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Nociceptive, Neuropathic and Nociplastic Pain in Clinical Practice: Mechanism-Oriented Assessment and Multimodal Management - Systematic Review

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Abstract

Background: Chronic pain is common and increasingly considered a disease - anatomical labels often fail to reflect sustaining mechanisms. The IASP/ICD-11 framework classifies pain as nociceptive, neuropathic, and nociplastic, which often coexist.

Aim: To synthesize mechanisms of nociceptive, neuropathic, nociplastic, and mixed pain, and outline a mechanism-oriented, multimodal management approach.

Methods: Narrative review of major guidelines, systematic reviews, and pivotal clinical trials.

Results: Nociceptive pain reflects ongoing peripheral nociceptor activation and peripheral sensitization; management targets the tissue source and inflammation. Neuropathic pain follows a lesion or disease of the somatosensory system with ectopic firing, neuroinflammation, and central sensitization; first-line drugs include tricyclic antidepressants, SNRIs, and gabapentinoids, while NSAIDs show little benefit in pure neuropathic states. Nociplastic pain involves altered nociceptive processing without clear tissue damage or nerve lesion and is linked to central sensitization, widespread hypersensitivity, fatigue, and sleep/cognitive symptoms; education, graded exercise, and cognitive-behavioral strategies are foundational. Mixed states are common, and sustained peripheral input may promote "centralization," requiring individualized combinations of therapies. In selected, well-phenotyped neuropathic syndromes, interventional options (e.g., blocks, steroid injections, pulsed radiofrequency, botulinum toxin A, neuromodulation) can be useful adjuncts to rehabilitation and optimized medication.

Conclusion: Mechanism-based assessment supports rational, individualized therapy selection. Effective care is multimodal, addressing peripheral generators, neural hyperexcitability, central sensitization, and psychosocial factors, with realistic goals emphasizing function and quality of life.

Key words: Chronic Pain, Nociceptive Pain, Neuropathic Pain, Nociplastic Pain, Central Nervous System Sensitization, Pain Management, Combined Modality Therapy

1. Introduction

Chronic pain affects a large share of adults worldwide and is increasingly treated as a condition in its own right, not just a symptom. When pain persists for at least three months, it commonly disrupts physical function, sleep, mood, social life and productivity. This makes better ways of understanding and treating chronic pain a priority across pain medicine, neurology, rheumatology, and rehabilitation.

Older classification systems describe pain mainly by location (e.g., low back pain) or by cause (e.g., postsurgical, cancer-related). These labels are still useful, but they often fail to explain why pain persists. Over the last decade, the IASP and WHO have promoted a mechanism-based framework, formalized in ICD-11, which distinguishes three key mechanisms: nociceptive, neuropathic, and nociplastic pain.

Nociceptive pain results from actual or threatened damage to non-neural tissues and is driven by activation of peripheral nociceptors. Injury and inflammation release mediators, such as prostaglandins, bradykinin, and cytokines, that lower nociceptor thresholds and produce peripheral sensitization. In most cases, the pain remains relatively localized, matches tissue pathology, and improves when the underlying lesion is treated.

Neuropathic pain, in contrast, arises from a lesion or disease of the somatosensory nervous system. Nerve injury can generate ectopic firing through ion-channel changes, demyelination, and neuroinflammation. Ongoing abnormal input then promotes central sensitization through spinal plasticity, reduced inhibition and glial activation with additional changes in brain networks and descending modulation. Clinically, this often presents as burning or electric-shock-like pain, allodynia, hyperalgesia, and a mix of sensory gain and loss, frequently alongside sleep and mood disturbance.

Nociplastic pain describes pain driven mainly by altered nociceptive processing when there is no clear evidence of ongoing tissue damage or a definable somatosensory lesion. It is closely linked to central sensitization and network-level changes in pain processing. Typical examples include fibromyalgia and chronic primary widespread pain, where patients often report widespread, fluctuating pain, sensory hypersensitivity, fatigue, cognitive symptoms, and sleep problems.

In practice, these mechanisms often overlap. Mixed pain states are common in conditions such as degenerative spine disease, osteoarthritis, postsurgical pain, and cancer-related pain. Over time, persistent nociceptive or neuropathic input can “centralize” pain, and psychosocial factors (stress, inactivity, catastrophizing, social isolation) can further amplify symptoms. For many patients, a purely anatomical approach is therefore not enough to guide treatment.

A mechanism-based view has clear therapeutic implications. NSAIDs are typically ineffective for pure neuropathic pain and are best reserved for mixed presentations with an inflammatory or nociceptive component. For neuropathic pain, first-line options more often include antidepressants with serotonergic/noradrenergic action, gabapentinoids and selected topical agents. Opioids, cannabis-based medicines, and interventional procedures may help some patients, but benefits are usually modest and limited by adverse effects and practical constraints. At the same time, non-pharmacological care has become central to chronic pain management. Exercise-based physiotherapy, cognitive-behavioral therapy, TENS, acupuncture, and pain neuroscience education target different levels of the pain system-from peripheral input to central processing and cognitive-emotional modulation. Interventional techniques (nerve blocks, steroid injections, neuromodulation, pulsed radiofrequency, botulinum toxin A) can provide additional, often time-limited benefit in selected cases.

This review integrates these elements into a single framework: it summarizes the mechanisms underlying nociceptive, neuropathic, nociplastic and mixed pain (with emphasis on peripheral and central sensitization), reviews evidence-based pharmacological options for neuropathic pain, and outlines key non-pharmacological and interventional approaches. The goal is to support more rational, individualized and multimodal care by aligning treatment choices with underlying mechanisms and the broader biopsychosocial context.

2. Pathophysiological Mechanisms of Chronic Pain

2.1. Mechanistic classification of chronic pain

Over the last decade, the field of pain medicine has shifted its emphasis from anatomical localization toward an understanding of the biological processes driving chronic pain. The IASP/ICD-11 framework formalized this mechanistic perspective, distinguishing nociceptive, neuropathic and nociplastic pain as the three principal categories observed in patients whose symptoms persist for at least three months (1-3). Each of these mechanisms reflects a different failure mode of the nociceptive system. Nociceptive pain originates from continued activation of peripheral nociceptors by actual or potential tissue injury in the absence of primary somatosensory system pathology. Neuropathic pain arises when a structural or functional lesion affects the peripheral or central somatosensory pathways (4,5). In contrast, nociplastic pain describes altered nociceptive processing that cannot be accounted for by peripheral tissue damage or identifiable neural lesions, as seen in conditions such as fibromyalgia or chronic primary pain syndromes (6-8). Importantly, these categories often overlap in daily clinical practice, particularly in musculoskeletal and oncological settings, where mixed pain states are more the rule than the exception (9,10).

2.2. Nociceptive pain: persistent nociceptor activation and peripheral sensitization

Nociceptive pain, according to the IASP definition, results from actual or threatened injury to non-neural tissues. Nociceptors-principally Aδ and C-fiber terminals situated in the skin, musculoskeletal tissues, periosteum and viscera-serve as the primary transducers of these stimuli.

At the peripheral level, tissue injury of various origins (trauma, inflammatory disease, ischemia or neoplastic growth) initiates a biochemical cascade featuring prostaglandins, bradykinin, histamine, NGF, ATP, TNF-α, IL-1β and IL-6. These mediators interact with ion channels on nociceptors, lowering their firing thresholds, enhancing spontaneous discharge, and collectively establishing a state of peripheral sensitization (11,12). Chronic inflammation further modulates receptor expression, including TRPV1 and mechanosensitive channels, augmenting responsiveness to otherwise innocuous stimuli (11).

After peripheral activation, signals ascend via Aδ and C fibers into the dorsal horn, particularly laminae I, II and V. Although chronic nociceptive input can induce measurable central adaptations-such as increased glutamatergic transmission or limited sensitization-these changes seldom dominate the clinical picture; the pain typically remains tethered to peripheral pathology. This observation is reinforced by the frequent resolution of nociceptive pain following successful treatment of the underlying tissue disorder (12,13).

Clinically, nociceptive pain is often well demarcated and provoked by mechanical or load-dependent stress. The sensory findings are usually proportional to identifiable pathology and neurological deficits or positive sensory phenomena are uncommon (11-13).

2.3. Neuropathic pain: lesion of the somatosensory nervous system

Neuropathic pain, in contrast, reflects a fundamentally different mechanism-one that depends on demonstrable injury or disease within the somatosensory apparatus itself (5). Peripheral neuropathies, nerve root compression and central lesions such as stroke or spinal cord injury fall within this definition.

Peripheral mechanisms include the emergence of ectopic spontaneous activity in injured axons, neuromas and dorsal root ganglion neurons. These changes correlate with altered expression of sodium channels (Nav1.3, Nav1.7, Nav1.8) and shifts in calcium channel function (14,15). In parallel, demyelination or aberrant sprouting may result in ephaptic cross-talk between fibers. Immune cells infiltrating the nerve or ganglion secrete cytokines and trophic factors that heighten neuronal excitability (15,16).

Once this abnormal input reaches the central nervous system, it drives robust and often persistent central sensitization. Dorsal horn neurons exhibit long-term potentiation-like plasticity, receptive fields expand, and low-threshold Aβ fibers may begin activating nociceptive pathways, manifesting clinically as dynamic allodynia (16,17). Loss or dysfunction of inhibitory interneurons further augments this state of disinhibition. Concomitantly, activated microglia and astrocytes release pro-nociceptive mediators, reinforcing the sensitized state (17). Neuroimaging studies reveal additional supraspinal changes, including cortical reorganization and disruption of descending inhibitory controls, yielding a complex interplay between sensory, emotional and cognitive networks (18).

Patients typically describe burning, shooting or shock-like pain, often accompanied by allodynia or hyperalgesia. Both positive sensory symptoms (paresthesias, dysesthesias) and negative deficits (hypoesthesia) may appear within a neuroanatomically coherent distribution. Psychological comorbidities such as sleep disruption and mood disorders are frequent (5,17,18).

2.4. Mixed pain: overlapping nociceptive, neuropathic and nociplastic mechanisms

In many chronic pain disorders, a single mechanism rarely accounts for the full clinical presentation. Mixed pain, a common pattern in degenerative spinal conditions, osteoarthritis and postoperative pain, arises when nociceptive input from tissue damage combines with neuropathic signaling from nerve compression or injury (9,10,19). Over time, the interplay between these peripheral generators can promote increasing central sensitization, blurring distinctions between originally separate processes.

Clinically, mixed pain blends mechanically provoked nociceptive symptoms with neuropathic descriptors such as burning or shock-like sensations in the same region, often complicating diagnosis and necessitating multimodal therapy.

2.5. Nociplastic pain and central sensitization

2.5.1. Concept of central sensitization

Central sensitization describes an amplified responsiveness within central nociceptive circuits, even when peripheral inputs remain stable or minimal. This heightened state manifests in dynamic allodynia, punctate hyperalgesia, aftersensations and exaggerated temporal summation to (16,20). Although initially reversible, repeated or intense nociceptive input can consolidate these changes, making them less dependent on ongoing peripheral drivers (12,16,20).

2.5.2. Cellular and network mechanisms

Several mechanisms contribute to sustained central sensitization. Repeated C-fiber activation produces NMDA-dependent long-term potentiation in dorsal horn synapses (20). Reduced inhibitory tone-stemming from interneuron dysfunction-and glial activation both shift the balance toward excitation; glia-derived mediators such as cytokines and BDNF further reinforce this transition (17). Additionally, maladaptive descending modulation from the brainstem, including reduced inhibitory noradrenergic and serotonergic input and enhanced facilitatory signaling, exacerbates pain amplification (7,8,18,21). Functional imaging consistently demonstrates altered connectivity across cortical and subcortical pain networks (7).

2.5.3. Nociplastic pain as a clinical manifestation

Nociplastic pain emerges when these central processes dominate the clinical picture. It characterizes syndromes such as fibromyalgia, chronic primary widespread pain and certain forms of non-specific low back pain or visceral hypersensitivity (6-8). These patients frequently report widespread pain disproportionate to observable pathology, sensory hypersensitivity and systemic symptoms such as fatigue, cognitive dysfunction, sleep disturbance and emotional dysregulation (7,8). Because nociplastic and other mechanisms may coexist, patients often occupy a continuum rather than discrete categories (7).

2.6. Dynamic interaction between mechanisms

The evolution of chronic pain is not static. Protracted nociceptive or neuropathic input can progressively shape central neural circuits, increasing vulnerability to nociplastic features.

Psychosocial factors-including catastrophic thinking, stress, reduced physical activity and social isolation-interact with biological pathways to further intensify central pain processing (7,8). As a result, individuals may transition from predominantly nociceptive presentations to mixed or nociplastic profiles over time. This underscores the clinical value of mechanism-based assessment and the need for treatments that address peripheral, neural and centrally mediated factors simultaneously (1-3,7).

3. Pharmacological Treatment

Pharmacological therapy represents one of the fundamental components in the management of neuropathic pain and is typically introduced early in the treatment pathway (21-24). Because neuropathic pain arises from injury or dysfunction of the somatosensory nervous system, its management differs substantially from the treatment strategies used for nociceptive pain (25,26). Conventional analgesics such as non-steroidal anti-inflammatory drugs often provide insufficient benefit, making targeted pharmacological agents necessary (21,22,27).

Most international guidelines emphasize that the goal of pharmacological treatment is not complete elimination of pain-an outcome rarely achievable-but rather a meaningful reduction in pain intensity, improvement in function, and enhancement of quality of life (21,22,25,28). Drug response in neuropathic pain is highly individualized, and only a portion of patients achieve satisfactory relief with any single medication (21,24,29). As a result, clinical practice often involves a stepwise approach that includes careful titration, monitoring of tolerability, switching between drug classes when necessary, and, in selected cases, the use of combination therapy (24,27,29,30).

Current treatment strategies typically begin with medications that modulate neuronal excitability or influence central pain processing, such as certain antidepressants, anticonvulsants, or topical agents used for localized neuropathic syndromes (21,22,27,30). Second-line and third-line therapies may be considered when first-line drugs provide only partial benefit or are poorly tolerated (22,28,30). Despite these limitations, pharmacological management remains a cornerstone of neuropathic pain treatment and is most effective when integrated into a broader multimodal approach involving psychological, rehabilitative, and patient-education strategies (23,28,31).

3.1 Non-steroidal anti-inflammatory drugs (NSAIDs) in the Pharmacological Management of Neuropathic Pain

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used analgesics worldwide and are widely prescribed for acute and chronic nociceptive pain. However, their role in the management of neuropathic pain is limited and remains insufficiently supported by high-quality evidence. Simple analgesics such as paracetamol and NSAIDs are generally considered ineffective for established neuropathic pain and are not recommended as first-line treatments in contemporary evidence-based guidelines, which consistently prioritize antidepressants, gabapentinoids and certain topical agents instead (21,22,32,33).

The most robust synthesis of available data is provided by a Cochrane review of oral NSAIDs for neuropathic pain, which concluded that there is insufficient evidence to support or refute the use of oral NSAIDs in adults with neuropathic pain (32). Only a small number of randomized controlled trials were identified, most of them small, methodologically limited and heterogeneous with respect to diagnosis, choice of NSAID and outcome measures. Across these trials, NSAIDs did not demonstrate consistent superiority over placebo in terms of pain relief or global improvement, and the overall quality of evidence was graded as very low (32). This lack of convincing clinical data contrasts with the widespread empirical use of NSAIDs in patients with neuropathic pain, often as a continuation of treatment for co-existing nociceptive or inflammatory conditions rather than because of proven efficacy for neuropathic mechanisms (34,35).

Current international guidelines for neuropathic pain, therefore do not recommend NSAIDs as a specific treatment for pure neuropathic pain states. Instead, they emphasize that NSAIDs may be considered primarily in patients with mixed pain, where an inflammatory or nociceptive component clearly co-exists alongside neuropathic mechanisms (21,22,36). In such scenarios, NSAIDs may contribute to relief of the inflammatory nociceptive component, while adjuvant analgesics with proven efficacy for neuropathic pain target the neuropathic component (36). There is currently no convincing clinical evidence that any particular NSAID (for example, COX-2-selective vs non-selective agents) provides superior benefit for neuropathic pain compared with others; available human data are too sparse and heterogeneous to support differential recommendations (32,34).

In addition to their limited and uncertain analgesic efficacy in neuropathic conditions, NSAIDs are associated with well-known dose- and time-dependent risks, including gastrointestinal bleeding, renal impairment and adverse cardiovascular events, which become particularly relevant in the often older, comorbid neuropathic pain population (35,37). Emerging work has also raised concern that intensive suppression of inflammation during acute pain might, in some contexts, interfere with normal resolution processes and potentially increase the risk of chronic pain, although these findings require further confirmation and have not been specifically validated for neuropathic pain (34). Taken together, the current body of evidence suggests that NSAIDs should not be regarded as specific analgesics for neuropathic pain; instead, their use should be individualized, short-term where possible, and largely confined to patients in whom a significant inflammatory or nociceptive component is present alongside neuropathic mechanisms.

3.2 Antidepressants in the Pharmacological Management of Neuropathic Pain

Antidepressants constitute one of the pillars of pharmacological treatment for neuropathic pain and are widely recommended as first-line therapies across international guidelines (21,22,24,38). Their analgesic effects are largely independent of antidepressant action and are mediated primarily through modulation of descending inhibitory pathways, inhibition of serotonin and noradrenaline reuptake, and effects on peripheral and central sensitization (22,39). Several classes of antidepressants have been evaluated, with tricyclic antidepressants (TCAs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) demonstrating the strongest evidence for efficacy. In contrast, selective serotonin reuptake inhibitors (SSRIs) show limited and inconsistent benefit (24,40).

3.2.1 Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants such as amitriptyline, nortriptyline, desipramine and imipramine are among the most thoroughly studied medications for neuropathic pain. Their analgesic effect arises from simultaneous inhibition of serotonin and noradrenaline reuptake, enhancement of descending inhibitory pathways, sodium-channel blockade, NMDA-modulation, anticholinergic effects, and pronounced central dampening of hyperexcitability (21,22,39). Because neuropathic pain is characterized by impaired descending inhibition and heightened spinal sensitization, TCAs directly target multiple relevant mechanisms, which may explain their consistently strong clinical performance (21,39).

Meta-analyses show that TCAs are associated with one of the lowest NNT values among all neuropathic pain treatments, typically 2.1-3.6, indicating high overall efficacy (21,41). Amitriptyline remains the most studied agent, with evidence of benefit across numerous conditions, including painful diabetic neuropathy, postherpetic neuralgia and mixed neuropathic syndromes (21,22,24). Nortriptyline and desipramine show similar analgesic potential but are often better tolerated because of reduced anticholinergic activity (22,41).

Despite their efficacy, TCAs are limited by their side-effect profile. Common adverse effects include dry mouth, constipation, orthostatic hypotension, sedation, and potential cardiotoxicity due to QT prolongation or conduction abnormalities (22,41). As a result, they are generally avoided in older patients or those with cardiovascular disease. They are best suited for younger, otherwise healthy adults, or patients with comorbid depression, insomnia, tension-type headache, or fibromyalgia, where secondary benefits may be clinically meaningful.

3.2.2 Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)

SNRIs, particularly duloxetine and venlafaxine, are among the most robustly supported pharmacological strategies for neuropathic pain. Their mechanism of action involves dual reuptake inhibition of serotonin and noradrenaline, enhancement of descending inhibition, and partial modulation of central sensitization (21,24,38). Compared with TCAs, SNRIs have a cleaner receptor profile and fewer off-target effects, resulting in better overall tolerability.

Duloxetine has consistently demonstrated significant improvement in pain intensity, sleep interference, and daily functioning in painful diabetic neuropathy with an NNT of approximately 5-6, making it one of the best-studied agents for this indication (38,42). Its analgesic effect is partly independent of mood effects and appears within 1-2 weeks. Venlafaxine has also shown benefit in diabetic neuropathy and some forms of central neuropathic pain, especially at doses ≥150 mg/day, which recruit noradrenergic activity (24,42). Compared with TCAs, SNRIs show slightly lower absolute efficacy, but they are better tolerated and have fewer anticholinergic or cardiac risks. Common side effects include nausea, insomnia, dizziness, and dose-dependent increases in blood pressure (venlafaxine) (38,42). These medications are therefore especially useful in older adults, those with comorbid depression or anxiety, and patients with metabolic or cardiovascular comorbidities who cannot safely take TCAs.

Furthermore, duloxetine has demonstrated efficacy in chemotherapy-induced peripheral neuropathy and chronic postsurgical pain, which broadens its clinical utility (38).

3.2.3 Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, paroxetine, sertraline and citalopram, have been evaluated in multiple small studies of neuropathic pain, but the overall evidence supporting their analgesic efficacy is weak and inconsistent. Their mechanism-selective serotonin reuptake inhibition with minimal noradrenergic effect-provides limited reinforcement of descending inhibitory pathways, which may explain their substantially lower analgesic potential compared with TCAs and SNRIs (22,39).

Across randomized trials, SSRIs generally produce little to no clinically relevant improvement in neuropathic pain, and results are inferior in direct comparisons with tricyclic antidepressants. For example, fluoxetine was consistently less effective than amitriptyline or desipramine in painful diabetic neuropathy and postherpetic neuralgia (24,40,43). Systematic reviews, including Cochrane analyses, conclude that SSRIs do not demonstrate reliable efficacy for neuropathic pain (21,24).

Because of the limited data, a precise number needed to treat (NNT) cannot be established. Available trials suggest that NNT for SSRIs would likely be very high (>10) or impossible to estimate due to absence of meaningful separation from placebo (21,24,40). This positions SSRIs as much less effective than TCAs (NNT ~2-3) or SNRIs (NNT ~5-6).

Given these limitations, major guidelines place SSRIs as third-line or adjunctive options, primarily for patients who cannot tolerate first-line therapies or have dominant comorbid depression or anxiety, where mood stabilization is a key therapeutic goal (22,40). Although SSRIs are generally well tolerated, adverse effects such as gastrointestinal discomfort, sexual dysfunction, insomnia, and in older adults hyponatremia or increased bleeding risk may occur. Overall, SSRIs are not recommended as primary analgesics for neuropathic pain but may have a niche role as adjunctive therapy in patients with significant psychiatric comorbidities.

3.2.4 Other antidepressants

Bupropion

Bupropion is a noradrenaline-dopamine reuptake inhibitor (NDRI) with minimal serotonergic activity. Theoretical rationale for its use in neuropathic pain is based on enhancement of descending noradrenergic and dopaminergic inhibitory pathways, which may modulate central sensitization and pain perception (39). Clinical evidence, however, is limited. A small randomized, placebo-controlled trial and several open-label observations suggest moderate analgesic effects of bupropion in some neuropathic pain conditions, particularly when depressive symptoms are also present (44).

Because available studies include small patient numbers, heterogeneous populations and short follow-up, a reliable number needed to treat (NNT) cannot be robustly calculated. Indirect estimates from the largest trial suggest that, if an NNT were computed for ≥50% pain relief, it would likely be high (probably >8-10) and thus clearly less favorable than for TCAs or SNRIs (21,24,44). As a result, bupropion is generally regarded as a third-line or adjunctive option, considered in patients with comorbid depression, fatigue, nicotine dependence or intolerance to first-line agents, rather than as a primary analgesic for neuropathic pain (21,24,44).

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts primarily through α_2-adrenergic receptor blockade, leading to increased release of noradrenaline and serotonin, and antagonism at selected serotonin receptor subtypes (39). This pharmacological profile provides a plausible basis for analgesic and sedative effects, particularly in patients with sleep disturbance, weight loss or poor appetite.

Evidence for mirtazapine in neuropathic pain consists mainly of small case series and observational studies, which report improvements in sleep quality, mood and, in some patients, reductions in pain intensity. However, the absence of adequately powered randomized controlled trials means that the analgesic effect remains uncertain, and high-quality data are inadequate to support formal guideline recommendations (21,24).

Given the limited and heterogeneous data, NNT for mirtazapine cannot be reliably established. Available reports do not allow robust calculation of responders versus non-responders, but the overall signal suggests that any analgesic effect is modest and clearly less predictable than that of TCAs or SNRIs. In practical terms, mirtazapine may be considered an off-label, third-line or adjunctive treatment, particularly in patients with neuropathic pain accompanied by insomnia, poor appetite or major depression, where its sedative and orexigenic properties may be advantageous (39).

Milnacipran and other SNRIs outside duloxetine/venlafaxine

Milnacipran is an SNRI with a relatively balanced inhibition of serotonin and noradrenaline reuptake, extensively studied in fibromyalgia, a chronic widespread pain condition associated with central sensitization (45). In fibromyalgia, milnacipran demonstrates moderate analgesic efficacy with NNT estimates typically in the range of 8-10 for global improvement or clinically meaningful pain reduction (45). However, data for classical peripheral neuropathic pain (e.g. diabetic neuropathy, postherpetic neuralgia, radiculopathy) are sparse, small and methodologically heterogeneous, and current neuropathic pain guidelines do not include milnacipran among standard options (21,22,38,45).

For neuropathic pain specifically, the NNT of milnacipran cannot be reliably defined, as available studies are underpowered and focused primarily on central pain and fibromyalgia rather than well-characterized peripheral neuropathic syndromes (21,24,45). By extrapolation from fibromyalgia data, any potential NNT in neuropathic pain would likely be considerably higher (less favorable) than for duloxetine or venlafaxine and should be interpreted with great caution (21,24,42,45).

Other SNRIs occasionally discussed, such as desvenlafaxine, have even less evidence in neuropathic pain, with only isolated or negative studies, and are not routinely recommended by major guidelines (1,2,4,18). These agents may be considered only in highly individualized cases, usually driven by psychiatric comorbidity rather than robust analgesic data.

3.3 Anticonvulsants in the treatment of neuropathic pain

Anticonvulsants constitute one of the major pharmacological classes used in neuropathic pain, with gabapentinoids (gabapentin and pregabalin) providing the strongest evidence for efficacy and the broadest clinical use. Their primary mechanism involves binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, leading to a reduction in presynaptic glutamate, substance P and norepinephrine release, thereby dampening central sensitization and hyperexcitability of dorsal horn neurons (21,22,39). Gabapentinoids do not act via GABA receptors despite their name, and their analgesic action is pharmacologically distinct from their antiepileptic effects (39).

Among anticonvulsants, pregabalin and gabapentin are the best supported by randomized controlled trials and meta-analyses. Pregabalin has demonstrated consistent efficacy in painful diabetic neuropathy, postherpetic neuralgia and neuropathic pain associated with spinal cord injury, with typical NNT values of 6-8 for achieving $\geq 50\%$ pain reduction (21,24,46). Gabapentin shows similar but slightly more variable effectiveness, with NNT ranging from 6.5

to 8.3, depending on dose and condition (21,24). Both drugs also improve sleep quality, anxiety symptoms and overall quality of life, which is clinically relevant given the multidimensional nature of neuropathic pain (21,33). Optimal dosing usually requires gradual titration, and higher doses (e.g. gabapentin ≥1800 mg/day) are often required for meaningful analgesia (24,46).

Despite favorable efficacy, gabapentinoids have important limitations. Up to 50% of patients may not achieve adequate pain relief even at optimized doses, and adverse effects such as somnolence, dizziness, peripheral oedema, ataxia and weight gain can limit tolerability (21,33). In older adults, these effects may increase the risk of falls, cognitive slowing and gait instability, necessitating cautious dose escalation (22). More recently, concerns have been raised about misuse and dependence, particularly in combination with opioids; however, when used appropriately within guideline-directed care, their safety profile remains generally acceptable (33). Renal dose adjustments are essential in patients with impaired kidney function (22,33).

Other anticonvulsants, such as carbamazepine and oxcarbazepine, are used more selectively. Carbamazepine remains the first-line therapy for classical trigeminal neuralgia, supported by robust evidence and excellent responder rates, with NNT approximately 1.7-2.5-one of the most favorable across all neuropathic pain treatments (22,47). Oxcarbazepine offers similar efficacy with improved tolerability but carries risks such as hyponatremia, particularly in older adults (22). Evidence for other agents such as lamotrigine, topiramate or valproate is limited or negative; systematic reviews identify insufficient or inconsistent benefit and therefore do not recommend them for routine management of neuropathic pain (21,24,48).

The choice of anticonvulsant is best individualized based on the type of neuropathic pain, patient comorbidities and tolerability profile. Gabapentinoids are especially beneficial in patients with insomnia, anxiety, generalized hyperalgesia or spinal cord injury-related pain, whereas carbamazepine is the gold standard for trigeminal neuralgia. In contrast, gabapentinoids should be used cautiously in older adults, patients with obesity, balance impairment, or renal dysfunction, where side effects or clearance issues may be significant (22,33).

Overall, anticonvulsants represent one of the most important and widely used drug classes in neuropathic pain management. They offer moderate, clinically meaningful relief, good safety when titrated appropriately, and an essential role in individualized, multimodal treatment strategies.

3.4 Opioids in the treatment of neuropathic pain

Opioids occupy a complex and controversial position in the management of neuropathic pain. Although their analgesic effects are mediated through μ-opioid receptor activation, modulation of descending inhibitory pathways and partial suppression of central sensitization, the responsiveness of neuropathic pain to opioids is generally lower than that of nociceptive pain (21,24). Meta-analyses indicate that opioids provide modest short-term benefit, but their long-term efficacy is limited, and adverse events frequently outweigh therapeutic gains, which has led most contemporary guidelines to recommend opioids only as second- or third-line options, and typically only when first-line agents are ineffective or contraindicated (21,22).

Across randomized controlled trials, traditional strong opioids such as morphine or oxycodone demonstrate small-to-moderate reductions in pain intensity with NNT values usually between 4 and 6, reflecting modest clinical benefit in carefully selected patients (21,24). Combination therapy with oxycodone-naloxone may improve tolerability by reducing opioid-induced constipation, but does not significantly enhance analgesic efficacy (22). Notably, evidence supporting long-term (>12-week) opioid therapy in neuropathic pain is scarce, with most studies showing diminishing effectiveness over time due to tolerance, opioid-induced hyperalgesia and dose escalation (22,24).

Among opioids, tramadol and tapentadol hold a more favorable position because of their dual mechanism of action-μ-opioid agonism combined with inhibition of serotonin and noradrenaline reuptake. This gives them a partially “antidepressant-like” modulatory effect on descending inhibitory pathways. Tramadol demonstrates modest analgesic benefit with NNT around 4-5 for painful diabetic neuropathy and polyneuropathy, making it one of the better-supported opioid options for neuropathic pain (21,49). Tapentadol shows similar or slightly better results in diabetic neuropathy, though data remain more limited(49). Because of their lower μ-receptor potency, these agents may offer improved safety over strong opioids, though seizure risk (tramadol), serotonin syndrome risk, and potential for misuse remain relevant concerns (24,49).

The use of opioids in neuropathic pain is constrained by several well-recognized risks. Adverse effects include constipation, nausea, sedation, dizziness, cognitive impairment, endocrine disturbances and, in higher doses, respiratory depression (21,22,24). Long-term use is associated with opioid use disorder, dependence, tolerance and opioid-induced hyperalgesia, all of which are particularly problematic in chronic conditions such as neuropathy (22). Older adults are especially vulnerable to falls, confusion and delirium, and patients with respiratory disease, sleep apnea or renal impairment require cautious dosing (22,24).

Given these risks, opioids should generally be reserved for selected patients with severe neuropathic pain who have not responded adequately to guideline-preferred first-line treatments such as gabapentinoids, SNRIs or TCAs. Short-term opioid therapy may be appropriate in acute exacerbations or in palliative care settings, where the benefit-risk balance differs markedly. Some patients with neuropathic pain due to cancer invasion, spinal cord injury or severe diabetic neuropathy may obtain meaningful symptomatic relief, but careful monitoring, dose limitation and regular reassessment of benefit are essential (22,49).

Overall, opioids provide only modest analgesia in neuropathic pain and should be prescribed cautiously within a multimodal approach, prioritizing agents with dual mechanisms (e.g. tramadol, tapentadol) when opioid therapy is considered justified.

3.5 Medical Cannabis and Cannabis-Based Medicines in Neuropathic Pain

Medical cannabis and cannabis-based medicines (CBMs) - including herbal cannabis, Nabiximols oromucosal spray (THC : CBD 1 : 1), synthetic THC (dronabinol) and nabilone - are increasingly discussed as treatment options for chronic neuropathic pain, but their place in therapy remains limited and controversial (50,51). Their analgesic effect is thought to be mediated mainly through CB_1 receptors in the central nervous system and CB_2 receptors in immune cells, leading to modulation of neurotransmitter release (e.g., glutamate, GABA) and partial reduction of central sensitization and nociceptive transmission (52). Randomized controlled trials and meta-analyses show that CBMs produce at best a small to moderate reduction in pain intensity compared with placebo. For example, a meta-analysis of inhaled cannabis reported an NNT of ≈ 5.6 for short-term benefit (one in five to six patients) but with very short follow-up and low certainty of evidence (2). A comprehensive Cochrane review reported an NNT in the range of 11-20 for ≥30% pain relief but highlighted the evidence as low/very low quality (50,52). Short-term RCTs with smoked or vaporized cannabis confirm statistically significant but modest analgesic effects over days to a few weeks, without convincing long-term data (53).

Parallel to the modest efficacy, CBMs are associated with a relatively high rate of central nervous system adverse effects. Dizziness, somnolence, cognitive slowing, impaired concentration, dry mouth and fatigue are very common, and psychiatric adverse events - anxiety, dysphoria, paranoia, psychotic symptoms - occur in a relevant minority of patients (50,52). In meta-analyses, the number needed to harm (NNH) for relevant CNS or psychiatric side effects is often <10, meaning that adverse events may be almost as frequent as meaningful benefit (52). Long-term observational data also raise concerns about dependence, cannabis use disorder, cognitive impairment, driving impairment and potential cardiovascular risk, especially at higher THC doses or in vulnerable populations (54).

As a result, most expert groups and guidelines position medical cannabis and CBMs only as a third-line or “individual therapeutic trial” option in neuropathic pain. The European Pain Federation (EFIC) and other societies state that CBMs may be considered only by experienced clinicians, as adjunctive therapy and only after failure or intolerance of guideline-recommended first- and second-line treatments (gabapentinoids, antidepressants, topical agents, ± tramadol) (50,54). The International Association for the Study of Pain (IASP) has concluded that current evidence is insufficient to endorse cannabinoids for routine pain treatment (55). In practice, patients most likely to benefit are carefully selected individuals with severe, treatment-resistant neuropathic pain (e.g., multiple-sclerosis-related neuropathy, refractory peripheral neuropathic pain), in whom other evidence-based options have been optimized and who understand the limited expected benefit and potential risks. CBMs should be avoided or used with great caution in adolescents and young adults, patients with a history of psychosis or severe mood disorders, significant cardiovascular disease or substance-use disorders (52,54).

3.6 Topical Treatments for Neuropathic Pain

Topical treatments, including 5% lidocaine medicated plasters and 8% capsaicin patches, represent a valuable option in the management of localized peripheral neuropathic pain (LPNP) - for example, post-herpetic neuralgia (PHN) or focal diabetic neuropathy - and are increasingly recommended as second-line therapies when first-line systemic agents are unsuitable or poorly tolerated (56,57). The mechanism of action of lidocaine patches involves local sodium-channel blockade in the skin and subcutaneous nociceptors, thereby reducing ectopic discharges and peripheral sensitization, while capsaicin 8% patches act via TRPV1 receptor agonism followed by nociceptor defunctionalization, leading to a long-lasting reduction in pain signaling (58,59). Evidence from randomized controlled trials and meta-analyses shows that lidocaine 5% patches and capsaicin 8% patches provide moderate analgesic benefit with very favorable safety profiles. For example, a network meta-analysis found that lidocaine had the highest probability of being the most effective topical agent for PHN, and capsaicin 8% patch was non-inferior to oral pregabalin in certain peripheral neuropathic pain conditions, with fewer systemic adverse events (60). Another recent review reports moderate to high consensus that lidocaine is likely effective for diabetic peripheral neuropathy, idiopathic neuropathy and postsurgical neuropathy, and that capsaicin 8% is strongly effective in PHN and painful diabetic neuropathy (61). While NNT values are less frequently reported for topical agents, practical estimates suggest NNTs in the range of approximately 8-10 for capsaicin 8% patch in peripheral neuropathic pain settings (59,60).

Advantages of topical treatments include minimal systemic absorption, reduced risk of systemic side effects (e.g., sedation, dizziness, orthostatic hypotension common with systemic agents) and suitability for elderly or medically frail patients. However, limitations include the necessity for localized pain distribution (they are not suitable for diffuse neuropathic pain), skin-site reactions (burning, erythema, application-site pain especially with high-dose capsaicin), and higher upfront cost. Furthermore, head-to-head long-term comparative trials versus systemic therapies are still limited, and the durability of effect beyond three to six months remains less well characterized (56,58).

In clinical practice, topical therapies are best suited for patients with well-defined, limited areas of neuropathic pain, especially those who have contraindications to systemic treatment (e.g., multiple comorbidities, polypharmacy, high risk of systemic adverse effects). They should be avoided as monotherapy in patients with widespread neuropathic pain, severe allodynia involving large body surfaces, or when the neuropathic mechanism is predominantly central rather than peripheral. Monitoring is comparatively simple: mainly observing for local skin reactions and ensuring correct application technique.

Overall, topical treatments constitute an important component in a multimodal management strategy for neuropathic pain. They may be considered earlier in the therapeutic algorithm for appropriate candidates and often serve as a bridge or adjunct to systemic therapy.

4. Non-pharmacological Management of Chronic Pain Mechanisms

Effective management of chronic pain increasingly relies on a mechanism-oriented and multimodal therapeutic framework. Non-pharmacological interventions constitute a central component of this approach and, across multiple chronic pain phenotypes, often provide benefits comparable to or exceeding those of pharmacological treatment. The strongest evidence base exists for musculoskeletal and nociplastic pain conditions, yet targeted non-pharmacological strategies contribute meaningfully to the management of nociceptive, neuropathic and mixed pain as well. The following section outlines these interventions in relation to the dominant underlying mechanisms.

4.1. Physiotherapy

In disorders driven primarily by nociceptive mechanisms, such as osteoarthritis, mechanical low back pain or post-traumatic presentations, physiotherapy remains the first-line modality. Exercise therapy-whether focused on strengthening, aerobic conditioning or mobility-has repeatedly been shown to improve joint loading patterns, diminish inflammatory activity and enhance endogenous analgesic processes (62,63). Manual therapy techniques, including mobilization and soft-tissue manipulation, may contribute additional benefit by modulating mechanoreceptor activity and facilitating biomechanical correction (63). Re-establishing normal movement patterns through functional retraining plays a further role in counteracting maladaptive motor responses that often accompany persistent nociceptive input. Randomized trials consistently confirm that structured exercise is associated with improved pain and functional outcomes in chronic nociceptive conditions (62).

In neuropathic pain, traditional physiotherapy approaches tend to produce more variable results; nevertheless, several techniques have demonstrated targeted efficacy. Neurodynamic mobilization may reduce intraneural oedema and restore axonal transport in patients with radiculopathy or entrapment neuropathies (64). Programs incorporating graded desensitization to tactile or thermal stimuli aim to attenuate heightened peripheral and central excitability. Moreover, interventions such as motor imagery and mirror therapy-initially developed for complex regional pain syndrome and phantom limb pain-appear to influence cortical reorganization in ways that reduce neuropathic pain intensity (65).

Patients whose symptoms reflect a mixture of nociceptive and neuropathic mechanisms generally benefit from an integrated physiotherapeutic approach. Exercise can reduce nociceptive drive, whereas neurodynamic techniques address components of radicular irritation, and pacing or graded activity strategies help prevent escalation of central sensitization (63,64).

In conditions dominated by nociplastic mechanisms, including fibromyalgia and chronic widespread pain, physiotherapy shifts its emphasis toward interventions that modulate central processing rather than peripheral tissues. Low-intensity aerobic exercise enhances descending inhibitory pathways while also improving fatigue (66). Graded activity and graded exposure counteract fear-avoidance patterns and sensory hypersensitivity, whereas mind-body practices such as tai chi or yoga modulate autonomic hyperarousal and broader symptom burden (67). Among all available non-pharmacological strategies, exercise remains one of the most consistently effective interventions for nociplastic pain syndromes (66,67).

4.2. Cognitive-Behavioral Therapy (CBT)

Although cognitive-behavioral therapy is not traditionally categorized within physical rehabilitation, its relevance across all chronic pain mechanisms is substantial. In nociceptive pain, CBT primarily targets maladaptive cognitions-particularly catastrophizing and pain-related fear-that intensify sympathetic activation and muscular tension, thereby augmenting pain perception (68). Enhancing self-efficacy through CBT often improves adherence to physiotherapy and reduces functional impairment even when pain arises from identifiable structural pathology.

Neuropathic pain frequently coexists with psychological distress, hypervigilance and disrupted sleep. CBT addresses these components by modifying attentional biases toward pain, stabilizing mood, improving sleep hygiene and strengthening coping strategies. Evidence suggests that CBT yields moderate reductions in pain intensity and more pronounced improvements in overall quality of life, especially among patients with diabetic neuropathy or neuropathic back pain (68,69). Because mixed pain incorporates both sensory-physiological and cognitive-emotional dimensions, CBT becomes an especially valuable adjunct in this group, reducing central amplification and enhancing the efficacy of concurrent physiotherapeutic interventions.

In nociplastic disorders, CBT constitutes a core therapeutic modality. By diminishing catastrophizing, hypervigilance and stress-related fluctuations in symptom severity, CBT directly influences key components of central sensitization. Randomized controlled trials demonstrate reductions in widespread hyperalgesia and meaningful functional improvement following CBT in patients with nociplastic pain (68-70).

4.3. Transcutaneous Electrical Nerve Stimulation (TENS)

TENS, through activation of large-diameter Aβ fibers, engages segmental inhibitory mechanisms within the dorsal horn and can provide short-term analgesia in nociceptive musculoskeletal pain. High-frequency stimulation appears most effective, although inter-individual variability remains substantial and benefits tend to be transient (71).

In neuropathic pain, the mechanisms of action are more complex. TENS may enhance descending inhibition, modulate sodium channel expression and reduce ectopic neural discharge, partially counteracting the peripheral and central hyperexcitability characteristic of neuropathic states (72). Although its overall efficacy is moderate, patients with diabetic neuropathy or radiculopathy often report clinically relevant improvements when TENS is delivered at adequate intensity and consistency.

In nociplastic disorders characterized by central sensitization, TENS may temporarily diminish hyperalgesia and improve tolerance to movement-based therapy; however, the durability of these effects is typically limited (72)

4.4. Acupuncture

Acupuncture has accumulated substantial evidence in several predominantly nociceptive pain conditions, including chronic low back pain, knee osteoarthritis and migraine. Mechanistic studies indicate that needle stimulation engages Aδ and C fibers, activates endogenous opioid systems and produces modulation within limbic-brainstem circuits, collectively contributing to analgesia (73).

In neuropathic pain, acupuncture appears to exert its effects via modulation of neuroinflammatory processes, restoration of central neural plasticity and improvement of peripheral microcirculation (73). These mechanisms may attenuate nerve hypersensitivity and reduce symptom severity in peripheral neuropathies.

In nociplastic or centrally mediated pain states, acupuncture may influence descending inhibitory pathways and autonomic regulation, leading to reductions in symptom burden, although responses vary among individuals (73).

4.5. Patient Education

Education constitutes a foundational element of chronic pain management across all mechanistic categories. In nociceptive pain, explanatory frameworks centered on tissue healing trajectories, safe loading and the importance of maintaining activity help counteract fear-avoidance and prevent harmful over-resting.

In neuropathic pain, patients often benefit from detailed explanations regarding nerve healing processes, expected symptom variability, and the nature of pain flares, which collectively help reduce anxiety and heighten coping capacity. For mixed pain, mechanism-based education assists patients in understanding why both nociceptive and neuropathic sensations may arise simultaneously, thereby improving adherence to multimodal treatment strategies (74).

In nociplastic pain, Pain Neuroscience Education (PNE) has become one of the most important therapeutic tools. PNE aims to reframe the meaning of pain by clarifying how central sensitization affects perception, why pain does not reliably indicate tissue damage, and how movement, stress and cognition shape nociceptive processing. Randomized trials demonstrate that PNE reduces catastrophizing, increases pain thresholds and enhances the outcomes of exercise-based rehabilitation (74-76). As a result, PNE is now strongly recommended in fibromyalgia, chronic low back pain and chronic primary pain syndromes.

5. Interventional Management of Neuropathic Pain

Nerve Blocks in the Management of Neuropathic Pain

Nerve blocks constitute an important component of interventional management for peripheral and sympathetically maintained neuropathic pain and are widely used both as diagnostic tools and short-term therapeutic interventions. These include peripheral nerve blocks, targeting specific injured or hyperactive nerves, and sympathetic ganglion blocks, such as stellate ganglion block or lumbar sympathetic block, aimed at reducing sympathetically maintained pain. Their mechanism relies primarily on temporary interruption of ectopic discharges, inhibition of peripheral sensitization and decreased abnormal afferent signaling to the dorsal horn, thereby modulating central excitability (77,78).

In clinical practice, peripheral nerve blocks provide a transient reduction in pain in conditions such as post-traumatic neuralgia, postsurgical neuropathic pain or focal entrapment neuropathies. Evidence indicates that although many patients experience meaningful but short-lived relief, sustained long-term benefit is achieved in only a subset whose pain arises from discrete, well-localized neural pathology (79). Sympathetic blocks appear particularly beneficial in complex regional pain syndrome (CRPS) and certain sympathetically maintained neuropathic pain syndromes, reducing pain, allodynia, vasomotor symptoms and improving limb mobility; however, repeated procedures are often necessary due to the limited duration of effect (78,80).

Patients most likely to benefit from nerve blocks are those with clearly identifiable target nerves, localized pain distribution, and relatively preserved central processing without widespread sensitization. In contrast, limited benefit is expected in patients with diffuse neuropathic pain, severe polyneuropathy, long-standing neuropathic changes or centralized pain mechanisms, where peripheral interruption has minimal physiological impact (77,79). The overall safety profile of nerve blocks is favorable, although potential complications include local infection, bleeding, hematoma, transient motor blockade, inadvertent intraneural injection, hypotension after sympathetic block, and rare systemic toxicity related to local anesthetics (80).

In modern multimodal neuropathic pain care, nerve blocks serve primarily as adjunctive treatments-useful for short-term relief, functional rehabilitation, diagnostic clarification, or as a bridge to more durable interventions such as pulsed radiofrequency or neuromodulation. Their value lies in targeted analgesia with minimal systemic burden, but clinicians should emphasize realistic expectations: nerve blocks typically offer temporary benefit, and their optimal use occurs as part of a broader interventional and rehabilitative strategy.

5.1 Steroid Injections in the Management of Neuropathic Pain

Steroid injections-including epidural steroid injections (ESIs), transforaminal epidural injections, and perineural or periradicular corticosteroid applications-represent commonly used interventional procedures for neuropathic pain of spinal origin, particularly radicular pain due to nerve root inflammation or compression. Their therapeutic effect is based on the potent anti-inflammatory and membrane-stabilizing properties of corticosteroids, which reduce perineural oedema, inhibit pro-inflammatory cytokines, and attenuate ectopic discharges in irritated nerve roots, thereby moderating both peripheral and central sensitization (78,81). In specific indications-especially acute or subacute radiculopathies secondary to disc herniation-steroid injections can offer clinically meaningful short-term relief of radiating neuropathic leg pain (78).

Evidence from randomized controlled trials shows that epidural and transforaminal steroid injections provide modest but significant short-term improvement in pain and function in lumbar and cervical radiculopathy, with the greatest effect occurring in the first weeks after treatment (78,82). However, long-term efficacy remains limited: systematic reviews conclude that benefits typically diminish after 3-6 months, and repeated injections may be required to maintain relief, though cumulative evidence still supports their use in carefully selected patients

(81,82). Perineural steroid injections for focal neuropathic pain (such as post-traumatic neuralgia or entrapment neuropathies) may provide transient benefit by reducing local inflammation, although data are less robust than for radicular pain (83). Stellate ganglion or lumbar sympathetic steroid injections may improve pain and vasomotor instability in CRPS, but the quality of evidence remains low and effects are often temporary (83-85).

Patients most likely to benefit from steroid injections are those with clear neuroanatomical correlation between symptoms and imaging, acute or subacute radicular pain, significant inflammatory components, or functional impairment preventing progress in rehabilitation. In contrast, steroid injections are less effective in chronic radiculopathy without active inflammation, severe long-standing nerve damage, diffuse polyneuropathy, or pain dominated by central sensitization (78,82,83). Risks include bleeding, infection, dural puncture, transient sensory or motor deficit, and, rarely, catastrophic events such as spinal cord ischemia in cervical transforaminal injections due to inadvertent arterial injection of particulate steroids (84,85). Systemic steroid effects may also occur-transient hyperglycemia, fluid retention, facial flushing-especially in diabetic or frail patients (81,84).

Overall, steroid injections are best used as adjunctive, time-limited interventions to facilitate functional recovery, reduce acute inflammatory radicular pain, and create a therapeutic window for physiotherapy or pharmacological optimization. They provide short-term relief in well-selected patients but should not be considered a stand-alone long-term therapy for chronic neuropathic pain.

5.2 Neuromodulation in the Management of Neuropathic Pain

Neuromodulation encompasses a group of advanced interventional therapies-including Spinal Cord Stimulation (SCS), Dorsal Root Ganglion Stimulation (DRG-S) and Peripheral Nerve Stimulation (PNS)-that target aberrant neural activity within the somatosensory system. These modalities modulate pain transmission through electrical stimulation of dorsal columns, dorsal root ganglia or peripheral nerves, altering synaptic activity, reducing central sensitization and enhancing descending inhibitory pathways (78,86). Neuromodulation is generally recommended for chronic neuropathic pain refractory to optimized pharmacotherapy, rehabilitation and minimally invasive interventions, and plays an increasingly central role in the management of complex neuropathic conditions.

Spinal Cord Stimulation (SCS) is the most established form of neuromodulation, with strong evidence supporting its use in complex regional pain syndrome (CRPS) and failed back surgery syndrome (FBSS) with neuropathic radicular pain (78,87). Traditional tonic SCS provides significant pain relief in approximately 50-60% of appropriately selected patients; however, newer waveforms have improved outcomes. High-frequency 10 kHz SCS and burst stimulation have demonstrated superior pain reduction and improved patient tolerability by avoiding paresthesias, with randomized trials confirming greater reductions in neuropathic leg and back pain compared with conventional SCS (87). SCS has also shown promise in peripheral neuropathies, including refractory diabetic neuropathy, although evidence remains less robust than for CRPS or FBSS (88).

Dorsal Root Ganglion Stimulation (DRG-S) has emerged as a major advancement in the treatment of focal neuropathic pain syndromes, particularly CRPS I/II and localized mononeuropathies. DRG-S delivers highly targeted stimulation with minimal postural variation and superior coverage of anatomically restricted pain distributions. The ACCURATE trial demonstrated that DRG-S provided significantly higher treatment success rates than traditional SCS at 3 and 12 months in patients with CRPS and causalgia (89). Its selective targeting makes it especially effective for neuropathic pain of the foot, groin, knee and upper limb-areas often challenging for conventional SCS (86,89).

Peripheral Nerve Stimulation (PNS) provides an additional option for post-traumatic neuralgia, postsurgical neuropathic pain, and single-nerve injuries, offering focused modulation of peripheral nociceptive inputs. Contemporary ultrasound-guided, minimally invasive PNS systems have demonstrated meaningful pain reductions and functional improvement, with relatively low morbidity and favorable patient tolerability (86,88). Although long-term, large RCT data remain limited, clinical experience supports its role in discrete neuropathic pain syndromes where central neuromodulation may be disproportionate.

Neuromodulation is generally considered in patients who have failed guideline-recommended treatments, present with stable psychological profile, have pain clearly neuropathic in nature, and demonstrate positive response during trial stimulation, which predicts long-term success (78,87). Despite its benefits, neuromodulation carries risks including lead migration, infection, hardware malfunction, and the need for surgical revision; however, serious complications remain relatively uncommon in modern practice (87,89).

Overall, neuromodulation represents one of the most effective advanced treatments for severe, refractory neuropathic pain, providing durable pain relief, functional improvement and reduced reliance on systemic medications, particularly in CRPS, FBSS and focal neuropathies. Its expanding evidence base supports increasingly individualized, anatomically targeted approaches.

5.3 Pulsed Radiofrequency (PRF) in the Management of Neuropathic Pain

Pulsed radiofrequency (PRF) is a minimally invasive interventional neuromodulation technique increasingly used in the management of neuropathic pain, particularly when traditional nerve blocks provide only transient relief or when more invasive neuromodulation is not yet indicated. Unlike conventional thermal radiofrequency ablation, PRF delivers short bursts of high-frequency current while maintaining tissue temperature below neurodestructive levels (typically <42°C), thereby producing a non-ablative modulation of neuronal activity rather than structural nerve injury (90,91). The mechanism of PRF is believed to involve changes in synaptic transmission, modulation of dorsal horn wide-dynamic-range neurons, alteration of microglial activation, and reduction of ectopic firing in pain pathways (90,92).

Clinical evidence supports PRF as a valuable option in focal neuropathic pain syndromes, with favorable outcomes in radicular pain, postherpetic neuralgia (PHN), trigeminal neuralgia, intercostal neuralgia, and CRPS, particularly when applied to the dorsal root ganglion (DRG) or peripheral nerves (91,92). PRF of the gasserian ganglion has shown benefit in trigeminal neuralgia while avoiding the sensory deficits associated with destructive radiofrequency ablation (93). Similarly, PRF applied to the DRG has demonstrated clinically meaningful pain reduction in radiculopathies, with randomized and prospective studies reporting superior safety compared with thermal ablation and more sustained relief than local anesthetic blocks alone (91,94).

PRF is especially attractive due to its excellent safety profile. Because it does not cause neuronal destruction, risks of sensory loss, dysesthesias or deafferentation pain are markedly lower than with continuous RF ablation. Reported complications are rare and typically mild, including transient soreness at the puncture site or short-lived neuritis (93,94). This favorable safety-to-benefit ratio makes PRF a suitable option for patients with localized neuropathic pain, refractory radiculopathy, PHN, or neuralgia after surgery or trauma, particularly when patients are not ideal candidates for neurodestructive or implantable therapies.

The patients most likely to benefit from PRF are those with well-defined pain distribution, a clearly identifiable target nerve or ganglion, and neuropathic features dominated by peripheral or segmental sensitization. PRF is less effective in widespread polyneuropathy or centralized pain states, where focal neuromodulation has limited physiological impact. Optimal application often involves ultrasound or fluoroscopy guidance, precise needle placement near the DRG or affected nerve, and consideration of repeated sessions when pain recurs (90-92). Although long-term data remain somewhat limited, available evidence supports PRF as an effective intermediate therapy bridging the gap between simple nerve blocks and advanced neuromodulation systems.

5.4 Botulinum Toxin Type A in the Management of Neuropathic Pain

Botulinum toxin type A (BoNT-A) has emerged as an important minimally invasive option for the treatment of localized peripheral neuropathic pain, particularly when systemic therapies are ineffective or poorly tolerated. Although traditionally used for spasticity and migraine, growing evidence indicates that BoNT-A exerts direct antinociceptive and anti-inflammatory effects. Its mechanisms include inhibition of acetylcholine release, suppression of peripheral sensitization by blocking release of substance P, CGRP and glutamate, and modulation of TRPV1 and sodium channels on nociceptors, thereby reducing peripheral and central excitability over weeks to months (95,96).

Clinical studies and meta-analyses have demonstrated significant benefit of BoNT-A in postherpetic neuralgia (PHN), painful diabetic neuropathy, post-surgical neuropathic pain, trigeminal neuralgia, and peripheral nerve injury-related neuropathies. Randomized controlled trials show that subcutaneous or intradermal BoNT-A injections provide clinically meaningful pain reduction lasting 8-12 weeks, often exceeding the duration of relief achieved by local anesthetic nerve blocks (95-97). A meta-analysis of RCTs reported an NNT between 3 and 5 for achieving ≥50% pain reduction in neuropathic pain, highlighting BoNT-A as one of the more effective adjunctive modalities for focal neuropathic syndromes (97). Benefits are particularly notable in PHN and diabetic neuropathy, with improvements in both spontaneous pain and allodynia (96,97).

Patients most likely to benefit are those with well-localized neuropathic pain, small or moderate treatment fields (e.g., thoracic dermatomes in PHN, localized trigeminal or limb neuropathic pain), and partial failure or intolerance to systemic agents. BoNT-A is especially useful in medically complex or elderly patients because of its excellent systemic safety profile. Adverse events are generally mild and focal, including transient local weakness, mild bruising or injection-site discomfort (95). Systemic spread is rare at doses used for neuropathic pain. Limitations include the need for repeated injections every 3-4 months and variable insurance or reimbursement coverage in some regions.

Overall, BoNT-A represents a safe, effective and well-tolerated interventional therapy for localized peripheral neuropathic pain, supported by growing high-quality evidence. It is best employed as an adjunctive treatment within a multimodal strategy, positioned between conservative measures and more invasive neuromodulatory approaches.

Discussion

This review supports the view that chronic pain is best understood as a dynamic interaction of nociceptive, neuropathic and nociplastic mechanisms rather than a fixed, purely anatomical diagnosis. The ICD-11/IASP mechanistic framework provides a practical language for this approach, but in everyday care most patients present with overlapping features. For clinicians, the key task is therefore not simply to label pain as "one type," but to estimate the relative contribution of each mechanism over time and to adjust treatment as the phenotype evolves.

Across many conditions, persistent peripheral input-whether from ongoing tissue inflammation or nerve injury-appears to be a common trigger for progressive central sensitization. Once central amplification becomes established, symptoms often extend beyond the original site of injury and become more influenced by sleep, stress, mood, and behavioral responses such as avoidance and catastrophizing. This explains why targeting only peripheral pathology frequently fails in long-standing pain, and why early, mechanism-matched treatment of nociceptive and neuropathic generators may be clinically important, even if definitive preventive data remain limited. Pharmacological evidence emphasizes moderate average effect sizes and substantial interindividual variability. NSAIDs remain appropriate for nociceptive pain and the inflammatory component of mixed pain but are not supported as specific treatment for pure neuropathic pain and carry relevant GI, renal, and cardiovascular risks. For neuropathic pain, TCAs, SNRIs, and gabapentinoids remain the best-supported first-line options, while other antidepressants and anticonvulsants have narrower or less consistent roles. Opioids and cannabis-based medicines may help a subset of patients, but the benefit is typically modest and must be weighed against adverse effects, dependence risk, and uncertain long-term outcomes.

Topical lidocaine and high-dose capsaicin are valuable for localized peripheral neuropathic pain because they offer symptom reduction with minimal systemic burden. Importantly, the review also reinforces that chronic pain management cannot be medication-centered. Exercise-based rehabilitation, CBT and related psychological therapies, pain neuroscience education, and selected modalities such as TENS or acupuncture address central amplification, functional impairment, and the cognitive-emotional drivers of pain. Interventional techniques can provide targeted, often time-limited relief and may facilitate rehabilitation; advanced neuromodulation is most appropriate for carefully selected, refractory neuropathic pain syndromes. Taken together, the strongest clinical rationale is for a multimodal plan that targets peripheral generators, neural hyperexcitability, central sensitization, and psychosocial factors simultaneously, with regular reassessment and shared decision-making. Key gaps remain. Many trials still enroll patients based on anatomical diagnoses rather than mechanistic phenotypes, long-term comparative data are limited, and predictors of response are weak. Future research should prioritize feasible clinical phenotyping, pragmatic multimodal trials, and real-world effectiveness data to better match treatment combinations to patient profiles.

Conclusion

Chronic pain is best conceptualized as a spectrum disorder of the nociceptive system in which nociceptive, neuropathic and nociplastic processes often coexist and change over time. A mechanism-based assessment aligned with the ICD-11/IASP framework improves clinical reasoning and supports individualized, multimodal care. In practice, effective management combines appropriately selected pharmacotherapy with exercise-based rehabilitation, psychological interventions, patient education, and-when indicated-targeted interventional procedures. Realistic goals should focus on meaningful improvements in function, participation, sleep, and quality of life rather than complete pain elimination.

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