Narrative Review Article

Current Therapeutic Strategies for Neuropathic Pain: Mechanisms, Drug Options, and Interventional Approaches

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ABSTRACT

Neuropathic pain is a chronic condition resulting from a lesion or disease of the somatosensory nervous system. Despite diverse etiologies, neuropathic pain involves shared mechanisms such as neuronal hyperexcitability, central sensitization, and impaired inhibitory pathways. Neuropathic pain substantially limits mobility and leads to a general decline in overall health and quality of life. A wide array of therapeutic approaches is used in patients care, ranging from systemic pharmacologic agents to localized and minimally invasive interventions. This review summarizes recent approvals on treatments for neuropathic pain and evaluates the benefits, risks, and appropriate clinical contexts for oral, topical, and interventional modalities. Systemic pharmacologic therapeutic drugs, such as serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, gabapentinoids, nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are widely used, although the efficacy varies based on the underlying mechanisms and patient-specific factors. Topical formulations, such as lidocaine and capsaicin, provide targeted analgesia with minimal systemic exposure and are suitable therapy for localized peripheral neuropathic syndromes. Minimally invasive procedures, including corticosteroid injections, nerve blocks, and radiofrequency ablation, offer additional choices for pain relief. Overall, optimal neuropathic pain management includes stepped, multimodal and individualized strategies that integrates systemic pharmacologic, topical, and interventional approaches. Ongoing research advances in mechanism-based and minimally invasive therapies hold promises for improving long-term outcomes in patients with neuropathic pain.

Keywords: Neuropathic Pain; SNRIs; Tricyclic Antidepressants; Gabapentin; NSAIDs; Topical Analgesics; Corticosteroid Injections; Nerve Blocks; Radiofrequency Ablation

INTRODUCTION

Pain is a complex sensory and emotional experience arising from actual or potential tissue damage, mediated by intricate peripheral and central neural pathways (1). Chronic pain affects more than 20% of adults worldwide and is associated with significant functional impairment, reduced quality of life, and increased healthcare burden (2). Neuropathic pain is defined as chronic pain resulting from a lesion or disease of the somatosensory nervous system. While it can manifest systemically, it is most frequently observed in the limbs, lower back, neck, and hips. Approximately 2% of adults in the United States experience neuropathic pain (3). Individuals suffering from this condition often face limited mobility, reduced independence, mood

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disorders, and a general decline in overall health (4, 5). Despite its high prevalence and profound clinical impact, neuropathic pain remains challenging to treat due to its heterogeneous etiologies and complex underlying mechanisms. Existing therapeutic options frequently yield incomplete or variable relief, which reflects the inherent limitations of single-modality approaches and demonstrates the need for integrated, mechanism-informed treatment strategies. Accordingly, a comprehensive evaluation of multimodal therapeutic approaches, including pharmacologic, interventional, and non-pharmacologic modalities, is warranted. The objective of this review is to synthesize current evidence on the management of neuropathic pain, critically evaluate the efficacy and limitations of available therapies, and provide a conceptual framework to support optimized, patient-centered pain management.

TYPES OF NEUROPATHIC PAIN

There are two types of neuropathic pain, namely central neuropathic pain and peripheral neuropathic pain (6). The most common cases of central neuropathic pain are caused by injury to the brain or spinal cord, such as stroke, spinal cord injury, and multiple sclerosis (MS) (7). The most common cases of peripheral neuropathic pain include post-traumatic neuropathy, diabetic neuropathy, postherpetic neuralgia, chemotherapy-related neuropathy, and nerve impingement (8). Overall, peripheral neuropathic pain is more prevalent (5).

Trigeminal Neuralgia (TN)/Post-Traumatic Trigeminal Neuropathy (PTTN)

TN is a chronic neuropathic pain disorder, characterized by sudden, severe, electric shock–like facial pain along one or more branches of the trigeminal nerve. It is most caused by vascular compression of the trigeminal root entry zone, leading to focal demyelination and hyperexcitability of trigeminal afferents (9). Patients typically experience brief paroxysms of pain triggered by light mechanical stimulation, chewing, speaking, or exposure to cold air. Although relatively rare, TN has a profound impact on the quality of life due to its intensity and unpredictability. First-line pharmacologic treatments, including carbamazepine and oxcarbazepine, reduce neuronal hyperexcitability. In contrast, surgical interventions such as microvascular decompression or stereotactic radiosurgery are reserved for refractory cases (9).

PTTN arises after direct injuries to one or more branches of the trigeminal nerve, often following dental procedures, facial fractures, or surgical trauma. Approximately 3% of individuals with trigeminal nerve injury develop PTTN, who present with persistent neuropathic symptoms such as severe pain, hyperalgesia, allodynia, numbness, and functional impairment (10). Unlike TN, which is typically episodic, PTTN manifests continuous neuropathic pain with sensory deficits. Emerging evidence suggests that cytokines and chemokines contribute to central sensitization in PTTN by modulating nociceptive signaling pathways in the central nervous system (11).

Diabetic Neuropathy (DN)

DN is a common complication of diabetes, characterized by peripheral nerve damage and progressive loss of sensory function, which affects approximately 50% of individuals with diabetes (12, 13). The most prevalent form is distal symmetrical polyneuropathy. More than 75% of DN patients exhibit either large- or small-fiber neuropathy (14, 15). Large-fiber involvement causes impaired vibration sense and painless paresthesia, whereas small-fiber neuropathy leads to burning pain, thermal sensitivity, and impaired pain perception. A less common subtype, diabetic proximal neuropathy (also known as diabetic amyotrophy or asymmetric neuropathy), presents with pelvic girdle weakness and pain in the lower back, hip, and anterior thigh (13, 14).

DRUGS AND MOLECULAR MECHANISMS FOR NEUROPATHIC PAIN CONTROL

Despite the diverse etiologies of neuropathic pain, treatment options often overlap. A number of therapeutic molecules have been approved and applied in patient care. This manuscript reviews and compares the risks and benefits of these treatments.

Serotonin-Norepinephrine Reuptake Inhibitors

Serotonin (5-HT) and norepinephrine (NE) play central roles in the descending pain-modulatory pathways, which originate in the brainstem and project to the spinal dorsal horn. Under normal conditions, these neurotransmitters inhibit nociceptive transmission by reducing the excitability of pain-signaling neurons (16). In neuropathic pain, however, these pathways often become impaired. This leads to reduced inhibitory

control and increased central sensitization (16). Consequently, patients may experience heightened pain responses, including hyperalgesia and allodynia. Restoring serotonergic and noradrenergic tone in these pathways is therefore a major therapeutic target in neuropathic pain management (16). SNRIs enhance this inhibitory control by blocking the reuptake transporters responsible for clearing 5-HT and NE from the synaptic cleft. This increases their levels at synapses in the central nervous system, which in turn strengthens descending inhibition and reduces the transmission of pain signals in the spinal cord (17, 18).

Venlafaxine

Available in immediate and extended-release forms, Venlafaxine is a bicyclic compound structurally distinct from other SNRIs. It is primarily metabolized by the liver. Its metabolism can be influenced by genetic polymorphisms. As a relatively weak inhibitor of 5-HT and NE uptake, venlafaxine displays a clear dose-response relationship and a higher affinity for serotonin reuptake inhibition than for norepinephrine (19-21). Venlafaxine is FDA-approved for major depression, generalized anxiety disorder, panic disorder, and social phobia. Side effects are predominantly serotonergic, including headaches, nausea, fatigue, sexual dysfunction, dry mouth, and night sweats (22, 23).

Duloxetine

Duloxetine offers more balanced inhibition of 5-HT and NE reuptake. It is metabolized via the hepatic P-450 isoenzyme system and is a moderate inhibitor of CYP2D6 (19, 24). Duloxetine exhibits a 10-fold higher selectivity for serotonin reuptake inhibition over norepinephrine and has a slightly lower serotonergic dominance than venlafaxine (25). It is indicated for diabetic peripheral neuropathy, major depression, generalized anxiety disorder, fibromyalgia, and chronic musculoskeletal pain (including osteoarthritis) (26). Similar to venlafaxine, its efficacy and safety profile may be affected by genetic polymorphisms (27).

Although SNRIs are widely used for conditions including diabetic neuropathy, chemotherapy-induced peripheral neuropathy, postherpetic neuralgia, and central neuropathic pain, individual response varies due to genetic differences in metabolism (28, 29).

Tricyclic Antidepressants (TCAs)

TCAs were originally developed to treat major depressive disorder by inhibiting neurotransmitter reuptake in the synaptic cleft (30). They reduce neuropathic pain through a combination of central and peripheral mechanisms. TCAs inhibit the reuptake of serotonin and norepinephrine, thereby strengthening the descending inhibitory pathways in the spinal cord that suppress pain transmission (31). They also block voltage-gated sodium channels, which in turn decreases abnormal nerve firing often responsible for burning and electric-shock sensations (32). Additionally, they modulate NMDA receptor activity to reduce central sensitization and provide sedative benefits through antihistamine and anticholinergic effects. Through these multimodal actions, TCAs such as amitriptyline effectively treat various neuropathic pain conditions, including diabetic neuropathy, postherpetic neuralgia, and post-traumatic neuropathic pain (33).

Adverse effects of TCAs include constipation, dizziness, xerostomia (dry mouth), blurred vision, and urinary retention, largely attributed to their anticholinergic and antihistaminic activity (34). Cardiac assessment prior to prescription is strongly recommended, as TCAs can prolong QT intervals and cause cardiotoxicity, particularly in overdose (35). An increased risk of suicidal behavior has been observed in individuals under the age of 24 (36). While TCAs demonstrate efficacy comparable to SNRIs for neuropathic pain, their overall tolerability is less favorable due to anticholinergic, sedative, and cardiovascular risks (37). Consequently, dosing should be carefully monitored, and SNRIs are generally preferred as first-line systemic therapy for neuropathic pain.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) & Acetaminophen

NSAIDs are a broad class of medications that possess anti-inflammatory, analgesic, and antipyretic properties. They are widely used to reduce inflammation, relieve pain, and lower fever. Prostaglandins are lipid mediators derived from arachidonic acid through the cyclooxygenase (COX-1 and COX-2) pathway. Prostaglandins not only promote inflammation, vasodilation, and fever, but also play a significant role in modulating pain signaling in the peripheral and central nervous systems (38). NSAIDs function by blocking COX1 and COX2 enzymes, thereby preventing prostaglandin synthesis (39) and reducing inflammation and nociceptive signaling (40).

Common non-selective NSAIDs include ibuprofen,

naproxen, aspirin, diclofenac, indomethacin, ketoprofen, piroxicam, meloxicam, and nabumetone. More selective COX-2 inhibitors (coxibs), such as celecoxib and etoricoxib, are designed to provide similar analgesic effects with fewer gastrointestinal side effects (41). NSAIDs are available in oral, injectable, and topical formulations, including topical diclofenac and ketoprofen, which provide localized relief with minimal systemic absorption (42).

Despite their utility, NSAIDs carry risks. Traditional NSAIDs and coxibs increase the risk of gastrointestinal (GI) and cardiovascular side effects (43). Long-term use is linked to peptic ulcers, renal dysfunction, and hepatic issues (44). Specifically, renal effects arise from the inhibition of prostaglandin synthesis in the kidneys. Because COX-1 is vital for GI protection, its inhibition can lead to adverse GI effects (40). COX-2 selective NSAIDs offer a more favorable GI safety profile (45) but are associated with increased thrombotic risks, such as stroke or myocardial infarction (46). Among traditional NSAIDs, Naproxen presents the most favorable cardiovascular safety profile and can be dosed to achieve analgesia superior to some other agents (47). Topical NSAID formulations are also available. Although they offer less systemic analgesia, they are associated with significantly fewer systemic adverse events (48). Even though coxibs, such as celecoxib, have lower GI risks, rofecoxib was withdrawn from the market due to cardiovascular events (49). Despite these side effects, NSAIDs remain a cornerstone of pain management, consistently outperforming placebos.

Acetaminophen is an analgesic distinct from NSAIDs. It is metabolized to p-aminophenol, which is converted to AM404. AM404 induces analgesia by blocking excitatory synaptic transmission in the spinal dorsal horn and acting on receptors such as cannabinoid, COX, and transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors in the central nervous system (50). Acetaminophen is primarily used for acute pain (e.g., headaches and musculoskeletal pain) and osteoarthritis. Because it is a weak inhibitor of COX, acetaminophen exhibits minimal anti-inflammatory activity. It may also possess mild sleep-inducing properties, potentially due to pain relief or placebo effects (51). The primary risk associated with acetaminophen is hepatotoxicity; overdose can lead to acute liver failure (52). While effective for acute pain, its utility in chronic neuropathic pain is limited compared to NSAIDs.

Gabapentin

Gabapentin is one of the most prescribed medications for neuropathic pain due to its effectiveness, favorable safety profile, and non-addictive nature (53). Gabapentin is available in immediate-release formulations and as the prodrug gabapentin enacarbil, which improves bioavailability. It is not metabolized hepatically and does not induce or inhibit cytochrome P450 enzymes. Although initially developed as an anticonvulsant, it is now widely used for conditions such as postherpetic neuralgia, diabetic neuropathy, radiculopathy, and other nerve-related pain syndromes (54). In neuropathic pain, damaged or dysfunctional nerves generate abnormal firing patterns that manifest as burning, tingling, electric-shock sensations, or hypersensitivity. Gabapentin provides gradual but meaningful pain relief by reducing this pathological activity. Its primary mechanism involves binding to the α2δ subunit of voltage-gated calcium channels**,** reducing calcium influx and subsequently decreasing the release of excitatory neurotransmitters (e.g., glutamate and substance P) that drive neuronal hyperexcitability and chronic pain signaling (55, 56). Although Gabapentin has been shown to increase serotonin levels in healthy subjects, its influence on serotonergic or dopaminergic pathways remains under investigation.

Gabapentin is generally well tolerated (57). The CDC acknowledges gabapentin as a safer alternative to opioids in chronic pain management (58). Risks include dizziness, fatigue, peripheral edema, depressive symptoms, allergic reactions, rhabdomyolysis, and withdrawal-related seizures if stopped abruptly (59). Additional side effects include gastrointestinal upset, mood changes, and weight gain (54). Toxicity is a particular concern in patients with chronic kidney disease due to impaired drug clearance (60). Because gabapentin is excreted unchanged by the kidneys, dose adjustments are required in renal impairment. Abrupt discontinuation should be avoided to prevent withdrawal symptoms or seizures. Overall, gabapentin is regarded as a safe, non-addictive, and evidence-supported first-line or adjunct therapy for neuropathic pain, as it offers substantial symptom improvement with significantly lower risk than opioids or invasive procedures (37).

DRUG DELIVERY METHODS

Oral Delivery in Neuropathic Pain Treatment

Oral delivery is the most common method and includes tablets, capsules, and liquids. It provides convenient

systemic absorption but may cause gastrointestinal or hepatic side effects, especially with long-term NSAID or acetaminophen use (61).

Topical Delivery in Neuropathic Pain Treatment

Topical delivery, such as creams, gels, and patches, allows targeted treatment with minimal systemic exposure, making agents like lidocaine, capsaicin, and topical NSAIDs ideal for localized neuropathic or musculoskeletal pain (62). Topical agents are applied directly to the skin to target peripheral nerves and soft tissue. They rely on passive diffusion through the stratum corneum to block pain pathways locally or peripherally with minimal systemic absorption (48). This localized mechanism avoids systemic drug interactions and titration requirements (48).

Capsaicin

Capsaicin is a topical analgesic used primarily for peripheral neuropathic pain. As a TRPV1 receptor agonist, it desensitizes nociceptive sensory neurons, thereby reducing their ability to transmit pain signals (63). This mechanism makes capsaicin effective in treating conditions such as postherpetic neuralgia**,** HIV-associated neuropathy**,** post-surgical or post-traumatic neuropathic pain, and, in some cases, diabetic peripheral neuropathy (63, 64). Because its action is localized to peripheral nerves, capsaicin is not used for central neuropathic pain but remains a well-established option for managing peripheral neuropathic conditions with minimal systemic effects (64). Capsaicin is available in creams and patches. While capsaicin causes a burning sensation, this discomfort can often be managed with tactile distraction techniques (65).

Lidocaine

Lidocaine is a peripheral neuropathic pain inhibitor. It works as a voltage-gated sodium channel blocker that reduces the excitability of peripheral sensory nerves and prevents them from transmitting pain signals (66). Because its action is local and not systemic, lidocaine is primarily used to treat peripheral neuropathic pain conditions, such as postherpetic neuralgia**,** post-surgical or post-traumatic neuropathy**,** localized neuropathic pain syndromes**,** and certain types of diabetic peripheral neuropathy (67). It is not used for central neuropathic pain but well-established for localized peripheral neuropathic pain due to its strong safety profile and minimal systemic absorption (68). There are a few types of lidocaine formats for pain relief, including topical patch, cream, spray. Topical lidocaine provides pain relief with very low systemic absorption and minimal side effects, making it a safe option for neuropathic conditions (69).

Menthol

Menthol is a topical analgesic used to treat peripheral neuropathic pain due to its ability to activate the transient receptor potential melastatin 8 (TRPM8) ion channel, which is responsible for cold sensation. When applied to the skin, menthol stimulates TRPM8 receptors on sensory neurons, which produces a cooling effect that competes with and reduces pain signaling (70). Activation of TRPM8 triggers inhibitory pathways in the peripheral nervous system, decreasing neuronal excitability and dampening the transmission of nociceptive signals to the spinal cord (70, 71). Menthol also indirectly modulates central pain processing by engaging descending inhibitory circuits (72). These combined effects make menthol effective for conditions such as chemotherapy-induced peripheral neuropathy, localized nerve pain, and musculoskeletal pain with neuropathic feature**s**, for which menthol offers analgesia with minimal systemic absorption and a strong safety profile (73, 74).

Topical treatments are associated with few risks. Lidocaine carries a theoretical risk of injury to desensitized tissue, while capsaicin and menthol may cause temporary discomfort. However, given their safety profile, topical agents are crucial components of multimodal pain management (75).

Injectable Delivery Systems in Neuropathic Pain Treatment

Neuropathic pain relievers including subcutaneous, intramuscular, and intra-articular injections, provide rapid or high-concentration local effects. Corticosteroid joint injections and trigger point injections fall into this category, which offer short-term anti-inflammatory relief (76).

Steroid Joint Injection

Corticosteroid injections treat musculoskeletal conditions by interacting with intracellular glucocorticoid receptors. Once bound, corticosteroids regulate gene expression to inhibit the production of cytokines and chemokines, reducing vasodilation, permeability, and swelling (77). These injections provide moderate short-term pain relief and functional improvement (78). Hydrocortisone has been shown to decrease joint

temperature and synovial fluid cell counts (79). These injections are most effective in the knee joint, with some benefits observed in hip osteoarthritis (80). However, diagnosis is critical, as back pain mimicking hip pain may lead to ineffective treatment (81). Adverse effects include articular cartilage toxicity, hyperglycemia, immunosuppression, and infection. Severe but rare reactions include nerve damage and steroid arthropathy. Due to potential cartilage toxicity and the temporary nature of relief, corticosteroid use should be judicious (82).

Transdermal Systems in Neuropathic Pain Treatment

Transdermal drug delivery systems provide a controlled, continuous release of analgesic medications through the skin into systemic circulation. These systems bypass first-pass metabolism and maintain stable plasma drug levels, reducing side effects associated with oral dosing. Common transdermal agents used in neuropathic pain include lidocaine patches, which deliver local sodium-channel blockade to reduce peripheral nerve excitability, and capsaicin patches, which achieve sustained nociceptor desensitization by downregulating TRPV1 receptors. Overall, transdermal systems offer a non-invasive, well-tolerated, and targeted method for neuropathic pain management, particularly beneficial for patients who cannot tolerate systemic medications or require localized therapy (83).

Nerve Blocks

Nerve blocks are minimally invasive procedures that deliver anesthetics, corticosteroids, or other agents directly around peripheral or central nerves to interrupt pain signaling (84, 85). They are commonly used when oral medications are insufficient or not tolerated (85). Local anesthetic nerve blocks (e.g., lidocaine or bupivacaine) provide temporary relief by inhibiting sodium channels and blocking neuronal depolarization (86). Steroid nerve blocks, often combined with anesthetics, suppress inflammatory cytokine activity around irritated nerves. Therefore, they are useful in radiculopathy, post-traumatic neuropathy, and nerve entrapment syndromes (87). Sympathetic nerve blocks, such as stellate ganglion blocks or lumbar sympathetic blocks, target the autonomic nervous system and are effective in conditions including complex regional pain syndrome (CRPS) and painful diabetic neuropathy (88). Epidural and transforaminal nerve root blocks deliver medication near spinal nerve roots to treat radiculopathy, postherpetic neuralgia, and spinal stenosis–related neuropathic pain (89). Facet joint medial branch blocks help diagnose and treat facet-mediated back and neck pain (90). Additionally, trigeminal nerve blocks (infraorbital, mandibular, or sphenopalatine ganglion blocks) are used for trigeminal neuralgia and post-traumatic trigeminal neuropathy (91).

While generally considered safe, there are several potential risks in nerve blocking therapies. Common transient effects include localized soreness, bruising, and temporary numbness or weakness due to the spread of anesthetic to adjacent motor fibers (86). More serious but uncommon complications include bleeding, hematoma formation, and infection, particularly in deep blocks or in patients with coagulopathy or diabetes (87). Nerve injury, ranging from temporary neurapraxia to rare persistent neuropathy, may occur from direct needle trauma, intraneural injection, or neurotoxicity from local anesthetics (89). Steroid-containing blocks introduce additional risks such as steroid-induced hyperglycemia, immunosuppression, and, in rare cases, arachnoiditis or epidural lipomatosis after repeated administration (88).

Radiofrequency Ablation (RFA)

RFA is a minimally invasive palliative intervention that targets sensory nerves using radiofrequency energy to interrupt pain signaling pathways. It is frequently used for facet-mediated and joint-mediated pain syndromes, including chronic neuropathic hip pain. In this context, RFA targets branches of the femoral, obturator, and accessory obturator nerves, using ultrasound or fluoroscopic guidance to position a needle that delivers thermal or pulsed radiofrequency energy. Clinical studies show that RFA provides 30 to 80% pain reduction for conditions such as hip osteoarthritis, osteonecrosis, and labral pathology (92). A randomized 12-week study comparing pulsed PRF with conservative therapy demonstrated significantly greater pain relief and functional improvement in the PRF group (93, 94). Risks are generally minor and include procedural pain, bruising, numbness, and transient paresthesia. No severe complications are typically reported (92). Overall, RFA represents a safe, effective long-term option for patients who may not be candidates for invasive surgery.

Given the breadth of pharmacologic and interventional options discussed above, a comparative synthesis may aid clinical interpretation. Table 1 summarizes the major therapeutic classes for neuropathic pain, including their mechanisms of action, clinical indications, advantages, limitations, and key risks.

Table 1. Summary of Major Therapeutic Classes for Neuropathic Pain.

Therapeutic Class	Mechanism of Action	Clinical Indications	Advantages	Limitations	Key Risks / Adverse Effects
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) (e.g., duloxetine, venlafaxine)	Inhibition of serotonin (5-HT) and norepinephrine (NE) reuptake, enhancing descending inhibitory pain pathways	Diabetic peripheral neuropathy, chemotherapy-induced neuropathy, postherpetic neuralgia, central neuropathic pain	Effective systemic therapy; address impaired descending inhibition; beneficial for comorbid mood disorders	Variable response; efficacy influenced by genetic polymorphisms and metabolism	Nausea, fatigue, sexual dysfunction, dry mouth, hypertension; CYP-mediated drug interactions
Tricyclic Antidepressants (TCAs) (e.g., amitriptyline)	Inhibition of 5-HT and NE reuptake; blockade of voltage-gated sodium channels; modulation of NMDA receptor activity	Diabetic neuropathy, postherpetic neuralgia, post-traumatic neuropathic pain	Multimodal analgesic mechanisms; efficacy comparable to SNRIs	Reduced tolerability; limited use in older or cardiac-risk patients	Anticholinergic effects, sedation, QT prolongation, cardiotoxicity, increased suicide risk in younger patients
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	Inhibition of COX-1 and COX-2 enzymes, reducing prostaglandin-mediated inflammatory nociceptive signaling	Adjunct treatment for inflammatory pain with neuropathic components	Widely available; effective for inflammatory pain	Limited efficacy for pure neuropathic pain	Gastrointestinal bleeding, renal dysfunction, cardiovascular risk
Acetaminophen	Central analgesic action via AM404; modulation of cannabinoid, COX, and TRPV1 pathways in the spinal dorsal horn	Acute pain, osteoarthritis	Favorable gastrointestinal safety profile; low cost	Weak anti-inflammatory activity; limited efficacy in chronic neuropathic pain	Hepatotoxicity with overdose or chronic high dosing
Gabapentin	Binding to the α2δ subunit of voltage-gated calcium channels, reducing calcium influx and release of excitatory neurotransmitters	Postherpetic neuralgia, diabetic neuropathy, radiculopathy, nerve injury	Opioid-sparing; favorable long-term safety; non-addictive	Gradual onset of analgesia; requires dose titration	Dizziness, fatigue, peripheral edema, weight gain; withdrawal seizures if abruptly discontinued
Topical Lidocaine	Local blockade of voltage-gated sodium channels in peripheral sensory nerves	Postherpetic neuralgia, post-surgical or post-traumatic neuropathy, localized peripheral neuropathic pain	Minimal systemic absorption; strong safety profile	Ineffective for central neuropathic pain	Local skin irritation; theoretical risk of injury to desensitized tissue

Continued Table 1. Summary of Major Therapeutic Classes for Neuropathic Pain.

Therapeutic Class	Mechanism of Action	Clinical Indications	Advantages	Limitations	Key Risks / Adverse Effects
Topical Capsaicin	Activation followed by desensitization of TRPV1 receptors on nociceptive sensory neurons	Postherpetic neuralgia, HIV-associated neuropathy, post-traumatic or post-surgical peripheral neuropathic pain	Sustained peripheral analgesia; minimal systemic exposure	Initial burning sensation; limited to peripheral pain	Local burning, erythema, transient discomfort
Topical Menthol	Activation of TRPM8 receptors producing cold sensation and inhibitory modulation of pain signaling	Chemotherapy-induced peripheral neuropathy, localized neuropathic pain	Minimal systemic absorption; favorable safety profile	Mild to moderate analgesic efficacy	Transient skin irritation
Corticosteroid Injections	Glucocorticoid receptor-mediated suppression of inflammatory cytokine and chemokine expression	Joint-mediated and inflammatory neuropathic pain	Rapid short-term pain relief	Temporary benefit; repeated use discouraged	Cartilage toxicity, hyperglycemia, immunosuppression, infection
Nerve Blocks	Local anesthetic sodium-channel blockade with or without steroid-mediated anti-inflammatory effects	Radiculopathy, trigeminal neuralgia, CRPS, nerve entrapment syndromes	Targeted pain interruption; diagnostic and therapeutic utility	Short duration of relief; operator-dependent	Bleeding, infection, nerve injury, transient motor weakness
Radiofrequency Ablation (RFA)	Thermal or pulsed radiofrequency disruption of afferent sensory nerve transmission	Facet-mediated pain, hip osteoarthritis–associated neuropathic pain, refractory cases	Prolonged pain relief; minimally invasive	Requires careful patient selection	Procedural pain, transient numbness or paresthesia
Therapeutic Classes	Mechanism of Action	Clinical Indications	Advantages	Limitations	Key Risks / Adverse Effects
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) (e.g., duloxetine, venlafaxine)	Inhibition of serotonin (5-HT) and norepinephrine (NE) reuptake transporters, enhancing descending inhibitory pain pathways in the spinal cord	Diabetic peripheral neuropathy, chemotherapy-induced neuropathy, postherpetic neuralgia, central neuropathic pain	Effective systemic therapy; target impaired descending inhibitory pathways; treat comorbid mood disorders	Variable individual response; efficacy influenced by genetic polymorphisms and metabolism	Nausea, fatigue, sexual dysfunction, dry mouth, hypertension; CYP-mediated drug interactions
Tricyclic Antidepressants (TCAs) (e.g., amitriptyline)	Inhibition of 5-HT and NE reuptake; blockade of voltage-gated sodium channels; modulation of NMDA receptor activity	Diabetic neuropathy, postherpetic neuralgia, post-traumatic neuropathic pain	Multimodal analgesic mechanisms; efficacy comparable to SNRIs	Reduced tolerability; not preferred as first-line therapy	Anticholinergic effects, sedation, QT prolongation, cardiotoxicity, increased suicide risk in younger patients

Continued Table 1. Summary of Major Therapeutic Classes for Neuropathic Pain.

Therapeutic Class	Mechanism of Action	Clinical Indications	Advantages	Limitations	Key Risks / Adverse Effects
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	Inhibition of COX-1 and COX-2 enzymes, reducing prostaglandin synthesis and inflammatory nociceptive signaling	Inflammatory pain with neuropathic components; adjunct therapy	Widely available; effective for inflammatory pain	Limited efficacy for pure neuropathic pain	Gastrointestinal bleeding, renal dysfunction, cardiovascular risk
Acetaminophen	Central analgesic action via AM404; modulation of cannabinoid, COX, and TRPV1 receptors in the spinal dorsal horn	Acute pain, osteoarthritis	Favorable gastrointestinal safety profile; low cost	Weak anti-inflammatory activity; limited efficacy in chronic neuropathic pain	Hepatotoxicity with overdose or chronic high dosing
Gabapentin	Binding to the α2δ subunit of voltage-gated calcium channels, reducing calcium influx and release of excitatory neurotransmitters	Postherpetic neuralgia, diabetic neuropathy, radiculopathy, nerve injury	Favorable safety profile; non-addictive; opioid-sparing	Gradual onset of analgesia; dose titration required	Dizziness, fatigue, peripheral edema, weight gain; withdrawal seizures if abruptly discontinued
Topical Lidocaine	Local blockade of voltage-gated sodium channels in peripheral sensory nerves	Postherpetic neuralgia, post-surgical or post-traumatic neuropathy, localized peripheral neuropathic pain	Minimal systemic absorption; strong safety profile	Ineffective for central neuropathic pain	Local skin irritation; theoretical risk of injury to desensitized tissue
Topical Capsaicin	Activation and subsequent desensitization of TRPV1 receptors on nociceptive sensory neurons	Postherpetic neuralgia, HIV-associated neuropathy, post-traumatic or post-surgical peripheral neuropathic pain	Sustained peripheral analgesia; minimal systemic exposure	Initial burning sensation; not effective for central neuropathic pain	Local burning, erythema, transient discomfort

DISCUSSION

Neuropathic pain remains a significant clinical challenge due to its diverse etiologies, complex pathophysiology, and variable patient responses to treatment. The present review demonstrates that no single modality provides universal relief, and treatment effectiveness is highly dependent on the underlying mechanism of each patient's condition. This reinforces the importance of a mechanistic, rather than purely symptomatic, approach to neuropathic pain management.

Pharmacologic treatments such as NSAIDs, gabapentin, TCAs, and SNRIs remain foundational, but each has notable limitations. NSAIDs, while widely used, primarily address inflammatory components rather than neuropathic mechanisms and carry substantial gastrointestinal and cardiovascular risks with chronic use. Gabapentin demonstrates more targeted efficacy by modulating calcium channel activity, although its effectiveness varies widely, and sedation or dizziness may limit adherence. TCAs and SNRIs exert benefit through enhancement of descending inhibitory

pathways, but side effects, especially anticholinergic and cardiovascular risks for TCAs, restrict their use in certain populations. These limitations suggest that although oral agents provide accessible first-line treatment, their ability to fully address chronic neuropathic pain remains incomplete.

Topical therapies and localized injections offer an important shift toward mechanism-specific and site-specific management. Lidocaine and capsaicin patches deliver targeted analgesia with minimal systemic exposure. This makes them particularly valuable for localized peripheral neuropathic pain syndromes such as postherpetic neuralgia. However, topical therapies often lack sufficient potency for widespread or severe neuropathic pain, limiting their use to adjunctive roles.

Minimally invasive interventions, such as corticosteroid injections and nerve blocks, provide temporary relief by reducing inflammation or interrupting nociceptive transmission. Yet their duration of benefit is variable, and repeated administration poses risks, including cartilage degradation and procedural complications. Among procedural treatments, RFA stands out for its ability to provide prolonged relief, sometimes lasting months, by disrupting the afferent pain pathway while maintaining a favorable safety profile. Based on evidence that supports its utility in conditions such as hip osteoarthritis and facet-mediated pain, RFA may represent an underutilized intermediate step between pharmacotherapy and surgery.

A key insight from this review is the value of a stepped-care model, which involves initiating treatment with low-risk oral or topical medications, progressing to targeted injections or nerve blocks for incomplete responders, and reserving RFA or other minimally invasive procedures for refractory cases. This approach aligns with current pain management guidelines and acknowledges the heterogeneity of patient responses. Future therapeutic directions should emphasize individualized care informed by genetic, neurophysiological, and imaging biomarkers. Additionally, emerging regenerative interventions, such as stem cell therapy, platelet-rich plasma, and platelet-rich fibrin, warrant further investigation as potentially safer and longer-lasting alternatives to steroids and repeated nerve blocks. As the field of personalized medicine expands, tailoring neuropathic pain treatment to the patient's molecular and structural characteristics will likely improve outcomes and reduce reliance on broad-spectrum pharmacotherapy.

CONCLUSION

Neuropathic pain encompasses both central and peripheral disorders that share common pathophysiological features, including neuronal hyperexcitability, maladaptive plasticity, and impaired inhibitory control. A broad spectrum of therapeutic options that range from systemic pharmacologic agents and topical therapies to targeted interventional procedures can provide meaningful pain relief, although efficacy varies substantially based on etiology, disease mechanism, and patient-specific factors. As such, no single therapy is universally effective.

Current evidence supports a stepped, multimodal approach to neuropathic pain management, in which low-risk systemic or topical treatments are initiated, followed by targeted injections, nerve blocks, or radiofrequency ablation for refractory cases. However, important gaps remain in defining optimal treatment sequencing, predicting individual treatment response, and determining the durability of benefit across diverse patient populations.

Future directions in neuropathic pain management increasingly emphasize mechanism-based and personalized strategies. Advances in neuroimaging, pharmacogenomics, and molecular profiling hold promise for tailoring therapies to specific pain phenotypes and underlying biological pathways. Emerging interventions, including regenerative and neuromodulatory approaches, warrant further investigation as potential alternatives to repeated steroid-based or ablative procedures. High-quality comparative studies and long-term outcome data are needed to better inform clinical decision-making and refine patient selection.

In summary, effective management of neuropathic pain requires an individualized, mechanism-informed, and adaptive treatment strategy. Continued integration of translational research with clinical practice will be essential to advancing therapeutic precision and improving long-term outcomes for patients with neuropathic pain.

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CONFLICT OF INTEREST

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