pain: Findings from a multicenter, randomized, double-blind, controlled study. *Pain Ther*. 2025 Aug;14(4):1311-1329. <https://doi.org/10.1007/s40122-025-00745-3>
- [73] Gou X, Yu X, Bai D, Tan B, Cao P, Qian M, et al. Pharmacology and mechanism of action of HSK16149, a selective ligand of alpha2delta subunit of voltage-gated calcium channel with analgesic activity in animal models of chronic pain. *J Pharmacol Exp Ther*. 2021 Mar;376(3):330-337. <https://doi.org/10.1124/jpet.120.000315>
- [74] Kataria R, Kadal KK, Shanmugam S, Setya P. A comparative study on the efficacy, safety and cost effectiveness of gabapentin and pregabalin in the treatment of neuropathic pain. *Cureus*. 2025 Nov 1;17(11):e95916. <https://doi.org/10.7759/cureus.95916>
- [75] Hamed SA. Sexual dysfunctions induced by pregabalin. *Clin Neuropharmacol*. 2018 Jul/Aug;41(4):116-122. <https://doi.org/10.1097/WNF.0000000000000286>
- [76] Shi Y, Song C. Effectiveness and safety of gabapentin versus pregabalin in the treatment of postherpetic neuralgia: A retrospective cohort study. *Br J Hosp Med (Lond)*. 2024 Dec 30;85(12):1-11. <https://doi.org/10.12968/hmed.2024.0485>

- [77] Matsuoka H, Iwase S, Miyaji T, Kawaguchi T, Ariyoshi K, Oyamada S, et al. Additive duloxetine for cancer-related neuropathic pain nonresponsive or intolerant to opioid-pregabalin therapy: A randomized controlled trial (JORTC-PAL08). *J Pain Symptom Manage*. 2019 Oct;58(4):645-653. <https://doi.org/10.1016/j.jpainsymman.2019.06.020>
- [78] Jha S, Sahani OP, Siddiqui S, Verma MK, Mazumder A, Waghdhare S. Effectiveness of pregabalin compared to duloxetine in diabetic peripheral neuropathic pain: An observational study. *J Assoc Physicians India*. 2019 Nov;67(11):32-36.
- [79] Iseppon F, Luiz AP, Linley JE, Wood JN. Pregabalin silences oxaliplatin-activated sensory neurons to relieve cold allodynia. *eNeuro*. 2023 Feb 21;10(2):ENEURO.0395-22.2022. <https://doi.org/10.1523/eneuro.0395-22.2022>
- [80] Gao C, Zhao Y, Yang T, Gao X, Meng C. Duhuo Jisheng decoction alleviates neuroinflammation and neuropathic pain by suppressing microglial M1 polarization: A network pharmacology research. *J Orthop Surg Res*. 2023 Aug 28;18(1):629. <https://doi.org/10.1186/s13018-023-04121-9>
- [81] Wang B, Le D, Liu L, Zhang X, Yang F, Lai G, et al. Targeting exosomal double-stranded RNA-TLR3 signaling pathway attenuates morphine tolerance and hyperalgesia. *Cell Rep Med*. 2024 Oct 15;5(10):101782. <https://doi.org/10.1016/j.xcrm.2024.101782>
- [82] Hernangomez M, Klusakova I, Joukal M, Hradilova-Svizenska I, Guaza C, Dubovy P. CD200R1 agonist attenuates glial activation, inflammatory reactions, and hypersensitivity immediately after its intrathecal application in a rat neuropathic pain model. *J Neuroinflammation*. 2016 Feb 18;13:43. <https://doi.org/10.1186/s12974-016-0508-8>
- [83] Wu W, Zhang X, Wang S, Li T, Hao Q, Li S, et al. Pharmacological inhibition of the cGAS-STING signaling pathway suppresses microglial M1-polarization in the spinal cord and attenuates neuropathic pain. *Neuropharmacology*. 2022 Oct 1;217:109206. <https://doi.org/10.1016/j.neuropharm.2022.109206>
- [84] Cheng H, Chen N, Tang Y, Shih P, Chen W, Chiu Y, et al. Intrathecal STAT3 inhibitor Bt354 ameliorates chronic constriction injury-induced nociceptive sensitization by modulating neuroinflammation. *Neurotherapeutics*. 2025 Oct;22(6):e00763. <https://doi.org/10.1016/j.neurot.2025.e00763>
- [85] Zong Y, Cao R, Li Y, Hou W, Li S, Xu L, et al. [Mongolian medicine Naru-3 reduces neuroinflammation in maintenance stage of neuropathic pain by inhibiting astrocyte activation]. *China J Chin Mater Med*. 2024 Jun;49(11):2991-3001. <https://doi.org/10.19540/j.cnki.cjcmm.20240204.401>
- [86] Huang J, Zhou T, Sun Y, Ma Y, Deng Y, Chen K, et al. Mesenchymal stromal cells play an analgesic role through a Npy2r sensory neuron-mediated lung-to-brain axis. *Adv Sci (Weinh)*. 2025 Nov;12(43):e04922. <https://doi.org/10.1002/adv.202504922>
- [87] Chen C, Chen F, Yao C, Shu S, Feng J, Hu X, et al. Intrathecal injection of human umbilical cord-derived mesenchymal stem cells ameliorates neuropathic pain in rats. *Neurochem Res*. 2016 Dec;41(12):3250-3260. <https://doi.org/10.1007/s11064-016-2051-5>
- [88] Tashiro S, Nishimura S, Shinozaki M, Takano M, Konomi T, Tsuji O, et al. The amelioration of pain-related behavior in mice with chronic spinal cord injury treated with neural stem/progenitor cell transplantation combined with treadmill training. *J Neurotrauma*. 2018 Nov 1;35(21):2561-2571. <https://doi.org/10.1089/neu.2017.5537>
- [89] Pieczonka K, Nakashima H, Nagoshi N, Yokota K, Hong J, Badner A, et al. Human spinal oligodendrogenic neural progenitor cells enhance pathophysiological outcomes and functional recovery in a clinically relevant cervical spinal cord injury rat model. *Stem Cells Transl Med*. 2023 Sep 15;12(9):603-616. <https://doi.org/10.1093/stcltm/szad044>
- [90] Poongodi R, Yang T, Huang Y, Yang K, Chen H, Chu T, et al. Stem cell exosome-loaded Gelfoam improves locomotor dysfunction and neuropathic pain in a rat model of spinal cord injury. *Stem Cell Res Ther*. 2024 May 20;15(1):143. <https://doi.org/10.1186/s13287-024-03758-5>
- [91] Trounson A, McDonald C. Stem cell therapies in clinical trials: Progress and challenges. *Cell Stem Cell*. 2015 Jul 2;17(1):11-22. <https://doi.org/10.1016/j.stem.2015.06.007>
- [92] Uccelli A, Laroni A, Freedman MS. Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological diseases. *Lancet Neurol*. 2011 Jul;10(7):649-656. [https://doi.org/10.1016/S1474-4422\(11\)70121-1](https://doi.org/10.1016/S1474-4422(11)70121-1)
- [93] Galipeau J, Sensebe L. Mesenchymal stromal cells: Clinical challenges and therapeutic opportunities. *Cell Stem Cell*. 2018 Jun 1;22(6):824-833. <https://doi.org/10.1016/j.stem.2018.05.004>
- [94] Shang Z, Wang M, Zhang B, Wang X, Wanyan P. Clinical translation of stem cell therapy for spinal cord injury still premature: Results from a single-arm meta-analysis based on 62 clinical trials. *BMC Med*. 2022 Sep 5;20(1):284. <https://doi.org/10.1186/s12916-022-02482-2>
- [95] Du J, Cheng N, Deng Y, Xiang P, Liang J, Zhang Z, et al. Astrocyte senescence-like response related to peripheral nerve injury-induced neuropathic pain. *Cell Mol Biol Lett*. 2023 Aug 15;28(1):65. <https://doi.org/10.1186/s11658-023-00474-5>
- [96] Zuo S, Wang Z, Jiang X, Zhao Y, Wen P, Wang J, et al. Regulating tumor innervation by nanodrugs potentiates cancer immunotherapy and relieve chemotherapy-induced neuropathic pain. *Biomaterials*. 2024 Sep;309:122603. <https://doi.org/10.1016/j.biomaterials.2024.122603>
- [97] Hefner S, Oprita G, Pantke S, Hage A, Leffler A. Nav1.8, TRPV1 and TRPA1 as possible targets of ambroxol when used for topical treatment of neuropathic pain. *J Pain*. 2025 Dec;37:105563. <https://doi.org/10.1016/j.jpain.2025.105563>
- [98] Malta I, Netto G, Dos Santos R, Veras F, Galdino G. Synergistic effect of cannabidiol and transcutaneous electrical nerve stimulation on neuropathic and inflammatory pain in mice. *Neuroreport*. 2023 Feb 1;34(3):165-169. <https://doi.org/10.1097/WNR.0000000000001877>
- [99] Sindhuri V, Koo MJ, Jeon SH, Ha KT, Kim S, Koo S. Electroacupuncture alleviates neuropathic pain by inhibiting

- spinal CCL2-driven microglial activation. *Int J Mol Sci.* 2025 Sep 17;26(18):9049. <https://doi.org/10.3390/ijms26189049>
- [100] Saraiva C, Praca C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. *J Control Release.* 2016 Aug 10;235:34-47. <https://doi.org/10.1016/j.jconrel.2016.05.044>
- [101] Gilon I, Baron R, Jensen T. Neuropathic pain: Principles of diagnosis and treatment. *Mayo Clin Proc.* 2015 Apr;90(4):532-545. <https://doi.org/10.1016/j.mayocp.2015.01.018>
- [102] Ye Z, Gastfriend BD, Umlauf BJ, Lynn DM, Shusta EV. Antibody-targeted liposomes for enhanced targeting of the blood-brain barrier. *Pharm Res.* 2022 Jul;39(7):1523-1534. <https://doi.org/10.1007/s11095-022-03186-1>
- [103] Lee D, Shen AM, Shah M, Garbuzenko OB, Minko T. In vivo evaluation of nose-to-brain delivery of liposomal donepezil, memantine, and BACE-1 siRNA for Alzheimer's disease therapy. *Int J Mol Sci.* 2024 Sep 26;25(19):10357. <https://doi.org/10.3390/ijms251910357>
- [104] Wang C, Xue Y, Markovic T, Li H, Wang S, Zhong Y, et al. Blood-brain-barrier-crossing lipid nanoparticles for mRNA delivery to the central nervous system. *Nat Mater.* 2025 Oct; 24(10):1653-1663. <https://doi.org/10.1038/s41563-024-02114-5>
- [105] Kaiser EE, Waters ES, Yang X, Fagan MM, Scheulin KM, Sneed SE, et al. Tanshinone IIA-loaded nanoparticle and neural stem cell therapy enhances recovery in a pig ischemic stroke model. *Stem Cells Transl Med.* 2022 Oct 21;11(10):1061-1071. <https://doi.org/10.1093/stcltm/szac062>
- [106] Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-based medicines: A review of FDA-approved materials and clinical trials to date. *Pharm Res.* 2016;33(10): 2373-2387. <https://doi.org/10.1007/s11095-016-1958-5>
- [107] Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. *Bioeng Transl Med.* 2019 Sep 5;4(3):e10143. <https://doi.org/10.1002/btm2.10143>
- [108] Metselaar JM, Lammers T. Challenges in nanomedicine clinical translation. *Drug Deliv Transl Res.* 2020 Jun;10(3):721-725. <https://doi.org/10.1007/s13346-020-00740-5>
- [109] Nasare NV, Banerjee BD, Suryakantrao Deshmukh P, Mediratta PK, Saxena AK, Ahmed RS, et al. CYP2D6*2 polymorphism as a predictor of failed outpatient tramadol therapy in postherpetic neuralgia patients. *Am J Ther.* 2016 May-Jun;23(3):e697-e707. <https://doi.org/10.1097/MJT.0b013e31826fc491>
- [110] Benavides R, Vsevolozhskaya O, Cattaneo S, Zaykin D, Brenton A, Parisien M, et al. A functional polymorphism in the ATP-binding cassette B1 transporter predicts pharmacologic response to combination of nortriptyline and morphine in neuropathic pain patients. *Pain.* 2020 Mar;161(3):619-629. <https://doi.org/10.1097/j.pain.0000000000001750>
- [111] Margarit C, Roca R, Inda MD, Muriel J, Ballester P, Moreu R, et al. Genetic contribution in low back pain: A prospective genetic association study. *Pain Pract.* 2019 Nov;19(8):836-847. <https://doi.org/10.1111/papr.12816>
- [112] Poli P, Peruzzi L, Maurizi P, Mencucci A, Scocca A, Carnevale S, et al. The pharmacogenetics of cannabis in the treatment of chronic pain. *Genes (Basel).* 2022 Oct 11;13(10):1832. <https://doi.org/10.3390/genes13101832>
- [113] Jiang F, Xu Y, Ye X, Zheng B, Zhang G, Li R. Identification of gene expression signatures associated with neuroinflammation in discogenic sciatica using machine learning and experimental validation. *Front Genet.* 2026 Mar 5;17:1666639. <https://doi.org/10.3389/fgene.2026.1666639>
- [114] Copley S, Yassa PE, Batterham AM, Buchser E, Mekhail N, Duarte RV, et al. A clinical evaluation of the accuracy of an intrathecal drug delivery device. *Neuromodulation.* 2023 Aug; 26(6):1240-1246. <https://doi.org/10.1016/j.neurom.2022.10.052>
- [115] Kopsky DJ, Keppel Hesselink JM. Single-blind placebo-controlled response test with phenytoin 10% cream in neuropathic pain patients. *Pharmaceuticals (Basel).* 2018 Nov 12;11(4):122. <https://doi.org/10.3390/ph11040122>
- [116] Goree JH, Nijhuis H, Smith GL, Petersen EA, Pope JE, Antony AB, et al. First objective evidence characterizing differences in cervical and thoracic spinal cord neurophysiology using ECAP-controlled closed-loop technology. *Pain Ther.* 2025 Dec;14(6):1833-1846. <https://doi.org/10.1007/s40122-025-00782-y>
- [117] Gilron I, Robb S, Tu D, Holden RR, Jackson AC, Duggan S, et al. Randomized, double-blind, controlled trial of a combination of alpha-lipoic acid and pregabalin for neuropathic pain: The PAIN-CARE trial. *Pain.* 2024 Feb 1;165(2):461-469. <https://doi.org/10.1097/j.pain.0000000000003038>
- [118] Kanbayashi Y, Amaya F, Ikoma K, Ueno H, Tabuchi Y, Ishikawa T, et al. Predictors of the usefulness of mirogabalin for neuropathic pain: A single-institution retrospective study. *Pharmazie.* 2020 Nov 1;75(11):602-605. <https://doi.org/10.1691/ph.2020.0741>
- [119] Jirachapitak S, Euasobhon P, Cenpakdee S, Wangnamthip S, Rushatamukayanunt P. Intravenous lidocaine response as a predictor for oral oxcarbazepine efficacy in neuropathic pain syndrome: A prospective cohort study. *Med Sci Monit.* 2024 Sep 19;30:e945612. <https://doi.org/10.12659/MSM.945612>
- [120] Mills EP, Bosma RL, Rogachov A, Cheng JC, Osborne NR, Kim JA, et al. Pretreatment brain white matter integrity associated with neuropathic pain relief and changes in temporal summation of pain following ketamine. *J Pain.* 2024 Sep; 25(9):104536. <https://doi.org/10.1016/j.jpain.2024.104536>
- [121] Emir B, Johnson K, Kuhn M, Parsons B. Predictive modeling of response to pregabalin for the treatment of neuropathic pain using 6-week observational data: A spectrum of modern analytics applications. *Clin Ther.* 2017 Jan;39(1):98-106. <https://doi.org/10.1016/j.clinthera.2016.11.015>
- [122] Zhou X, Shen Y, Zhao C, Luo F. Lidocaine aerosol sprayed on oral and/or nasal mucosa for the rescue of acute trigeminal neuralgia exacerbations: A retrospective study. *Cephalalgia.* 2023 May;43(5):3331024231168086. <https://doi.org/10.1177/03331024231168086>
- [123] Monteagudo Moreno L, Cia Blasco P, Malo Urries M, Nuez Polo A, Marin Zaldivar C. Predictors of response in patients with traumatic peripheral neuropathic pain treated with the 8% capsa-

- icin patch. *Rev Esp Anesthesiol Reanim (Engl Ed)*. 2025 Aug-Sep;72(7):501880. <https://doi.org/10.1016/j.redare.2025.501880>
- [124] Tanaka T, Shiiba S, Yoshino N, Harano N, Sago T, Kito S, et al. Predicting the therapeutic effect of carbamazepine in trigeminal neuralgia by analysis of neurovascular compression utilizing magnetic resonance cisternography. *Int J Oral Maxillofac Surg*. 2019 Apr;48(4):480-487. <https://doi.org/10.1016/j.ijom.2018.09.012>
- [125] Min K, Oh Y, Lee SH, Ryu JS. Symptom-based treatment of neuropathic pain in spinal cord-injured patients: A randomized crossover clinical trial. *Am J Phys Med Rehabil*. 2016 May;95(5):330-338. <https://doi.org/10.1097/PHM.0000000000000382>
- [126] Yang Y, Adi T, Effraim PR, Chen L, Dib-Hajj SD, Waxman SG. Reverse pharmacogenomics: Carbamazepine normalizes activation and attenuates thermal hyperexcitability of sensory neurons due to Na(v) 1.7 mutation I234T. *Br J Pharmacol*. 2018 Jun;175(12):2261-2271. <https://doi.org/10.1111/bph.13935>
- [127] Jain SM, Balamurugan R, Tandon M, Mozaffarian N, Gudi G, Salhi Y, et al. Randomized, double-blind, placebo-controlled trial of ISC 17536, an oral inhibitor of transient receptor potential ankyrin 1, in patients with painful diabetic peripheral neuropathy: Impact of preserved small nerve fiber function. *Pain*. 2022 Jun 1;163(6):e738-e747. <https://doi.org/10.1097/j.pain.00000000000002470>
- [128] Xing X, Sun K, Yan M. Delayed initiation of supplemental pain management is associated with postherpetic neuralgia: A retrospective study. *Pain Physician*. 2020 Jan;23(1):65-72. <https://doi.org/10.36076/ppj.2020/23/65>
- [129] Przeklasa-Muszynska A, Kocot-Kepska M, Dobrogowski J, Wiatr M, Mika J. Intravenous lidocaine infusions in a multidirectional model of treatment of neuropathic pain patients. *Pharmacol Rep*. 2016 Oct;68(5):1069-1075. <https://doi.org/10.1016/j.pharep.2016.06.010>
- [130] Qiu L, Chen X, Fu J, Chen X, Wang X. Intravenous patient-controlled analgesia with esketamine improves early depressive symptoms in patients with postherpetic neuralgia: A single-center retrospective cohort study. *BMC Psychiatry*. 2024 Aug 27;24(1):582. <https://doi.org/10.1186/s12888-024-06035-0>
- [131] Ushida T, Katayama Y, Hiasa Y, Nishihara M, Tajima F, Katoh S, et al. Mirogabalin for central neuropathic pain after spinal cord injury: A randomized, double-blind, placebo-controlled, phase 3 study in Asia. *Neurology*. 2023 Mar 14;100(11):e1193-e1206. <https://doi.org/10.1212/WNL.000000000000201709>
- [132] Sendel M, Ehmke L, Dunst A, Vollert J, Bruckmuller H, Brugge S, et al. Response to high-dose topical capsaicin in neuropathic pain: Absence of deep pain as a predictor of analgesic effect. *Eur J Pain*. 2026 Jan;30(1):e70200. <https://doi.org/10.1002/ejp.70200>
- [133] Alexander J, Edwards RA, Savoldelli A, Manca L, Grugni R, Emir B, et al. Integrating data from randomized controlled trials and observational studies to predict the response to pregabalin in patients with painful diabetic peripheral neuropathy. *BMC Med Res Methodol*. 2017 Jul 20;17(1):113. <https://doi.org/10.1186/s12874-017-0389-2>
- [134] Zhang A, Zhang W, Xu H, Guo C, Yuan L, Xu Y, et al. Diabetes mellitus contributes to carbamazepine resistance in patient with trigeminal neuralgia. *Neurosurg Rev*. 2021 Apr;44(2):1119-1125. <https://doi.org/10.1007/s10143-020-01304-4>
- [135] Nakajima Y, Kuribayashi K, Tada A, Nagano A, Minami T, Kanehiro A, et al. Enhancing duloxetine with mirogabalin for treating taxane-induced peripheral neuropathy in advanced lung cancer. *Cancer Control*. 2025 Jan-Dec;32:10732748251353327. <https://doi.org/10.1177/10732748251353327>
- [136] Edwards RA, Bonfanti G, Grugni R, Manca L, Parsons B, Alexander J. Predicting responses to pregabalin for painful diabetic peripheral neuropathy based on trajectory-focused patient profiles derived from the first 4 weeks of treatment. *Adv Ther*. 2018 Oct;35(10):1585-1597. <https://doi.org/10.1007/s12325-018-0780-3>
- [137] Rogachov A, Bhatia A, Cheng JC, Bosma RL, Kim JA, Osborne NR, et al. Plasticity in the dynamic pain connectome associated with ketamine-induced neuropathic pain relief. *Pain*. 2019 Jul;160(7):1670-1679. <https://doi.org/10.1097/j.pain.0000000000001545>
- [138] Landmann G, Stockinger L, Gerber B, Benrath J, Schmeltz M, Rukwied R. Local hyperexcitability of C-nociceptors may predict responsiveness to topical lidocaine in neuropathic pain. *PLoS One*. 2022 Jul 14;17(7):e0271327. <https://doi.org/10.1371/journal.pone.0271327>
- [139] Labau JIR, Estacion M, Tanaka BS, de Greef BTA, Hoeijmakers JGJ, Geerts M, et al. Differential effect of lacosamide on Nav1.7 variants from responsive and non-responsive patients with small fibre neuropathy. *Brain*. 2020 Mar 1;143(3):771-782. <https://doi.org/10.1093/brain/awaa016>
- [140] Wang D, Lu J, Xu X, Yuan Y, Zhang Y, Xu J, et al. Satellite glial cells give rise to nociceptive sensory neurons. *Stem Cell Rev Rep*. 2021 Jun;17(3):999-1013. <https://doi.org/10.1007/s12015-020-10102-w>
- [141] Xue T, Song Y, Zhao J, Fan G, Liu Z. Inhibition of S100A4 decreases neurotoxic astrocyte reactivity and attenuates neuropathic pain via the TLR4/NF-kappaB pathway in a rat model of spinal nerve ligation. *J Headache Pain*. 2025 May 1;26(1):97. <https://doi.org/10.1186/s10194-025-02045-9>
- [142] Alshelh Z, Brusaferrri L, Saha A, Morrissey E, Knight P, Kim M, et al. Neuroimmune signatures in chronic low back pain subtypes. *Brain*. 2022 Apr 29;145(3):1098-1110. <https://doi.org/10.1093/brain/awab336>
- [143] Gomez K, Stratton HJ, Duran P, Loya S, Tang C, Calderon-Rivera A, et al. Identification and targeting of a unique Na(v)1.7 domain driving chronic pain. *Proc Natl Acad Sci U S A*. 2023 Aug 8;120(32):e2217800120. <https://doi.org/10.1073/pnas.2217800120>
- [144] Xia L, Luo H, Ma Q, Xie Y, Li W, Hu H, et al. GPR151 in nociceptors modulates neuropathic pain via regulating P2X3 function and microglial activation. *Brain*. 2021 Dec 16;144(11):3405-3420. <https://doi.org/10.1093/brain/awab245>
- [145] Shin J, Wu J, Park H, Kim SI, Shin N, Shin HJ, et al. Microglial pyroptosis drives neuropathic pain and targeting NLRP3 alleviates pain and neuroinflammation. *Biochim Biophys Acta Mol*

- Basis Dis. 2025 Apr;1871(4):167737. <https://doi.org/10.1016/j.bbadis.2025.167737>
- [146] Robinson D, Khatib M, Lavon E, Kafri N, Abu Rashed W, Yassin M. Long-term efficacy and safety of inhaled cannabis therapy for painful diabetic neuropathy: A 5-year longitudinal observational study. *Biomedicines*. 2025 Sep 30;13(10):2406. <https://doi.org/10.3390/biomedicines13102406>
- [147] Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. *Nat Rev Dis Primers*. 2017 Feb 16;3:17002. <https://doi.org/10.1038/nrdp.2017.2>
- [148] Zakrzewska JM, Palmer J, Morisset V, Giblin GM, Obermann M, Ettlin DA, et al. Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: A double-blind, placebo-controlled, randomised withdrawal phase 2a trial. *Lancet Neurol*. 2017 Apr;16(4):291-300. [https://doi.org/10.1016/S1474-4422\(17\)30005-4](https://doi.org/10.1016/S1474-4422(17)30005-4)
- [149] Mantyh PW, Koltzenburg M, Mendell LM, Tive L, Shelton DL. Antagonism of nerve growth factor-TrkA signaling and the relief of pain. *Anesthesiology*. 2011 Jul;115(1):189-204. <https://doi.org/10.1097/ALN.0b013e31821b1ac5>
- [150] Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med*. 2010 Oct 14;363(16):1521-1531. <https://doi.org/10.1056/NEJMoa0901510>
- [151] Mogil JS. Animal models of pain: Progress and challenges. *Nat Rev Neurosci*. 2009 Apr;10(4):283-294. <https://doi.org/10.1038/nrn2606>
- [152] Tappe-Theodor A, Kuner R. Studying ongoing and spontaneous pain in rodents – challenges and opportunities. *Eur J Neurosci*. 2014;39 Jun (11):1881-1890. <https://doi.org/10.1111/ejn.12643>
- [153] Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol*. 2010 Aug;9(8):807-819. [https://doi.org/10.1016/S1474-4422\(10\)70143-5](https://doi.org/10.1016/S1474-4422(10)70143-5)
- [154] Araujo LC, Silva D, Rocha-Braga LC, Ciena AP, Chacur M. Therapeutic synergy between swimming and photobiomodulation in a rat model of neuropathic pain. *Lasers Med Sci*. 2025 Oct 20;40(1):444. <https://doi.org/10.1007/s10103-025-04705-3>
- [155] Wan K, Jia M, Zhang H, Lan Y, Wang S, Zhang K, et al. Electroacupuncture alleviates neuropathic pain by suppressing ferroptosis in dorsal root ganglion via SAT1/ALOX15 signaling. *Mol Neurobiol*. 2023 Oct;60(10):6121-6132. <https://doi.org/10.1007/s12035-023-03463-z>
- [156] Xue C, Kui W, Huang A, Li Y, Li L, Gu Z, et al. Electroacupuncture suppresses neuronal ferroptosis to relieve chronic neuropathic pain. *J Cell Mol Med*. 2024 Apr;28(7):e18240. <https://doi.org/10.1111/jcmm.18240>
- [157] Li Y, Liu X, Fu Q, Fan W, Shao X, Fang J, et al. Electroacupuncture ameliorates depression-like behaviors comorbid to chronic neuropathic pain via Tet1-mediated restoration of adult neurogenesis. *Stem Cells*. 2023 Apr 25;41(4):384-399. <https://doi.org/10.1093/stmcls/sxad007>
- [158] Ma L, Liu Y, Zhang H, Huang C, Li A, Qu X, et al. Electroacupuncture attenuates neuropathic pain via suppressing BIP-IRE-1alpha-mediated endoplasmic reticulum stress in the anterior cingulate cortex. *Biol Res*. 2024 May 29;57(1):34. <https://doi.org/10.1186/s40659-024-00511-3>
- [159] Lee S, Lee CS, Moon JY, Song HG, Yoo Y, Kim J, et al. Electroacupuncture may improve burning and electric shock-like neuropathic pain: A prospective exploratory pilot study. *J Altern Complement Med*. 2020 Dec;26(12):1136-1143. <https://doi.org/10.1089/acm.2020.0307>
- [160] Leite Ferreira L, Pereira Generoso L, Medeiros AC, de Medeiros P, Leonardo de Freitas R, Lourenco da Silva M, et al. Infralimbic medial prefrontal cortex alters electroacupuncture effect in animals with neuropathic chronic pain. *Behav Brain Res*. 2022 Apr 29;424:113803. <https://doi.org/10.1016/j.bbr.2022.113803>
- [161] Devigili G, Di Stefano G, Donadio V, Frattale I, Grazzi L, Mantovani E, et al. Therapeutic approach to fibromyalgia: A consensus statement on pharmacological and non-pharmacological treatment from the neuropathic pain special interest group of the Italian neurological society. *Neurol Sci*. 2025 May;46(5):2263-2288. <https://doi.org/10.1007/s10072-025-08048-3>
- [162] Hill G, Johnson F, Uy J, Serrada I, Benyamin B, Van Den Berg M, et al. Moderate intensity aerobic exercise may enhance neuroplasticity of the contralesional hemisphere after stroke: A randomised controlled study. *Sci Rep*. 2023 Sep 2;13(1):14440. <https://doi.org/10.1038/s41598-023-40902-2>
- [163] Calfee K, Lee S. 0224 bidirectional associations between sleep health and chronic pain interference in middle-age and older adults. *Sleep*. 2025;48(Supplement_1):A100-A100. <https://doi.org/10.1093/sleep/zsaf090.0224>
- [164] Riegner G, Dean J, Wager TD, Zeidan F. Mindfulness meditation and placebo modulate distinct multivariate neural signatures to reduce pain. *Biol Psychiatry*. 2025 Jan 1;97(1):81-88. <https://doi.org/10.1016/j.biopsych.2024.08.023>
- [165] Breton Z, Stern E, Pinault M, Lhuillery D, Petit E, Panel P, et al. A digital program for daily life management with endometriosis: Pilot cohort study on symptoms and quality of life among participants. *JMIR Form Res*. 2025 Feb 28;9:e58262. <https://doi.org/10.2196/58262>
- [166] Boren LL, Locke AM, Friedman AS, Blackmore CC, Woolf R. Team-based medicine: Incorporating a clinical pharmacist into pain and opioid practice management. *PM R*. 2019 Nov;11(11):1170-1177. <https://doi.org/10.1002/pmrj.12127>
- [167] Chong MS, Bahra A, Zakrzewska JM. Guidelines for the management of trigeminal neuralgia. *Cleve Clin J Med*. 2023 Jun 1;90(6):355-362. <https://doi.org/10.3949/ccjm.90a.22052>
- [168] Oliveira DS, Velia Ferreira Mendonca L, Sofia Monteiro Sampaio R, Manuel Pereira Dias de Castro-Lopes J, Ribeiro de Azevedo LF. The impact of anxiety and depression on the outcomes of chronic low back pain multidisciplinary pain management-A multicenter prospective cohort study in pain clinics with one-year follow-up. *Pain Med*. 2019 Apr 1;20(4):736-746. <https://doi.org/10.1093/pm/pny128>
- [169] Yuba T, Yamamoto S, Uematsu H, Yoshida T. Impact of a multidisciplinary pain management team on acute and chronic pain management after total knee arthroplasty. *J Anesth*. 2025

- Dec;39(6):869-877. <https://doi.org/10.1007/s00540-025-03529-3>
- [170] Peng J, Yi M, Jeong H, McEwan PP, Zheng J, Wu G, et al. The voltage-gated proton channel Hv1 promotes microglia-astrocyte communication and neuropathic pain after peripheral nerve injury. *Mol Brain*. 2021 Jun 28;14(1):99. <https://doi.org/10.1186/s13041-021-00812-8>
- [171] Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2012 Dec 12;12(12):CD008242. <https://doi.org/10.1002/14651858.CD008242.pub2>
- [172] Trivedi PD, Posani S, Balla N, Sheezan MM, Hussain AS, Xavier R, et al. Efficacy of pregabalin, amitriptyline, and gabapentin for neuropathic pain. *Bioinformation*. 2024 Apr 30;20(4):386-390. <https://doi.org/10.6026/973206300200386>
- [173] Naik H, Steiner DJ, Versavel M, Palmer J, Fong R. Safety, tolerability and pharmacokinetics of single and repeat doses of vixotrigine in healthy volunteers. *Clin Transl Sci*. 2021 Jul;14(4):1272-1279. <https://doi.org/10.1111/cts.12935>
- [174] Li W, Zhao Y, Liu H, Liu J, Chan S, Zhong Y, et al. Roles of thermosensitive transient receptor channels TRPV1 and TRPM8 in paclitaxel-induced peripheral neuropathic pain. *Int J Mol Sci*. 2024 May 27;25(11):5813. <https://doi.org/10.3390/ijms25115813>
- [175] Percie du Sert N, Rice AS. Improving the translation of analgesic drugs to the clinic: Animal models of neuropathic pain. *Br J Pharmacol*. 2014 Jun;171(12):2951-2963. <https://doi.org/10.1111/bph.12645>
- [176] Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. *Clin Pharmacol Ther*. 2021 Oct;110(4):888-896. <https://doi.org/10.1002/cpt.2149>