Review Article

Neuropathic Pain: Pharmacological Management with Emphasis on Anesthetic Agents and Neuromodulatory Therapies

Gabriel Muñoz Jackson[1*], Ivonne Consumi Flores[2], María José Solís Marín[3], Alexandra Mora Quirós[4], Isis Karolina Vega Vega[5], Mariana Bolaños Castro[6]

[1]Internal Medicine Specialist, San Juan de Dios Hospital, San José, Costa Rica
[2]Medical Doctor, Independent Researcher, San José, Costa Rica
[3]Medical Doctor, Tony Facio Castro Hospital, Limón, Costa Rica
[4]Medical Doctor, Caja Costarricense de Seguro Social, San José, Costa Rica
[5]Medical Doctor, San Rafaela de Alajuela Hospital, Alajuela, Costa Rica
[6]Medical Doctor, San Juan de Dios Hospital, San José, Costa Rica
[*]Corresponding author email: **gabriel7_cr5@yahoo.com**

International Archives of Integrated Medicine, Vol. 13, Issue 4, April, 2026.
Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 1-4-2026 **Accepted on:** 15-4-2026
Source of support: Nil **Conflict of interest:** None declared.

DOI: **10.5281/zenodo.19810138**

How to cite this article: Gabriel Muñoz Jackson, Ivonne Consumi Flores, María José Solís Marín, Alexandra Mora Quirós, Isis Karolina Vega Vega, Mariana Bolaños Castro. Neuropathic Pain: Pharmacological Management with Emphasis on Anesthetic Agents and Neuromodulatory Therapies. Int. Arch. Integr. Med., 2026; 13(4): 78-93.

Abstract

Neuropathic pain is a complex and multifactorial condition resulting from lesions or diseases affecting the somatosensory system, characterized by persistent pain that is often resistant to conventional treatments. Its pathophysiology involves a combination of peripheral and central mechanisms, including ectopic impulse generation, peripheral and central sensitization, ion channel dysfunction, and neurotransmitter imbalance. These processes lead to increased neuronal excitability and maladaptive plasticity, contributing to the chronicity of pain. Clinically, neuropathic pain is classified as peripheral or central depending on the location of the lesion and is associated with conditions such as diabetic neuropathy, postherpetic neuralgia, radiculopathy, chemotherapy-induced neuropathy, and spinal cord injury. Patients typically present with spontaneous pain described as burning or electric sensations, as well as evoked pain such as allodynia. Diagnosis relies on clinical evaluation supported

by validated tools and complementary studies, including electrophysiology and imaging. Management is guided by a stepwise and individualized approach aimed at reducing pain, improving function, and enhancing quality of life. First-line treatments include gabapentinoids, tricyclic antidepressants, and serotonin–norepinephrine reuptake inhibitors, while second- and third-line options include topical therapies, opioids, and interventional procedures. Anesthetic agents such as lidocaine and ketamine, along with neuromodulatory drugs, play an important role, particularly in refractory cases. Despite available therapies, treatment outcomes remain suboptimal due to limited efficacy and adverse effects. Emerging strategies, including precision medicine, targeted ion channel therapies, and neuromodulation techniques, offer promising avenues for improving long-term management and patient outcomes.

Key words

Neuropathic pain, central sensitization, peripheral sensitization, neuromodulators, local anesthetics, multimodal therapy.

Introduction

Neuropathic pain is a complex and challenging condition characterized by pain arising from a lesion or disease affecting the somatosensory system. The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory system". This condition significantly impacts patients' quality of life and presents substantial therapeutic challenges due to its heterogeneous nature and frequent resistance to conventional analgesics. Its global prevalence is considerable, with estimates ranging from 6.9% to 10%, although broader analyses suggest that it may affect between 3% and 17% of the general population depending on diagnostic criteria and population characteristics. Furthermore, neuropathic pain is commonly associated with conditions such as diabetes, multiple sclerosis, and spinal cord injuries, which contribute to its overall prevalence and clinical burden. The chronic nature of this condition, combined with its resistance to treatment, results in increased healthcare costs and reduced productivity, thereby amplifying its global impact [1, 2, 3].

From a clinical perspective, neuropathic pain is characterized by a range of symptoms including numbness, tingling, and electric shock–like sensations, all of which can severely impair daily functioning. These persistent and often severe symptoms contribute to a marked decline in functional status and overall quality of life. In addition, the chronic and frequently refractory nature of neuropathic pain is closely associated with psychological comorbidities such as depression and anxiety, further exacerbating patient burden. Effective management is therefore essential, as inadequate or delayed treatment may lead to long-term alterations in pain pathways, ultimately making the condition more difficult to control over time [4, 5].

Despite advances in understanding its pathophysiology, the treatment of neuropathic pain remains particularly challenging. First-line pharmacological therapies, including gabapentinoids, tricyclic antidepressants, and serotonin–norepinephrine reuptake inhibitors, often demonstrate limited efficacy and are frequently associated with significant adverse effects [5]. Consequently, a substantial proportion of patients fail to achieve adequate symptom control, resulting in high rates of treatment failure and refractoriness [4]. This therapeutic difficulty is further compounded by the complexity of neuropathic pain, which encompasses diverse etiologies and underlying mechanisms, thereby hindering the development of universally effective treatment strategies [6].

In this context, there has been growing interest in alternative therapeutic approaches, particularly those involving anesthetic agents and neuromodulators. Anesthetic agents such as bupivacaine have demonstrated potential in providing targeted pain relief through the modulation of neuroimmune interactions and the reduction of neuroinflammation [7]. Similarly, neuromodulation techniques, including spinal cord stimulation and peripheral nerve stimulation, offer promising strategies for achieving sustained analgesia by altering pain signaling pathways. These approaches are especially relevant given their capacity to provide more individualized treatment options while potentially reducing reliance on systemic medications associated with significant side effects [8].

The aim of this articles is o analyze the pharmacological management of neuropathic pain, with particular emphasis on the role of anesthetic agents and neuromodulators, in order to evaluate their mechanisms of action, clinical effectiveness, and potential as therapeutic alternatives in patients with refractory pain.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of hypopharyngeal and cervical esophageal carcinoma, with particular emphasis on prognostic determinants, diagnostic strategies, and contemporary therapeutic approaches. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the clinical heterogeneity of these tumors and the variability in staging systems and treatment paradigms, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate anatomical, oncologic, and functional considerations into a coherent and clinically applicable framework. Special attention was given to the impact of cervical esophageal invasion on survival, the role of multimodal therapy, organ-preservation strategies, and reconstructive approaches in advanced disease. The objective was to provide a structured synthesis capable of supporting multidisciplinary decision-making in complex upper aerodigestive tract malignancies.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and December 2025. The final search was performed in March2026. This timeframe was selected to capture contemporary advances in chemoradiotherapy protocols, surgical reconstruction techniques, immunotherapy integration, and updated staging recommendations. Foundational studies were incorporated when necessary to contextualize pathophysiological mechanisms or historical treatment evolution. The search strategy combined MeSH and free-text terms using Boolean operators related to hypopharyngeal carcinoma, cervical esophageal carcinoma, squamous cell carcinoma, cervical esophageal invasion, chemoradiotherapy, pharyngolaryngoesophagectomy, organ preservation, neoadjuvant therapy, survival outcomes, and reconstruction techniques. Searches were conducted in titles and abstracts as well as indexed subject headings to maximize sensitivity.

The initial search yielded 205 records. After removal of duplicates, 141 articles remained for title and abstract screening. Of these, 93 underwent full-text evaluation, and 50 studies were included in the final synthesis. Selection was performed independently by two authors, with disagreements resolved through discussion and consensus. Exclusion criteria comprised non–peer-reviewed publications, isolated case reports, editorials without outcome data, purely technical surgical descriptions lacking oncologic results, redundant datasets, and studies not

directly addressing prognostic impact, diagnostic evaluation, or therapeutic outcomes in hypopharyngeal or cervical esophageal carcinoma.

Eligible studies included randomized controlled trials, large observational cohorts, systematic reviews, meta-analyses, expert consensus statements, and contemporary international guidelines from head and neck oncology, thoracic surgery, and radiation oncology societies. Priority was assigned to multicenter investigations, studies with standardized TNM staging definitions, and research evaluating survival outcomes, loco-regional control, functional results, and treatment-related morbidity. Extracted variables included study design, tumor location and stage, presence of cervical esophageal invasion, treatment modality, reconstruction technique when applicable, survival metrics (overall survival and disease-free survival), recurrence patterns, and reported complications. Methodological quality and internal validity were assessed narratively, considering risk of bias, sample size, follow-up duration, consistency of staging criteria, and reproducibility of reported outcomes. In cases of conflicting evidence, greater interpretative weight was assigned to higher-level evidence and guideline-supported recommendations.

Reference lists of included studies were manually screened to identify additional relevant publications. Given its narrative design, this review is subject to potential selection bias and does not provide pooled quantitative estimates. Artificial intelligence–based tools were used exclusively to assist in literature organization and structural coherence, whereas critical appraisal, synthesis, and final interpretation were conducted independently by the authors to preserve methodological rigor.

Pathophysiological Mechanisms of Neuropathic Pain

Peripheral nerve injury initiates a cascade of pathophysiological events that contribute to the development and persistence of neuropathic pain. One of the earliest mechanisms involves the generation of ectopic impulses, which are abnormal spontaneous electrical discharges arising from injured nerve fibers. These aberrant signals are often associated with miswiring and inappropriate targeting of end organs by nociceptors, ultimately leading to clinical manifestations such as allodynia and hyperalgesia [9]. In parallel, the sprouting of sympathetic fibers within the dorsal root ganglia (DRG), along with the release of mediators such as norepinephrine and CXCL16, further amplifies neuronal hyperexcitability, thereby contributing to the maintenance of neuropathic pain states [7].

This peripheral dysfunction is closely linked to the process of peripheral sensitization, in which nociceptors exhibit an exaggerated response to both noxious and non-noxious stimuli. This heightened sensitivity is driven by inflammatory mediators, including cytokines and chemokines, which create a pro-inflammatory microenvironment. Additionally, oxidative stress and cellular senescence further exacerbate this state, reinforcing sustained nociceptor activation [10]. At the molecular level, ion channels play a crucial role in this process, particularly the sensitization of TRPV1 channels in DRG neurons, which has been strongly implicated in conditions such as chemotherapy-induced peripheral neuropathy [11].

As these peripheral mechanisms evolve, central sensitization emerges as a key contributor to chronic pain. This process is characterized by increased excitability of neurons in the spinal dorsal horn, resulting in amplified pain transmission. Synaptic plasticity and altered neurotransmission, particularly involving N-methyl-D-aspartate receptors (NMDARs), are central to this phenomenon [12]. Furthermore, voltage-gated calcium channels, especially those containing the α2δ-1 subunit, facilitate abnormal excitatory synaptic activity, thereby promoting

mechanical hypersensitivity and persistent pain signaling [13].

Ion channels more broadly play a fundamental role in the pathophysiology of neuropathic pain, as voltage-gated sodium and calcium channels regulate neuronal excitability and nociceptive transmission. Among these, the α2δ-1 subunit of calcium channels has been identified as a key modulator of enhanced synaptic transmission, while T-type calcium channels such as Cav3.2 contribute to both peripheral and central mechanisms involved in the initiation and maintenance of pain [13, 14].

Neurotransmitter imbalance represents another critical dimension in neuropathic pain. Increased excitatory signaling mediated by glutamate, particularly through NMDAR activation, is coupled with reduced inhibitory control due to GABAergic dysfunction, leading to a net increase in neuronal excitability [12, 14]. Additionally, monoaminergic systems involving serotonin and norepinephrine contribute to the modulation of pain pathways, while interactions between neurotransmitters and ion channels, such as TRPV1, further influence nociceptive signaling [13].

This imbalance between excitation and inhibition is further compounded by disinhibition and maladaptive plasticity within the spinal cord and higher neural structures. Reduced GABAergic activity results in diminished inhibitory control, allowing for persistent amplification of pain signals [10]. Concurrently, maladaptive plasticity leads to structural and functional reorganization of both spinal and cortical circuits following nerve injury, reinforcing the chronicity of pain [15].

At the cortical level, reorganization of sensory representations plays a pivotal role in sustaining neuropathic pain. Alterations in corticospinal circuits and their regulatory influence on spinal interneurons contribute to persistent dysregulation of pain processing [15]. Moreover, the maintenance of neuropathic pain is supported by ongoing structural plasticity and abnormal connectivity across both peripheral and central nervous systems, highlighting the complex and multifactorial nature of this condition [9].

Clinical Classification and Diagnostic Approach

Neuropathic pain is broadly classified into peripheral and central types based on the anatomical location of the lesion within the somatosensory system. Peripheral neuropathic pain arises from damage to the peripheral nervous system and is commonly associated with conditions such as diabetic neuropathy and chemotherapy-induced neuropathy. Diabetic neuropathy, which may affect up to half of patients with diabetes, represents one of the most prevalent causes, with neuropathic pain present in approximately 30–40% of cases [2, 16]. Similarly, chemotherapy-induced neuropathy results from the neurotoxic effects of antineoplastic agents, leading to structural and functional damage to peripheral nerves [17]. In contrast, central neuropathic pain results from lesions or diseases affecting the central nervous system, including conditions such as spinal cord injury and multiple sclerosis, where disruption of central pain pathways plays a key role in symptom generation [2].

Within this classification, several etiologies are frequently encountered in clinical practice. Diabetic neuropathy remains a leading cause, affecting both type 1 and type 2 diabetes populations and contributing substantially to the global burden of neuropathic pain [16]. Postherpetic neuralgia, a complication following herpes zoster infection, is characterized by persistent pain that continues even after the resolution of the cutaneous rash. Radiculopathy, often secondary to nerve root compression from intervertebral disc herniation, produces pain that radiates along the affected nerve distribution. Additionally, chemotherapy-induced neuropathy and spinal cord injury further exemplify peripheral and central mechanisms, respectively,

highlighting the diversity of underlying causes [2, 17].

Clinically, neuropathic pain presents with a characteristic symptom profile that includes both spontaneous and evoked components. Spontaneous pain typically manifests as burning, shooting, or electric-like sensations that occur in the absence of external stimuli, reflecting ongoing abnormal neural activity [18]. In contrast, evoked pain is triggered by stimuli that are normally non-painful, such as light touch or temperature changes, a phenomenon that underscores the presence of allodynia and heightened sensory responsiveness [2]. These symptom patterns are often described by patients using distinctive qualitative descriptors, such as burning or electric sensations, which aid in differentiating neuropathic pain from nociceptive pain [18].

Accurate diagnosis relies on a combination of clinical evaluation and validated diagnostic tools. Screening questionnaires such as DN4, LANSS, and painDETECT provide structured approaches for identifying neuropathic pain and are widely recommended in clinical practice. These tools are complemented by a thorough neurological examination, including sensory mapping, which is essential for detecting deficits and correlating symptom distribution with underlying neural structures [2]. In addition to clinical assessment, complementary studies play an important role in confirming the diagnosis and identifying underlying causes. Electrophysiological studies are particularly useful for demonstrating nerve damage and assessing the severity and extent of neuropathy [16]. Imaging modalities, on the other hand, can help identify structural abnormalities such as nerve compression or central lesions, thereby providing further insight into the etiology of neuropathic pain [19].

General Principles of Pharmacological Management

The management of neuropathic pain is guided by clearly defined therapeutic goals that extend beyond simple analgesia. The primary objective is pain reduction to a level that allows patients to maintain daily functioning and participate in routine activities [1, 20]. In parallel, improving functional capacity is essential, as neuropathic pain frequently limits mobility and independence in daily tasks. Equally important is the enhancement of quality of life, which requires addressing not only pain intensity but also associated symptoms such as sleep disturbances and mood disorders, both of which significantly contribute to overall patient burden [18].

To achieve these goals, treatment is typically structured using a stepwise, guideline-based approach. First-line therapies include gabapentinoids such as gabapentin and pregabalin, as well as tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors, all of which target key mechanisms involved in neuropathic pain processing. When these initial strategies fail or are not well tolerated, second-line therapies may be considered, particularly topical agents such as capsaicin or lidocaine patches, which are especially useful in cases of localized pain [5, 18]. In more refractory cases, third-line options are introduced, including opioids or interventional procedures, although these approaches are generally reserved due to concerns regarding safety and long-term efficacy [17].

Given the multifactorial nature of neuropathic pain, multimodal analgesia has emerged as an important therapeutic strategy. The use of combination therapy, involving multiple pharmacological agents with different mechanisms of action, may enhance analgesic effects while potentially reducing dose-related adverse events, although evidence supporting clear superiority over monotherapy remains limited [21]. In addition to pharmacological interventions, non-pharmacological approaches such as neurostimulation techniques and physical therapy can serve as valuable adjuncts,

contributing to a more comprehensive and integrated management plan [1].

A key component of effective management is the individualization of treatment based on patient-specific factors. Personalized therapeutic strategies take into account underlying comorbidities, such as diabetes or cancer, as well as potential drug interactions and tolerability profiles, thereby optimizing both safety and efficacy [17, 22]. Furthermore, phenotypic profiling, which involves a detailed assessment of clinical characteristics and symptom patterns, can help guide more targeted and mechanism-based treatment selection [1].

Neuropathic pain often requires long-term management, making regular follow-up and reassessment essential components of care. Treatment plans should be continuously adjusted based on therapeutic response and the emergence of adverse effects [20]. Ongoing monitoring of pain intensity, functional status, and quality of life is necessary to ensure that treatment objectives are being achieved and maintained over time [22].

Despite these structured approaches, significant limitations persist, particularly with the use of monotherapy. Many patients fail to achieve adequate pain relief with a single agent due to the complex and multifaceted mechanisms underlying neuropathic pain [22]. Additionally, the doses required to achieve meaningful analgesia are often associated with dose-limiting side effects, which can compromise adherence and tolerability [5]. A subset of patients remains refractory to standard treatments altogether, highlighting the need for alternative and more individualized therapeutic strategies [23].

Anesthetic Agents in Neuropathic Pain Management

Local anesthetics represent an important component in the management of neuropathic pain due to their ability to directly modulate neuronal excitability. Their primary mechanism of action involves the blockade of voltage-gated sodium channels, which are essential for the initiation and propagation of action potentials in neurons. By inhibiting these channels, agents such as lidocaine reduce abnormal neuronal firing and attenuate pain transmission [24].

Among these agents, topical lidocaine has gained widespread clinical use, particularly in localized neuropathic pain conditions. Lidocaine patches are approved for the treatment of post-herpetic neuralgia and have demonstrated efficacy in other conditions such as diabetic peripheral neuropathy, carpal tunnel syndrome, and chronic lower back pain [25]. Evidence from meta-analyses indicates that topical lidocaine can significantly reduce pain intensity in post-surgical neuropathic pain without increasing the incidence of adverse events [26]. Additionally, in the context of cancer-related neuropathic pain, lidocaine patches have shown effectiveness in reducing pain intensity, even when used in combination with opioid therapy, highlighting their value as an adjunctive treatment option [27].

In more complex or refractory cases, intravenous lidocaine infusions have been explored as a systemic therapeutic option. These infusions have been used in chronic neuropathic pain conditions, including spinal cord injury and diabetic neuropathy. However, the available evidence regarding their efficacy remains heterogeneous, and further large-scale studies are required to establish clear clinical recommendations [28]. Beyond chronic pain management, intravenous lidocaine has also demonstrated benefits in the perioperative setting, where it contributes to reduced postoperative pain, decreased opioid requirements, and enhanced recovery, facilitating earlier discharge in surgical patients [29].

Regional anesthesia techniques further expand the role of local anesthetics by enabling targeted delivery to specific neural structures. Peripheral nerve blocks and sympathetic blocks allow for

localized pain control and are particularly useful in conditions such as complex regional pain syndrome and other forms of focal neuropathic pain. These approaches provide the advantage of site-specific analgesia while minimizing systemic exposure and associated adverse effects [30].

In addition to local anesthetics, systemic anesthetic agents such as ketamine play a significant role in the management of refractory neuropathic pain. Ketamine exerts its effects primarily through antagonism of N-methyl-D-aspartate receptors, which are critically involved in central sensitization, a key mechanism underlying persistent neuropathic pain. This pharmacological action allows ketamine to reduce exaggerated central pain signaling and provide analgesia in patients who have not responded to conventional therapies. However, its clinical use is limited by the potential for adverse effects, necessitating careful patient selection and monitoring [24].

Recent advances have also focused on the development of emerging anesthetic-related therapies, particularly extended-release drug delivery systems. These formulations are designed to prolong the duration of analgesia and reduce the need for repeated dosing, thereby improving treatment adherence and patient convenience. Collectively, these strategies highlight the expanding role of anesthetic agents in the multimodal management of neuropathic pain, particularly in patients with refractory or localized conditions [30].

Neuromodulatory Pharmacological Agents

Antidepressants constitute a fundamental component in the pharmacological management of neuropathic pain due to their modulatory effects on central pain pathways and neurotransmitter systems. Tricyclic antidepressants, particularly amitriptyline and nortriptyline, have demonstrated significant efficacy in reducing neuropathic pain. Their mechanism of action is primarily based on the inhibition of norepinephrine and serotonin reuptake, leading to increased extracellular concentrations of these neurotransmitters. This effect is mediated through α1- and α2-adrenergic receptors, which contribute to the inhibition of glutamatergic input at the level of the spinal dorsal horn, thereby reducing excitatory pain transmission [31]. Among this class, nortriptyline has shown consistent effectiveness in decreasing pain severity across various chronic pain conditions; however, its efficacy does not appear to be superior to placebo in certain conditions such as fibromyalgia and osteoarthritis [32].

In parallel, serotonin–norepinephrine reuptake inhibitors represent another key class of antidepressants with established utility in neuropathic pain. Duloxetine, in particular, is consistently identified as one of the most effective agents for chronic pain management, providing moderate analgesic benefit while also improving quality of life [33]. Its efficacy at standard therapeutic doses, combined with a relatively favorable safety profile, has positioned it as a preferred option in many clinical guidelines. Nevertheless, limitations remain, particularly regarding the availability of long-term data on sustained efficacy and safety [31].

Alongside antidepressants, anticonvulsants play a central role in the treatment of neuropathic pain, largely through their effects on neuronal excitability and synaptic transmission. Gabapentinoids, including gabapentin and pregabalin, exert their therapeutic effects by modulating voltage-gated calcium channels, thereby reducing excitatory neurotransmitter release and attenuating nociceptive signaling. These agents are widely recommended as first-line therapies; however, their overall efficacy is often modest, and their use may be constrained by dose-dependent adverse effects. In addition to gabapentinoids, sodium channel blockers such as carbamazepine and oxcarbazepine are particularly effective in specific neuropathic conditions, most notably trigeminal neuralgia,

where their targeted mechanism provides substantial symptom relief. Despite their efficacy, these agents require careful monitoring due to potential side effects and safety concerns [5].

Recent advances in the understanding of neuropathic pain mechanisms have driven the development of ion channel modulators and novel therapeutic agents. Targeted sodium channel inhibitors represent an emerging area of interest, focusing on specific channel subtypes to enhance selectivity and minimize off-target effects. These agents aim to improve the therapeutic index compared to traditional sodium channel blockers and are currently under investigation. In parallel, the identification of new molecular targets has facilitated the exploration of innovative pharmacological strategies, offering promising directions for the development of non-opioid treatments and more effective long-term management of neuropathic pain [23].

Adjuvant and Alternative Pharmacological Therapies

Opioids occupy a limited role in the management of neuropathic pain due to concerns regarding their modest efficacy and significant risk profile. They are generally not considered first-line therapies, as their use is associated with adverse effects such as tolerance, dependence, and potential for addiction. In selected cases, agents with dual mechanisms of action, such as tramadol and tapentadol, may provide some benefit by combining opioid receptor agonism with additional modulation of monoaminergic pathways. However, despite this pharmacological advantage, these medications still carry risks related to dependence and side effects, which restrict their long-term use and necessitate careful patient selection and monitoring [21].

In contrast, topical therapies have emerged as valuable alternatives, particularly for localized neuropathic pain. High-concentration capsaicin patches have gained increasing attention due to their ability to directly target peripheral sensitization mechanisms at the site of pain. By acting on nociceptive fibers, these treatments reduce peripheral hyperexcitability and contribute to sustained analgesia. Clinical evidence supports their efficacy in conditions such as post-surgical neuropathic pain, and they are generally well tolerated, offering an advantage over systemic therapies that are often associated with broader adverse effects [34, 35].

Cannabinoids represent another evolving therapeutic option, with growing interest in their role in neuropathic pain management. These agents exert their effects through modulation of the endocannabinoid system, influencing pain processing at peripheral, spinal, and supraspinal levels [36]. Clinical data suggest that cannabis-based medicinal products, particularly those with balanced tetrahydrocannabinol and cannabidiol compositions, may offer a favorable balance between efficacy and safety when compared to traditional pharmacological treatments [37, 38]. Additionally, intrathecal administration of tetrahydrocannabinol and cannabidiol has demonstrated synergistic effects in reducing allodynia without significant adverse events, highlighting their potential as a targeted and well-tolerated therapeutic approach [39].

Botulinum toxin type A has also emerged as a promising option in the treatment of peripheral neuropathic pain. Its mechanism involves the modulation of neurotransmitter release at peripheral nerve terminals, which contributes to the reduction of peripheral sensitization and nociceptive signaling. Clinical studies have supported its efficacy in various neuropathic pain conditions, particularly when conventional therapies have proven insufficient [34].

Given the complexity of neuropathic pain, combination pharmacotherapy has been increasingly explored as a strategy to enhance treatment outcomes. Regimens combining agents such as pregabalin with amitriptyline or

duloxetine aim to target multiple pathophysiological mechanisms simultaneously, potentially improving analgesic efficacy while allowing for lower individual drug doses and reduced side effects. Evidence from clinical trials, including the OPTION-DM study, indicates that combination therapies can provide additional pain relief in patients who exhibit partial responses to monotherapy. However, no single combination has demonstrated clear superiority in terms of cost-effectiveness or overall patient outcomes, underscoring the need for individualized treatment approaches based on patient characteristics and response profiles [37].

Safety Profile, Adverse Effects, and Special Populations

The pharmacological management of neuropathic pain is frequently limited by the occurrence of adverse effects, which vary according to the drug class and can significantly influence treatment adherence and tolerability. Gabapentinoids, including pregabalin and gabapentin, are commonly associated with dizziness, somnolence, and peripheral edema. In addition, pregabalin has been linked to euphoria, raising concerns regarding its potential for misuse and dependence [40, 41]. Antidepressants, such as duloxetine and venlafaxine, may produce adverse effects including nausea, dry mouth, and dizziness, while tricyclic antidepressants are additionally associated with anticholinergic effects such as constipation and urinary retention [42]. Opioids, including morphine and methadone, present a well-established profile of adverse effects, including constipation, nausea, sedation, and a significant risk of dependency. Methadone, although effective for pain control, requires careful monitoring due to its complex pharmacokinetics and potential for accumulation [43]. Among newer agents, mirogabalin has demonstrated efficacy in reducing pain and sleep interference; however, it is also associated with weight gain, somnolence, and dizziness [44].

In addition to class-specific adverse effects, drug–drug interactions represent a major concern, particularly in patients exposed to polypharmacy. This is especially relevant in older adults, where the combination of gabapentinoids and opioids may lead to additive sedative effects, increasing the risk of falls, cognitive impairment, and overall morbidity [45, 46]. Furthermore, antidepressants may interact with other serotonergic agents, increasing the risk of serotonin syndrome, a potentially serious condition that requires careful clinical vigilance [42].

Special populations require additional considerations due to altered pharmacokinetics and pharmacodynamics. Elderly patients are particularly vulnerable to adverse effects, as age-related physiological changes can affect drug metabolism and excretion. In this population, it is recommended to initiate treatment at the lowest effective dose and titrate gradually to minimize the risk of toxicity. Similarly, in patients with renal or hepatic impairment, dose adjustments are essential, particularly for medications such as gabapentinoids and opioids, which rely on these organ systems for metabolism and elimination [45, 46].

Psychiatric comorbidities further complicate pharmacological management, as certain agents may exacerbate underlying conditions. Pregabalin, for instance, has been associated with increased reports of suicidality and psychotic symptoms, underscoring the need for careful monitoring in vulnerable populations. Additionally, the risk of dependency and misuse remains a critical consideration, particularly with opioids, which carry a well-documented potential for addiction, especially with prolonged use. Gabapentinoids, and pregabalin in particular, have also demonstrated potential for misuse, although the extent of their addictive properties remains under investigation [41, 42].

Given these complexities, ongoing monitoring and individualized dose adjustments are essential

components of safe and effective treatment. Regular assessment of pain control, functional outcomes, and adverse effects allows for timely optimization of therapy. Dose modifications should be guided by both efficacy and tolerability, with careful consideration of organ function and potential pharmacological interactions, ensuring a balanced approach between therapeutic benefit and safety [21, 45].

Evidence-Based Recommendations and Future Directions

The management of neuropathic pain is guided by several international organizations that provide structured frameworks for diagnosis and treatment. The International Association for the Study of Pain emphasizes a standardized definition and classification of neuropathic pain, which facilitates consistency in both clinical research and therapeutic approaches [1]. Complementarily, the National Institute for Health and Care Excellence offers comprehensive guidelines that integrate pharmacological and non-pharmacological strategies, with a strong emphasis on individualized patient care [17]. Similarly, the European Federation of Neurological Societies recommends specific first-line pharmacological treatments while also underscoring the need for continued research to develop more effective therapies with improved safety profiles [5].

Within these frameworks, the development of therapeutic recommendations relies heavily on structured evidence grading systems. The GRADE methodology is commonly used to evaluate the quality and strength of available evidence, thereby supporting the formulation of clinical guidelines and treatment algorithms [47]. These therapeutic algorithms generally follow a stepwise approach, beginning with first-line pharmacological agents and progressing to second-line options such as topical treatments or opioids when necessary. In more refractory cases, non-pharmacological interventions, including neuromodulation techniques, are incorporated as part of a comprehensive management strategy [3, 8].

Despite these advances, significant limitations persist within the current literature. One of the principal challenges is the marked heterogeneity of neuropathic pain, as variations in etiology, pathophysiology, and clinical presentation complicate the generalization of study findings and the development of universally effective treatments [48]. Additionally, the lack of objective diagnostic tools remains a critical barrier, as current assessments rely heavily on clinical evaluation and patient-reported outcomes, which may introduce variability and diagnostic uncertainty [5]. Furthermore, the overall efficacy of existing pharmacological treatments is often modest, and their use is frequently limited by adverse effects, highlighting the need for more effective and better-tolerated therapeutic options [20].

In response to these challenges, emerging therapies are increasingly focused on precision medicine approaches that aim to tailor treatment based on individual patient characteristics. Advances in the understanding of genetic and molecular mechanisms underlying neuropathic pain are facilitating the development of more personalized therapeutic strategies. In particular, research into microRNA regulation and transient receptor potential channels has identified potential targets for more specific and effective interventions [48]. In parallel, therapies targeting specific ion channels involved in nociceptive signaling are under investigation, with the goal of improving analgesic efficacy while minimizing off-target effects [5].

The integration of these pharmacological advances with interventional neuromodulation techniques represents another important area of development. Techniques such as spinal cord stimulation and transcranial magnetic stimulation are being refined to enhance personalization and therapeutic outcomes in patients with refractory neuropathic pain [8, 49]. Additionally, non-

invasive approaches, including transcranial direct current stimulation, have shown promising results, although further research is required to establish standardized protocols and confirm long-term efficacy [47].

Future research priorities are centered on addressing current methodological and clinical gaps. There is a clear need for the standardization of methodologies in clinical trials to improve the reliability and comparability of evidence. Moreover, greater emphasis should be placed on evaluating the long-term efficacy and safety of emerging therapies, including biologic agents and neuromodulation techniques, to ensure their sustained clinical applicability [50]. Finally, the integration of multimodal treatment strategies that combine pharmacological and non-pharmacological approaches is expected to enhance therapeutic outcomes and provide more comprehensive management of neuropathic pain [1].

Conclusions

Neuropathic pain is a multifactorial condition driven by complex interactions between peripheral and central mechanisms, including ectopic impulse generation, peripheral and central sensitization, ion channel dysfunction, neurotransmitter imbalance, and maladaptive plasticity. These processes collectively lead to persistent neuronal hyperexcitability and structural reorganization within the nervous system, which sustain chronic pain and complicate both diagnosis and treatment.

The clinical management of neuropathic pain requires a multimodal and individualized approach due to its heterogeneous etiologies, variable clinical presentations, and limited response to monotherapy. Although current pharmacological strategies, including anesthetic agents and neuromodulators, provide partial relief, their efficacy is often constrained by adverse effects and refractoriness, highlighting the need for personalized therapies, improved diagnostic tools, and the integration of emerging targeted and neuromodulatory interventions.

References

1. Attal N, Bouhassira D, Colvin L. Advances and challenges in neuropathic pain: a narrative review and future directions. British Journal of Anaesthesia [Internet]. 2023 May 18;131(1):79–92. Available from: https://doi.org/10.1016/j.bja.2023.04.021
2. Ørstavik K. Neuropathic pain - Still a challenge to assess. European Journal of Neurology [Internet]. 2023 May 23;30(8):2139–40. Available from: http://dx.doi.org/10.1111/ene.15889
3. Chary S, Boyle AB, Herx LM, MacDonald S. Neuropathic pain. In: Pallative Medecine [Internet]. 2021. p. 42–50. Available from: https://doi.org/10.1093/oso/9780198837008.003.0005
4. Pirvulescu I, Biskis A, Candido KD, Knezevic NN. Overcoming clinical challenges of refractory neuropathic pain. Expert Review of Neurotherapeutics [Internet]. 2022 Jul 3;22(7):595–622. Available from: https://doi.org/10.1080/14737175.2022.2105206
5. Thouaye M, Yalcin I. Neuropathic pain: From actual pharmacological treatments to new therapeutic horizons. Pharmacology & Therapeutics [Internet]. 2023 Oct 11;251:108546. Available from: https://doi.org/10.1016/j.pharmthera.2023.108546
6. Rugnath R, Orzechowicz C, Newell C, Carullo V, Rugnath A. A Literature Review: The Mechanisms and Treatment of Neuropathic Pain—A Brief discussion. Biomedicines [Internet]. 2024 Jan 17;12(1):204. Available from: https://doi.org/10.3390/biomedicines12010204

7. Wang Y, Ji X, Sun Y, Wang H, Wang T, Luo T, et al. Nano-Anesthetics regulate Neuro-Immune interaction for treating neuropathic pain. Advanced Science [Internet]. 2025 May 21;12(29):e02920. Available from: https://doi.org/10.1002/advs.202502920
8. Shirvalkar P. Neuromodulation for neuropathic pain syndromes. CONTINUUM Lifelong Learning in Neurology [Internet]. 2024 Oct 1;30(5):1475–500. Available from: https://doi.org/10.1212/con.0000000000001485
9. Gangadharan V, Zheng H, Taberner FJ, Landry J, Nees TA, Pistolic J, et al. Neuropathic pain caused by miswiring and abnormal end organ targeting. Nature [Internet]. 2022 May 25;606(7912):137–45. Available from: https://doi.org/10.1038/s41586-022-04777-z
10. Stojanovic B, Bevc IM, Stojanovic MD, Stojanovic BS, Lazarevic T, Spasic M, et al. Oxidative stress, inflammation, and cellular senescence in neuropathic pain: Mechanistic Crosstalk. Antioxidants [Internet]. 2025 Sep 25;14(10):1166. Available from: https://doi.org/10.3390/antiox14101166
11. Gao N, Li M, Wang W, Liu Z, Guo Y. The dual role of TRPV1 in peripheral neuropathic pain: pain switches caused by its sensitization or desensitization. Frontiers in Molecular Neuroscience [Internet]. 2024 Sep 9;17:1400118. Available from: https://doi.org/10.3389/fnmol.2024.1400118
12. Liu YJ, Li YL, Fang ZH, Liao HL, Zhang YY, Lin J, et al. NMDARs mediate peripheral and central sensitization contributing to chronic orofacial pain. Frontiers in Cellular Neuroscience [Internet]. 2022 Sep 27;16:999509. Available from: https://doi.org/10.3389/fncel.2022.999509
13. Koga K, Kobayashi K, Tsuda M, Kubota K, Kitano Y, Furue H. Voltage-gated calcium channel subunit α2δ-1 in spinal dorsal horn neurons contributes to aberrant excitatory synaptic transmission and mechanical hypersensitivity after peripheral nerve injury. Frontiers in Molecular Neuroscience [Internet]. 2023 Mar 23;16:1099925. Available from: https://doi.org/10.3389/fnmol.2023.1099925
14. Fayad SL, Ourties G, Gac BL, Jouffre B, Lamoine S, Fruquière A, et al. Centrally expressed Cav3.2 T-type calcium channel is critical for the initiation and maintenance of neuropathic pain. eLife [Internet]. 2022 Nov 23;11. Available from: https://doi.org/10.7554/elife.79018
15. Guan X, Zhu Y, Zhong J, Hollis E. Neuropathic Pain-Like responses in a chronic CNS injury model are mediated by Corticospinal-Targeted spinal interneurons. Journal of Neuroscience [Internet]. 2025 Jun 23;45(29):e1264242025. Available from: https://doi.org/10.1523/jneurosci.1264-24.2025
16. Jensen TS, Karlsson P, Gylfadottir SS, Andersen ST, Bennett DL, Tankisi H, et al. Painful and non-painful diabetic neuropathy, diagnostic challenges and implications for future management. Brain [Internet]. 2021 Mar 9;144(6):1632–45. Available from: https://doi.org/10.1093/brain/awab079
17. Mulvey MR, Paley CA, Schuberth A, King N, Page A, Neoh K. Neuropathic pain in cancer: What are the current guidelines? Current Treatment Options in Oncology [Internet]. 2024 Aug 5;25(9):1193–202. Available from: https://doi.org/10.1007/s11864-024-01248-7
18. Tesfaye S, Kempler P. Conventional management and current guidelines for

painful diabetic neuropathy. Diabetes Research and Clinical Practice [Internet]. 2023 Dec 1;206:110765. Available from: https://doi.org/10.1016/j.diabres.2023.110765

19. Wei M, Jiang Y, Shou J, Xing G, Li M. The role of brain mechanisms in diabetic peripheral neuropathy: recent advances and comprehensive analysis. Frontiers in Cellular Neuroscience [Internet]. 2025 Oct 29;19:1637357. Available from: https://doi.org/10.3389/fncel.2025.1637357
20. Borghi SM. Pharmacotherapy of neuropathic pain. Pharmaceuticals [Internet]. 2025 Jun 19;18(6):930. Available from: https://doi.org/10.3390/ph18060930
21. Balanaser M, Carley M, Baron R, Finnerup NB, Moore RA, Rowbotham MC, et al. Combination pharmacotherapy for the treatment of neuropathic pain in adults: systematic review and meta-analysis. Pain [Internet]. 2022 May 19;164(2):230–51. Available from: https://doi.org/10.1097/j.pain.0000000000002688
22. Marcianò G, Vocca C, Evangelista M, Palleria C, Muraca L, Galati C, et al. The Pharmacological Treatment of Chronic Pain: From guidelines to daily clinical practice. Pharmaceutics [Internet]. 2023 Apr 6;15(4):1165. Available from: https://doi.org/10.3390/pharmaceutics15041165
23. Cioffi CL, Lotsaris I, Chater RPC, Pati TK, Suleria K, Mahesh G, et al. Current nonopioid small molecule approaches toward the treatment of neuropathic pain. Journal of Medicinal Chemistry [Internet]. 2025 Aug 28;68(17):18064–98. Available from: https://doi.org/10.1021/acs.jmedchem.5c01126
24. Nguyen PT, Yarov-Yarovoy V. Towards Structure-Guided development of pain therapeutics targeting Voltage-Gated sodium channels. Frontiers in Pharmacology [Internet]. 2022 Jan 27;13:842032. Available from: https://doi.org/10.3389/fphar.2022.842032
25. Voute M, Morel V, Pickering G. Topical lidocaine for chronic pain treatment. Drug Design Development and Therapy [Internet]. 2021 Sep 1;Volume 15:4091–103. Available from: https://doi.org/10.2147/dddt.s328228
26. Mao P, Zhang Y, Liu B, Li Y, Chang Y, Zhu M, et al. Effect and safety profile of topical lidocaine on post-surgical neuropathic pain and quality of life: A systematic review and meta-analysis. Journal of Clinical Anesthesia [Internet]. 2023 Oct 10;92:111219. Available from: https://doi.org/10.1016/j.jclinane.2023.111219
27. Tsai JH, Liu IT, Su PF, Huang YT, Chiu GL, Chen YY, et al. Lidocaine transdermal patches reduced pain intensity in neuropathic cancer patients already receiving opioid treatment. BMC Palliative Care [Internet]. 2023 Jan 6;22(1):4. Available from: https://doi.org/10.1186/s12904-023-01126-3
28. Lee JH, Koutalianos EP, Leimer EM, Bhullar RK, Argoff CE. Intravenous lidocaine in chronic neuropathic pain. Clinical Journal of Pain [Internet]. 2022 Oct 26;38(12):739–48. Available from: https://doi.org/10.1097/ajp.0000000000001080
29. Mohamed D, Ke J, Honan J, Roman E, Roddy D, Sweeney T, et al. PO005 / #279 EFFECTIVENESS OF LIDOCAINE INFUSION IN CHRONIC PAIN STATES. Neuromodulation Technology at the Neural Interface [Internet]. 2022 Oct 1;25(7):S165. Available from: https://doi.org/10.1016/j.neurom.2022.08.180

30. Chen Y, Xu J, Li P, Shi L, Zhang S, Guo Q, et al. Advances in the use of local anesthetic extended-release systems in pain management. DrugDelivery [Internet]. 2023 Dec 21;31(1). Availablefrom: https://doi.org/10.1080/10717544.2023.2296349
31. Huang Y, Chen H, Chen SR, Pan HL. Duloxetine and Amitriptyline Reduce Neuropathic Pain by Inhibiting Primary Sensory Input to Spinal Dorsal Horn Neurons via α1- and α2-Adrenergic Receptors. ACS Chemical Neuroscience [Internet]. 2023 Mar 17;14(7):1261–77. Available from: https://doi.org/10.1021/acschemneuro.2c00780
32. Hashemzadeh S, Mortazavi M, Dezfouli RA. Quantitative analysis of nortriptyline's analgesic properties: a comparative systematic review and meta-analysis. BMJ Open [Internet]. 2024 Aug 1;14(8):e085438. Available from: https://doi.org/10.1136/bmjopen-2024-085438
33. Birkinshaw H, Friedrich CM, Cole P, Eccleston C, Serfaty M, Stewart G, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. Cochrane Database of Systematic Reviews [Internet]. 2023 May 10;2023(5):CD014682. Available from: https://doi.org/10.1002/14651858.cd014682.pub2
34. Kocot-Kępska M, Zajączkowska R, Mika J, Kopsky DJ, Wordliczek J, Dobrogowski J, et al. Topical Treatments and Their Molecular/Cellular Mechanisms in Patients with Peripheral Neuropathic Pain—Narrative Review. Pharmaceutics [Internet]. 2021 Mar 26;13(4):450. Availablefrom: https://doi.org/10.3390/pharmaceutics13040450
35. Casale R. Capsaicin 179-mg cutaneous patch in the treatment of post-surgical neuropathic pain: a scoping review of current evidence and place in therapy. Expert Review of Neurotherapeutics [Internet]. 2021 Aug 31;21(10):1147–58. Available from: https://doi.org/10.1080/14737175.2021.1974842
36. Quintero JM, Diaz LE, Galve-Roperh I, Bustos RH, Leon MX, Beltran S, et al. The endocannabinoid system as a therapeutic target in neuropathic pain: a review. Expert Opinion on Therapeutic Targets [Internet]. 2024 Sep 1;28(9):739–55. Available from: https://doi.org/10.1080/14728222.2024.2407824
37. Nutt DJ, Phillips LD, Barnes MP, Brander B, Curran HV, Fayaz A, et al. A multicriteria decision analysis comparing pharmacotherapy for chronic neuropathic pain, including cannabinoids and Cannabis-Based medical products. Cannabis and Cannabinoid Research [Internet]. 2021 Mar 18;7(4):482–500. Available from: https://doi.org/10.1089/can.2020.0129
38. Petzke F, Tölle T, Fitzcharles MA, Häuser W. Cannabis-Based Medicines and medical cannabis for chronic neuropathic pain. CNS Drugs [Internet]. 2021 Nov 21;36(1):31–44. Available from: https://doi.org/10.1007/s40263-021-00879-w
39. Casey SL, Mitchell VA, Sokolaj EE, Winters BL, Vaughan CW. Intrathecal actions of the cannabis constituents Δ(9)-Tetrahydrocannabinol and cannabidiol in a mouse neuropathic pain model. International Journal of Molecular Sciences [Internet]. 2022 Aug 3;23(15):8649. Available from: https://doi.org/10.3390/ijms23158649
40. Meaadi J, Obara I, Eldabe S, Nazar H. The safety and efficacy of gabapentinoids in the management of

neuropathic pain: a systematic review with meta-analysis of randomised controlled trials. International Journal of Clinical Pharmacy [Internet]. 2023 Feb 27;45(3):556–65. Available from: https://doi.org/10.1007/s11096-022-01528-y

41. McNeilage AG, Gholamrezaei A, Murnion B, Nielsen S, Ashton-James CE. Pregabalin dependence, withdrawal, suicidality and psychosis reports: A disproportionality analysis of the Australian adverse events database. British Journal of Clinical Pharmacology [Internet]. 2025 Sep 26;92(2):545–55. Available from: https://doi.org/10.1002/bcp.70279
42. Moisset X, Pagé MG, Pereira B, Choinière M. Pharmacological treatments of neuropathic pain: real-life comparisons using propensity score matching. Pain [Internet]. 2021 Aug 26;163(5):964–74. Available from: https://doi.org/10.1097/j.pain.0000000000002461
43. Júnior J, Barbosa M, Kubota G, Martins P, Moreira L, Fernandes A, et al. METHA-NeP: effectiveness and safety of methadone for neuropathic pain: a controlled randomized trial. Pain [Internet]. 2024 Oct 21;166(3):557–70. Available from: https://doi.org/10.1097/j.pain.0000000000003413
44. João RB, Chan JOT, João AB, Araújo LM, Dantas JM. Mirogabalin for Treatment of Neuropathic pain and Associated sleep Interference: An Updated Meta-Analysis. European Journal of Pain [Internet]. 2025 Sep 19;29(10):e70112. Available from: https://doi.org/10.1002/ejp.70112
45. Pickering G, Kotlińska-Lemieszek A, Skvarc NK, O'Mahony D, Monacelli F, Knaggs R, et al. Pharmacological pain treatment in older persons. Drugs & Aging [Internet]. 2024 Oct 27;41(12):959–76. Availablefrom: https://doi.org/10.1007/s40266-024-01151-8
46. Marchesi N, Fahmideh F, Pascale A, Allegri M, Govoni S. Neuropathic pain in aged people: an unresolved issue open to NovelDrug approaches, focusing on painful diabetic neuropathy. CurrentNeuropharmacology [Internet]. 2023 Aug 8;22(1):53–64. Availablefrom: https://doi.org/10.2174/1570159x21666230807103642
47. Duarte RJ, Shirahige L, Rodriguez-Prieto IE, Alves MM, Da Silva Lopes T, Baptista RF, et al. Evidence-Based umbrella Review of Non-Invasive Neuromodulation in chronic neuropathic pain. European Journal of Pain [Internet]. 2025 Jan 21;29(2):e4786. Available from: https://doi.org/10.1002/ejp.4786
48. Balzani E, Fanelli A, Malafoglia V, Tenti M, Ilari S, Corraro A, et al. A review of the clinical and therapeutic implications of neuropathic pain. Biomedicines [Internet]. 2021 Sep 16;9(9):1239. Availablefrom: https://doi.org/10.3390/biomedicines9091239
49. Lefaucheur JP, Fan Y, Fan B, Ramasawmy P, Antal A, Mitsikostas DD, et al. The evolving landscape of neuromodulation for pain care. Cell Reports Medicine [Internet]. 2024 Oct 1;5(10):101787. Available from: https://doi.org/10.1016/j.xcrm.2024.101787
50. Bies M, Ashmore Z, Qu W, Hunt C. Injectable Biologics for Neuropathic Pain: A Systematic review. Pain Medicine [Internet]. 2022 Apr 21;23(10):1733–49. Available from: https://doi.org/10.1093/pm/pnac066