

Neuropathic pain: a practical guide for the clinician

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ABSTRACT

Neuropathic pain, caused by various central and peripheral nerve disorders, is especially problematic because of its severity, chronicity and resistance to simple analgesics. The condition affects 2%–3% of the population, is costly to the health care system and is personally devastating to the people who experience it. The diagnosis of neuropathic pain is based primarily on history (e.g., underlying disorder and distinct pain qualities) and the findings on physical examination (e.g., pattern of sensory disturbance); however, several tests may sometimes be helpful. Important pathophysiologic mechanisms include sodium- and calcium-channel upregulation, spinal hyperexcitability, descending facilitation and aberrant sympathetic–somatic nervous system interactions. Treatments are generally palliative and include conservative non-pharmacologic therapies, drugs and more invasive interventions (e.g., spinal cord stimulation). Individualizing treatment requires consideration of the functional impact of the neuropathic pain (e.g., depression, disability) as well as ongoing evaluation, patient education, reassurance and specialty referral. We propose a primary care algorithm for treatments with the most favourable risk–benefit profile, including topical lidocaine, gabapentin, pregabalin, tricyclic antidepressants, mixed serotonin–norepinephrine reuptake inhibitors, tramadol and opioids. The field of neuropathic pain research and treatment is in the early stages of development, with many unmet goals. In coming years, several advances are expected in the basic and clinical sciences of neuropathic pain, which will provide new and improved therapies for patients who continue to experience this disabling condition.

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Neuropathic pain, caused by a lesion of the nervous system,^{1,2} is especially problematic because (a) it is often experienced in parts of the body that otherwise appear normal, (b) it is generally chronic, severe³ and resistant to over-the-counter analgesics,⁴ and (c) it is further aggravated by allodynia (touch-evoked pain).⁵ It may result from various causes that affect the brain, spinal cord and peripheral nerves, including cervical or lumbar radiculopathy, diabetic neuropathy, cancer-related neuropathic pain, postherpetic neuralgia, HIV-related neuropathy, spinal cord injury, trigeminal neuralgia and complex regional pain syndrome type II, among others.⁶ Complex regional pain syn-

drome type I is not considered a cause, because there is no definable nerve lesion. The epidemiology of neuropathic pain has not been adequately studied, partly because of the diversity of the associated conditions. Current pooled estimates suggest that neuropathic pain may affect as much as 3% of the population.^{7–13}

The personal impact of neuropathic pain is most vividly appreciated by people who experience this devastating condition. Those affected have described their pain using the McGill Pain Questionnaire¹⁴ with descriptors such as “punishing–cruel” and “tiring–exhausting.”^{15,16} Ample evidence indicates that neuropathic pain impairs patients’ mood, quality of life, activities of daily living and performance at work.^{9,17,18} People with the condition have been found to generate 3-fold higher health care costs compared with matched controls.¹⁹ In the United States, health care, disability and related costs associated with chronic pain have been estimated at \$150 billion annually,²⁰ of which almost \$40 billion is attributable to neuropathic pain.

Clinical presentation and patient evaluation

The blockade of nerve conduction in neuropathic conditions causes nerve dysfunction, which can result in numbness, weakness and loss of deep tendon reflexes in the affected nerve area. Neuropathic conditions also cause aberrant symptoms of spontaneous and stimulus-evoked pain. Spontaneous pain (continuous or intermittent) is commonly described as burning, shooting or shock-like.^{15,21–26} Stimulus-evoked pain includes allodynia (pain evoked by a nonpainful touch) and hyperalgesia (increased pain evoked by a painful stimulus). Allodynia can be caused by the lightest stimulation, such as skin contact with clothing or a light breeze. These sensory abnormalities may extend beyond nerve distributions (Fig. 1), which may lead to the inappropriate diagnosis of a functional or psychosomatic disorder. The diagnosis of neuropathic pain is based primarily on history and findings on physical examination.²⁷

Assessment of the patient with suspected neuropathic pain should focus on ruling out treatable conditions (e.g., spinal cord compression, neoplasm), confirming the diagnosis of neuropathic pain and identifying clinical features (e.g., insomnia, autonomic neuropathy) that might help individualize treatment. Box 1 lists principal details of the clinical evaluation, including history, physical examination and special tests.

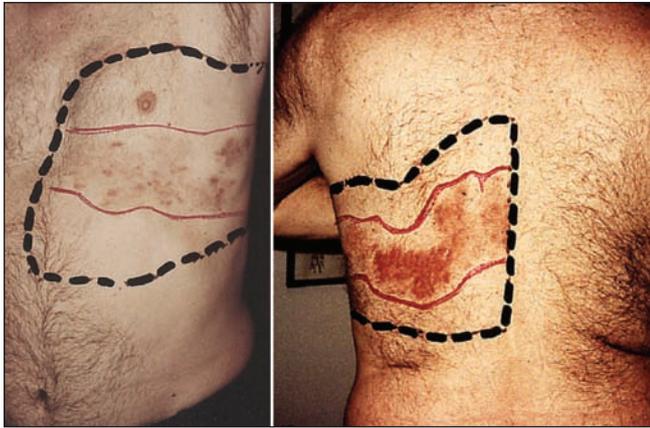


Fig. 1: Man with postherpetic neuralgia in the left fifth and sixth thoracic dermatomes. Red lines delineate area of sensory loss, and black dashed lines delineate area of allodynia (touch-evoked pain). Extension of allodynia above and below the originally affected dermatomes is a feature of central sensitization.

Pathophysiology and molecular mechanisms of neuropathic pain

Table 1 highlights the clinical and pathophysiologic features of common neuropathic pain syndromes that are caused by nerve injury or dysfunction. Knowledge of the cellular and molecular mechanisms of neuropathic pain has advanced with the development of various experimental models of nerve injury.⁵⁰ Both peripheral and central mechanisms (Fig. 2) have been proposed as being relevant to the pathogenesis of neuropathic pain.⁵¹

Peripheral mechanisms

Regeneration after nerve injury results in the formation of neuromas^{52,53} and sprouting of new nerve projections among uninjured neighbouring neurons.⁵⁴ Collateral sprouting then leads to altered sensory properties that may be realized as expanded receptive fields. Uncontrolled neuronal firing after experimental nerve injury is largely attributed to increased expression of sodium channels. This mechanism is supported by several lines of evidence, including blockade of neuropathic pain with sodium-channel-blocking local anesthetics.⁵⁵ Demyelination of diseased nerves may be another cause of increased neuronal excitability.⁵⁶

In addition to sodium channels, expression of voltage-gated calcium channels is also increased following nerve injury.⁵⁷ Calcium entry through voltage-gated calcium channels is necessary for the release of substance P⁵⁸ as well as glutamate from injured peripheral nerves. Within the dorsal root ganglion, increased expression of the α -2-delta subunit of voltage-gated calcium channels correlates with onset and duration of allodynia.⁵⁹ Clinical support of the role of this protein in neuropathic pain arises from the analgesic efficacy of α -2-delta voltage-gated calcium-channel antagonists, gabapentin and pregabalin.^{60,61}

Central mechanisms

Sustained painful stimuli result in spinal sensitization,⁶² which is defined as heightened sensitivity of spinal neurons, reduced activation thresholds and enhanced responsiveness to synaptic inputs (i.e., more likely to transmit pain to the brain).⁶³ This can manifest in expansion of the affected area, increased response to painful inputs and transmission of pain following nonpainful stimuli.⁶⁴ Central sensitization is largely mediated by the *N*-methyl-D-aspartate (NMDA) receptor. Although experimental NMDA-receptor blockade clearly suppresses central sensitization,⁶⁵ analgesic efficacy of NMDA antagonists has been disappointing, likely because of the narrow therapeutic window of available agents.⁶¹

Activation of descending pathways (the periaqueductal grey-rostral ventromedial medulla)⁶⁶ has been shown to reduce pain transmission in animals⁶⁷ and humans⁶⁸ and is thought to contribute to the analgesic effect of opioids and antidepressants. Paradoxically, this system can also facilitate pain transmission⁶⁹ and may contribute to some chronic pain states.⁷⁰

Sympathetically maintained pain

The importance of the sympathetic nervous system in neuropathic pain has been demonstrated by analgesia following sympathectomy in animals⁷¹ and humans,⁷² and by pain exacerbation through activation of the sympathetic nervous system.⁷³ Sympathetically maintained pain may be explained by sprouting of sympathetic neurons into dorsal root ganglia of injured sensory neurons⁷⁴ and postinjury sprouting of sympathetic fibres into the dermis.⁷⁵

Current management

Nonpharmacologic

Although many patients with neuropathic pain pursue complementary and alternative treatments, rigorous evidence supporting efficacy of nondrug therapy is limited. Some reports suggest benefits of conservative interventions such as exercise,⁷⁶ transcutaneous electrical nerve stimulation,⁷⁷ percutaneous electrical nerve stimulation,⁷⁸ graded motor imagery⁷⁹ and cognitive behavioural therapy or supportive psychotherapy.⁸⁰

Pharmacologic

One approach to estimate treatment efficacy using randomized controlled trial (RCT) data is based on the number-needed-to-treat (NNT) to obtain at least 50% pain relief in one patient. The NNT concept is hampered by methodologic variability across different RCTs, the short-term nature of most RCTs and the lack of consideration for other important outcomes (e.g., disability, quality of life). Also, most RCTs have involved patients with diabetic peripheral neuropathy and postherpetic neuralgia, and the results do not necessarily apply to all neuropathic pain conditions.

Antidepressants

Tricyclic antidepressants have repeatedly been shown to reduce neuropathic pain.⁸¹ Analgesic actions may be attributable to noradrenaline and serotonin reuptake blockade (presumably enhancing descending inhibition), NMDA-receptor antagonism and sodium-channel blockade.⁸² The NNT is about 3 both for balanced noradrenaline and serotonin reuptake inhibitors (e.g., amitriptyline) and predominantly noradrenaline reuptake inhibitors (e.g., nortriptyline).⁶¹

Selective serotonin reuptake inhibitors (NNT = 6.7)⁸³ and mixed serotonin–noradrenaline reuptake inhibitors (venlafaxine and duloxetine,⁸⁴ NNT = 4.1–5.5)⁶¹ do not appear to be as effective as tricyclic antidepressants.

Anticonvulsants

Based on methodologically flawed trials, carbamazepine and phenytoin have NNTs of 2.1–2.3 for diabetic peripheral neuropathy.⁶¹ Both have significant adverse effects, making them generally poor candidates for first-line therapy. Carbamazepine, however, is still considered first-line therapy for trigeminal neuralgia, a unique neuropathic pain condition (NNT = 1.7).⁶¹ Oxcarbazepine, a newer anticonvulsant structurally related to carbamazepine, may also be useful; however, only one RCT (in diabetic peripheral neuropathy) has been published.⁸⁵

Gabapentin, an α -2-delta subunit voltage-gated calcium-channel antagonist,⁸⁶ has repeatedly demonstrated analgesic

Box 1: Clinical evaluation of patients with suspected neuropathic pain

History

Pain intensity

- 0–10 rating scale (0 = no pain, 10 = worst pain imaginable)
- Rate pain at initial presentation and at subsequent visits to track treatment response

Sensory descriptors^{15,21–26}

- Pain qualities: hot, burning, sharp, stabbing, cold, allodynia (pain brought on by light touch, clothing or bed sheets)
- Common nonpainful sensations: tingling, prickling, itching, numbness and “pins and needles”

Temporal variation

- Neuropathic pain often gets worse towards the end of the day²⁸
- Neoplastic process should be suspected if pain has been progressively increasing over recent months

Functional impact

- Effect of pain on sleep,²⁹ ambulation, self-care, activities of daily living, work, social or sexual function, mood³⁰ and suicidal ideation³¹

Attempted treatments

- Neuropathic pain is generally resistant to acetaminophen and NSAIDs
- Determine and document adequacy of dose titration for titratable drugs (e.g., dose reached and duration of treatment, drug treatment stopped owing to adverse effects or lack of efficacy)³²

Alcohol or substance abuse

- Addiction history will affect decision to prescribe opioids or cannabinoids
- Consider earlier involvement with a psychologist or psychiatrist³³
- Consider safety of sedative analgesics with alcohol or other sedatives

Physical examination

Gross motor examination

- Motor weakness may occur around the involved nerves
- Attempt to differentiate between true weakness and antalgic weakness

Deep tendon reflexes

- May be diminished or absent around the involved nerves

Sensory examination

- Light touch, pin prick, vibration sense and proprioception may be diminished or absent in the involved nerve territory
- Sensory disturbance may aberrantly extend beyond a discrete nerve territory
- Dynamic allodynia (pain due to cotton wool lightly moving across the skin)
- Thermal allodynia (burning sensation in response to ice cube on skin)
- Pinprick hyperalgesia (exaggerated pain following pinprick to the skin)
- Pain when straight leg is raised, suggestive of irritation of lumbar nerve root
- Elicitation of myofascial trigger points to favour a diagnosis of myofascial pain over neuropathic pain
- Possible presence of Tinel’s sign (distally radiating paresthesias upon percussion of damaged or regenerating nerve fibres)

Skin examination

- Alterations in temperature, colour, sweating and hair growth suggestive of complex regional pain syndrome³⁴
- Residual dermatomal scars consistent with previous herpes zoster (shingles) infection
- Characteristic skin changes consistent with diabetes mellitus

Special tests

CT and MRI scans

- Facilitate specific diagnosis (e.g., herniated disc, nerve infiltration by tumour)

Electromyography and nerve conduction studies

- May provide objective evidence of nerve injury or dysfunction³⁵
- Nerve conduction studies evaluate large fibre function; therefore, small fibre neuropathy cannot be ruled out if results of nerve conduction studies are normal

Three-phase nuclear medicine bone scan

- May help diagnose complex regional pain syndrome³⁶

Clinical biochemistry

- Conduct tests to help identify cause of neuropathy; for example, glucose tolerance testing, thyroid function, measurement of vitamin B₁₂ levels, CD4+ T-lymphocyte count

efficacy and improvements in mood and sleep in several RCTs (NNT = 3.8).^{60,61} Pregabalin is a gabapentin analogue with a similar mechanism, higher calcium-channel affinity and better bioavailability.^{60,87} Pregabalin was superior to placebo in several RCTs in diabetic peripheral neuropathy and postherpetic neuralgia (NNT = 4.2).⁶¹

RCTs of other anticonvulsants, including valproate, lamotrigine and topiramate, have had equivocal results.⁶¹

Opioid analgesics

The role of opioid analgesics in neuropathic pain has been controversial. However, a recent meta-analysis provides convincing evidence of benefit.⁸⁸ Although 14 short-term RCTs (< 24 hours) showed contradictory results, 8 intermediate-term RCTs (≤ 8 weeks) demonstrated important efficacy. These RCTs demonstrated, on average, a 20%–30% pain reduction. For morphine and oxycodone, the NNT ranged from 2.5 to 2.6.⁶¹ However, beneficial effects on mood, quality of life and disability are not consistent.^{89,90} There were no reports of addiction or abuse in these RCTs, although the risk is likely to be low given the common exclusion criterion of substance abuse history.⁸⁸ Currently, there is a dearth of evidence supporting the long-term efficacy of opioids in controlling

neuropathic pain. However, the results of a recent retrospective review involving more than 100 patients (most of whom had neuropathic pain) who had received chronic opioid therapy for 1 year or more suggest that many patients may continue to enjoy persistent pain relief with opioids.⁹¹

Tramadol is a weak opioid and a mixed serotonin–noradrenaline reuptake inhibitor.⁹² Three RCTs of tramadol for neuropathic pain have yielded an overall NNT of 3.9.⁶¹

Methadone is a synthetic opioid potentially useful for controlling neuropathic pain because of its NMDA-antagonist properties.⁹³ However, its long half-life (24–36 hours) necessitates extremely careful dose titration.⁹⁴ Two small RCTs of methadone demonstrated benefit in managing neuropathic pain,^{95,96} and open-label experience suggests promise in a wide variety of neuropathic pain conditions.⁹⁷

NMDA antagonists

Because of the critical role of NMDA activity in central sensitization,⁹⁸ NMDA antagonists hold promise in the management of neuropathic pain. Unfortunately, available agents have limited efficacy and produce intolerable side effects. Ketamine, an intravenous anesthetic with NMDA-antagonist activity, has been found to be effective in small RCTs; however,

Table 1: Clinical features and pathophysiology of common neuropathic pain syndromes

Diagnosis (inciting cause)	Typical clinical features	Putative pathophysiology and clinical pathogenesis
Painful diabetic neuropathy (hyperglycemia)	Symmetrical sensory loss and burning pain in lower legs ³⁷	Hyperglycemia, hyperlipidemia, hypoinsulinemia, growth factor deficiency → oxidative stress and autoimmunity → progressive demyelination and axonal loss → sensory loss, paresthesia, dysesthesias, pain and allodynia ^{38–40}
Lumbosacral radiculopathy (herniated intervertebral disc)	Lancinating pain radiating into the anterior thigh (L2/3) or lower leg (L4–S1) with motor weakness or sensory loss	<ul style="list-style-type: none"> • Spinal nerve root compression⁴¹ • Inflammatory effects of extruded nucleus pulposus⁴² • Sensory and motor abnormalities, radiating pain
Postherpetic neuralgia (varicella zoster virus infection)	Unilateral pain, sensory loss or allodynia in the dermatome where herpes zoster had previously erupted ⁴³	<ul style="list-style-type: none"> • Dorsal horn atrophy, sensory ganglion (primary afferent neuron) cell, axon and myelin loss and fibrosis⁴⁴ • Sensitization of unmyelinated cutaneous nociceptors (“irritable nociceptors”) and/or • Small fibre deafferentation and allodynia and/or • Small and large fiber deafferentation • Sensory loss, pain and allodynia⁵
HIV-related neuropathy (HIV infection)	Symmetrical painful paraesthesias, most prominent in the toes and soles of the feet ⁴⁵	<ul style="list-style-type: none"> • Direct viral invasion of sensory neurons? • HIV-mediated macrophage infiltration of peripheral nerves? • Neurotoxicity of reverse transcriptase inhibitors • Sensory loss, pain and allodynia¹¹
Complex regional pain syndrome <ul style="list-style-type: none"> • Type 1 (previously “reflex sympathetic dystrophy” – no definable nerve lesion) • Type 2 (previously “causalgia” – nerve injury) 	Regional (e.g., limb) pain together with edema, cutaneous blood flow and sweating abnormalities ⁴⁶	<ul style="list-style-type: none"> • “Coupling” of sympathetic neurons with injured sensory neurons at peripheral neuroma sites or dorsal root ganglion sites of injured afferent nerves → development of noradrenergic sensitivity following nerve injury • Pain, allodynia, hyperalgesia, edema, cutaneous blood flow and sweating abnormalities⁴⁷
Postsurgical neuropathic pain (surgical procedure)	Peri-incisional sensory loss, pain and allodynia for more than 3 months after surgery; phantom pain following amputation or mastectomy	<ul style="list-style-type: none"> • Phantom pain in 30%–81% of amputations⁴⁸ • Thoracotomy pain in 11%–57%⁴⁸ • Postherniorrhaphy in 37% or less⁴⁸ • Postmastectomy pain in 66%–83%⁴⁸ • Poststernotomy in 54% or less⁴⁹

psychomimetic side effects are dose limiting.⁹⁹ Dextromethorphan, a common cough suppressant and NMDA antagonist, has produced uncertain results in controlling neuropathic pain, showing modest benefit in diabetic peripheral neuropathy, but not in postherpetic neuralgia.¹⁰⁰

Topical agents

Locally acting analgesics are attractive because they may cause minimal systemic side effects. The lidocaine patch 5% has been shown to relieve localized pain in postherpetic neuralgia with no increase in side effects (NNT = 4.4).⁶¹ Although the lidocaine patch 5% is not available in Canada, pharmacists can make up the gel or cream at a concentration

of 5%–10%.¹⁰¹ Capsaicin, an ingredient of hot peppers, has shown mixed results in RCTs,⁶¹ and some patients with postherpetic neuralgia have reported pain exacerbation. One RCT evaluating topical doxepin, capsaicin and their combination demonstrated significant analgesia with all 3 of these interventions.¹⁰²

Miscellaneous drugs

Mexiletine, an oral antiarrhythmic agent and sodium-channel blocker, was superior to placebo in only 2 of 7 RCTs.⁶¹ Clonidine, an α -2-agonist sympathetic blocker, was shown to be effective in a subset of patients with diabetic peripheral neuropathy.¹⁰³ Cannabinoids have been found to play a role in ex-

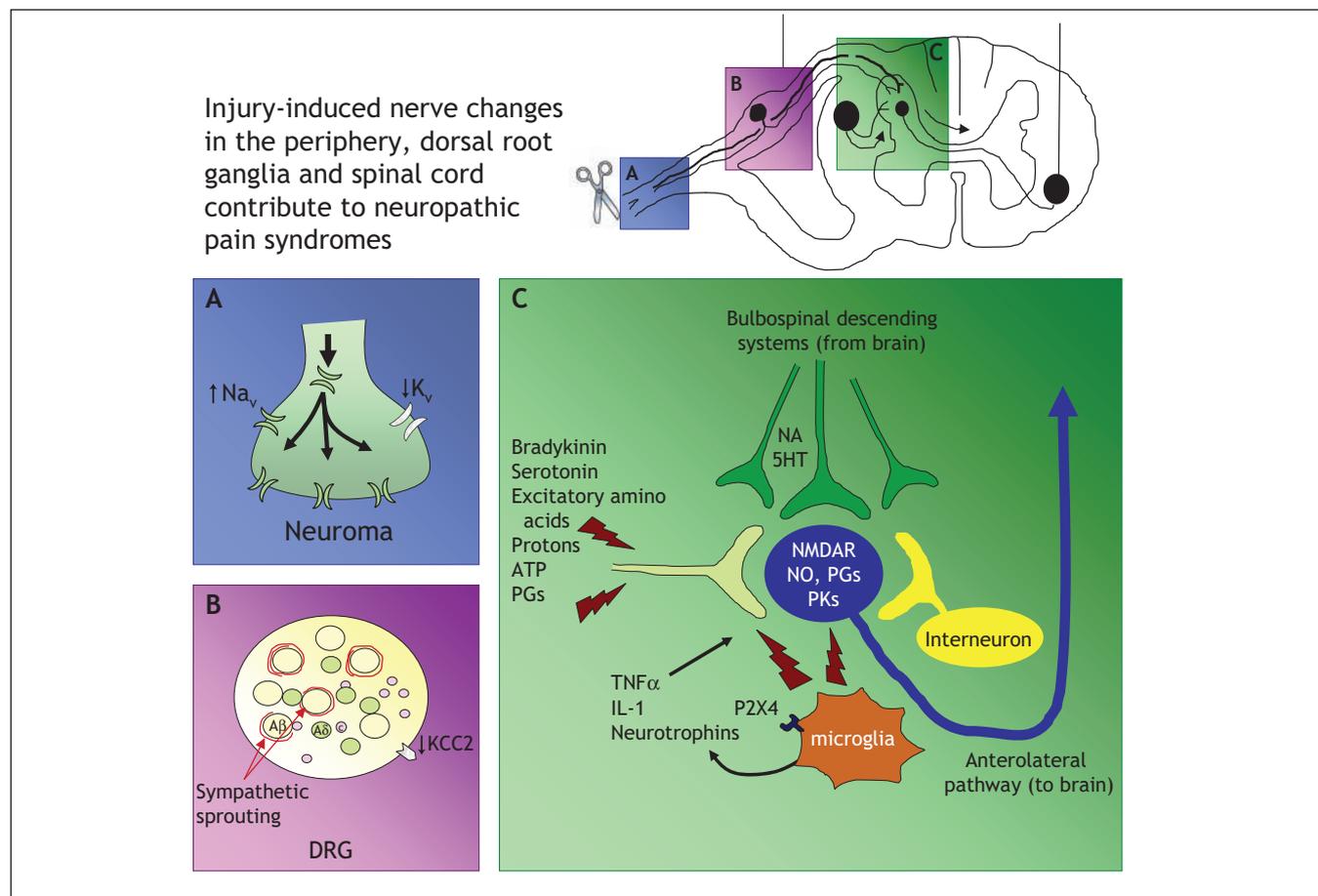


Fig 2: Neuropathic pain arises following nerve injury or dysfunction. **A:** After nerve damage, transcription and axonal trafficking of sodium channels to the site of injury is increased, with concomitant attenuation of potassium channels. The altered expression of ion channels results in neurons becoming hyperexcitable and generating ectopic activity, which is thought to lead to the genesis of spontaneous and paroxysmal pain. **B:** At the cell body of primary afferent neurons within the dorsal root ganglia (DRG), sympathetic neuronal sprouting occurs and may account for sympathetically maintained pain. **C:** Peripheral nerve injury causes a multitude of changes in gene transcription and activation of various kinases and proteins, including enhanced *N*-methyl-D-aspartate (NMDA) receptor activity. However, nerve injury also elicits hypertrophy and activation of glial cells, including microglia within the grey matter of the spinal cord. Microglia express P2X₄ purinergic receptors, allowing them to be activated by adenosine triphosphate (ATP). Following activation, microglia release various pronociceptive cytokines, such as interleukin-1 (IL-1), tumour necrosis factor α (TNF- α) and neurotrophins, including brain-derived neurotrophic factor, which in turn exacerbates nociceptive transmission and contributes to the sensitization and maintenance of neuropathic pain. Note: A β = A beta neuron, A δ = A delta neuron, C = C nociceptor, 5HT = serotonin, KCC2 = chloride transporter, NA = noradrenaline, Na_v = sodium channel, NO = nitric oxide, K_v = potassium channel, PGs = prostaglandins, PKs = protein kinases, P2X₄ = purinergic receptor.

perimental pain modulation,¹⁰⁵ and there is growing evidence of their efficacy in managing neuropathic pain. The cannabinoid dronabinol provided modest analgesic benefit in an RCT of central pain in multiple sclerosis.¹⁰⁶ An oromucosal spray containing a mixture of tetrahydrocannabinol and cannabidiol provided modest benefit in another RCT of central pain in multiple sclerosis¹⁰⁷ and in an RCT of neuropathic pain following brachial plexus avulsion.¹⁰⁸

Comparative trials

Given the limitations of comparing treatments across trials using NNTs, several investigators have compared treatments within single trials. For example, 3 comparative RCTs suggest that analgesia with desipramine^{109,110} or nortriptyline¹¹¹ is comparable to that of amitriptyline but with fewer side effects. Other studies suggest that opioids may be more efficacious than tricyclic antidepressants¹¹² or gabapentin¹⁶ and that gabapentin is comparable to amitriptyline¹¹³ and venlafaxine analgesia is comparable to that of imipramine.¹¹⁴ These are, however, early impressions from small RCTs. Larger RCTs that incorporate head-to-head comparisons are needed.

Combination pharmacotherapy

Given the limited effectiveness of current treatments, combining different drugs may result in improved results at lower doses and with fewer side effects. Many patients with neuropathic pain currently receive drug combinations,¹¹⁵ albeit in the absence of supportive evidence. In a recent RCT, analgesia with a morphine–gabapentin combination was superior to treatment with either drug alone.¹⁶ In a study involving IT patients who did not respond to gabapentin, a gabapentin–venlafaxine combination was superior to gabapentin alone.¹¹⁶ In another RCT, the addition of the neuroleptic fluphenazine to amitriptyline therapy provided no benefit.¹¹⁷ Future trials are needed to evaluate optimal drug combinations and dose ratios as well as safety, compliance and cost-effectiveness.¹¹⁸

Trigeminal neuralgia and other paroxysmal pain

Trigeminal neuralgia and glossopharyngeal neuralgia (idiopathic or related to multiple sclerosis) are unique conditions. They are characterized by orofacial, paroxysmal, shock-like pains triggered by light, localized, tactile stimulation with minimal constant pain between paroxysms. These syndromes are also distinguished by their high responsiveness to carbamazepine.¹¹⁹ Baclofen is a muscle relaxant shown to be useful in trigeminal neuralgia in the setting of resistance to carbamazepine.¹⁰⁴ High success rates have also been reported following invasive treatments such as microvascular decompression, trigeminal ganglion balloon compression and stereotactic (gamma knife) radiosurgery.¹²⁰

Interventional pain management

Although rigorous supportive evidence is limited, more invasive treatments may be considered for patients with in-

tractable neuropathic pain.^{121,122} Procedures include epidural or perineural injections of local anesthetics or corticosteroids, implantation of epidural and intrathecal drug delivery systems, neural ablative procedures (e.g., Gasserian ganglion glycerol injection or gamma knife surgery) and insertion of spinal cord stimulators, just to name a few. Consideration of highly invasive procedures such as insertion of intrathecal infusion pumps or spinal cord stimulators is generally reserved for patients with no surgically treatable pathology who have failed more conservative treatments and undergone psychological evaluation.¹²³ Although this level of caution may also be applied to nerve block procedures, some conditions could warrant nerve blocks earlier in the clinical course. For example, sympathetic nerve blocks in early complex regional pain syndrome may be a crucial adjunct for the facilitation of physiotherapy and rehabilitation.¹²⁴

Approach to neuropathic pain management in primary care

No single drug works for all neuropathic pain states, and given the diversity of pain mechanisms, patient responses and diseases, treatment must be individualized. Other than analgesia, factors to consider when individualizing therapy include tolerability, other benefits (e.g., improved sleep, mood and quality of life), low likelihood of serious adverse events and cost-effectiveness to the patient and the health care system.⁶¹ The evidence-based approach presented here may require revision as newer treatments and clinical evidence become available.

Pain management requires ongoing evaluation, patient education and reassurance. Diagnostic evaluation of treatable underlying conditions (e.g., spinal cord compression, herniated disc, neoplasm) should continue concurrently with pain management. Patients require education regarding the natural history of their condition and realistic treatment expectations (e.g., current treatments are not curative and analgesia is rarely complete). Even a 30% pain reduction is clinically important to patients.¹²⁵ Pain severity, patient complexity (e.g., coexisting depression or substance abuse), failure of attempted treatments and availability of health care resources should be considered when planning referrals to pain clinics and related specialists. Patient compliance and adequacy of analgesic drug titrations (e.g., dose and duration of treatment) should be continually evaluated and documented.

Neuropathic pain is best managed with a multidisciplinary approach. Nevertheless, several different treatments can be initiated in the primary care setting (Fig. 3). Treatments with the lowest risk of adverse effects should be tried first. Evidence supporting conservative nonpharmacologic treatments (e.g., physiotherapy, exercise, transcutaneous electrical nerve stimulation) is limited; however, given their presumed safety, nonpharmacologic treatments should be considered whenever appropriate.⁶¹ Simple analgesics (e.g., acetaminophen, NSAIDs) are usually ineffective in pure neuropathic pain but may help with a coexisting nociceptive condition (e.g., sciatica with musculoskeletal low-back pain). Early referrals to a

pain clinic for nerve blocks may be warranted in some cases to facilitate physiotherapy and pain rehabilitation.

Topical treatment with lidocaine, indicated for postherpetic neuralgia and focal neuropathy, could be tried first if it is available at a cost reasonable to the patient. For other neuropathic pain diagnoses or lidocaine treatment failures, we recommend initiating oral monotherapy with gabapentin or pregabalin, a tricyclic antidepressant, or a mixed serotonin–noradrenaline reuptake inhibitor. Of these treatments, gabapentin or pregabalin appear to be the best tolerated, with very few drug interactions. Tricyclic antidepressants appear to be more efficacious and much less expensive but have a higher likelihood of adverse effects and are relatively contraindicated for use in patients with serious cardiovascular disease (a screening electrocardiogram is recommended before prescribing tricyclic antidepressants), postural hypotension, urinary retention and angle-closure glaucoma. Among

available tricyclic antidepressants, nortriptyline and desipramine are more highly recommended because of fewer side effects. Newer mixed serotonin–noradrenaline reuptake inhibitors (e.g., venlafaxine, duloxetine) may not be as efficacious as tricyclic antidepressants but appear to be better tolerated.

Little is known about whether the response to one drug predicts the response to another. However, if the first oral medication tried is ineffective or not tolerated, one might switch to alternate monotherapy. In the event that all of the first-line oral monotherapies tried are ineffective or poorly tolerated, we would then recommend initiating monotherapy with tramadol or an opioid analgesic. Long-term prescribing of opioid analgesics requires special prescribing and regulatory considerations.^{126–129} In Canada, where tramadol is available only as a fixed-dose combination with acetaminophen, the upper dose limit of tramadol will be dic-

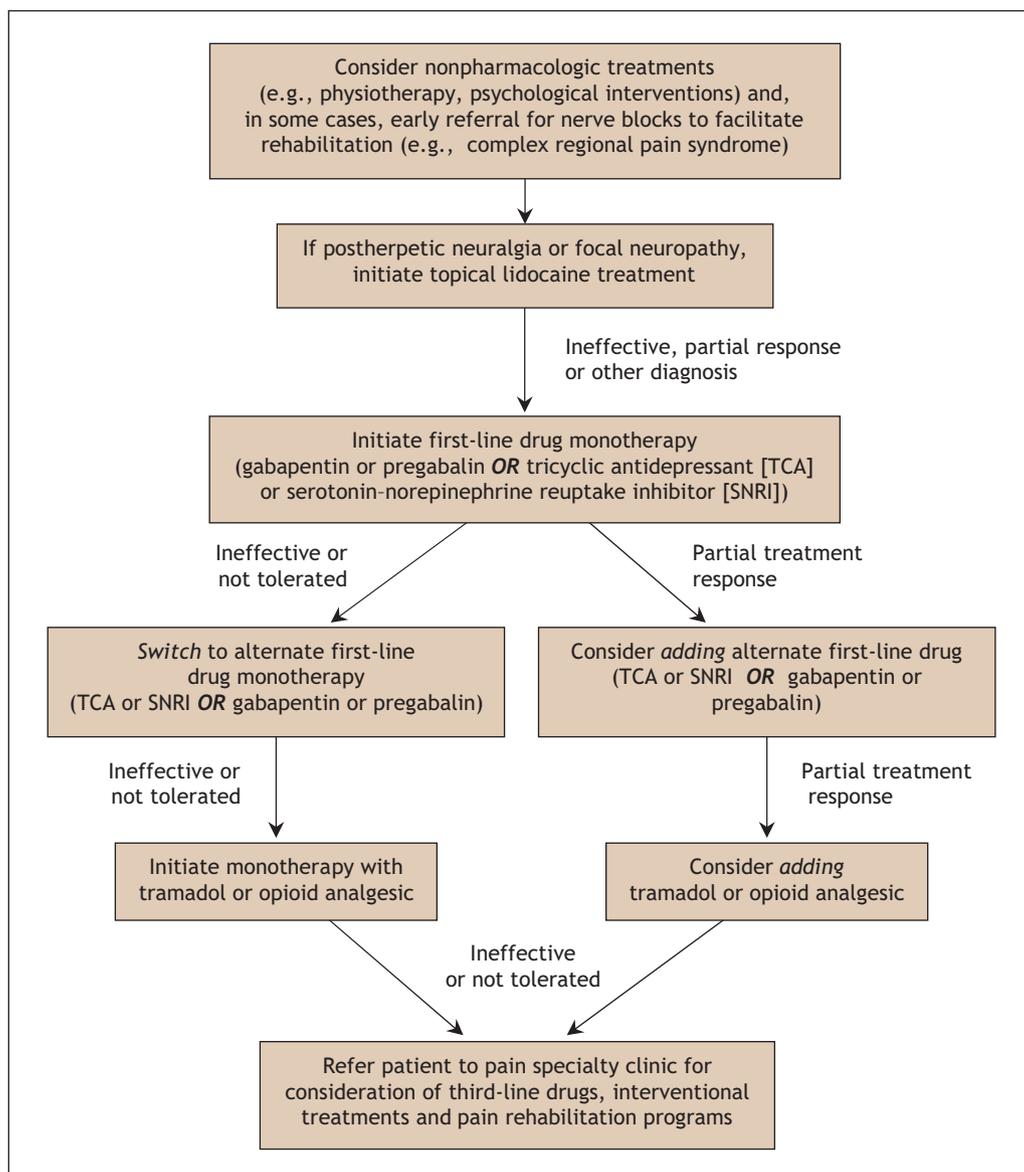


Fig. 3: Algorithm for the management of neuropathic pain in primary care.

Table 2: Neuropathic pain medications*

Drug	Drug interactions	Adverse effects	Dosage	Usual effective dose (and maximum)	Comments
Topical lidocaine 5%	Possible systemic absorption in patients taking oral therapy with class 1 antiarrhythmic drugs	Skin erythema, rash	1-3 patches every 12 h	3 patches every 12 h	Patch must be applied to painful area
Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline, desipramine)	Metabolism by CYP450 2D6 (note: rapid v. slow metabolizers), potentiates other sedatives	Cardiac conduction block, orthostatic hypotension, sedation, confusion, urinary retention, dry mouth, constipation, weight gain	10-25 mg/d, at bedtime or in divided doses every 12 h; increase dose weekly by 10-25 mg/d	50-150 mg/d; median 50-75 mg/d	More adverse effects with amitriptyline and imipramine; contraindicated in patients with glaucoma and those taking MAOIs
SNRIs					
Duloxetine	Metabolism by CYP450 2D6	Sedation, ataxia, nausea, dry mouth, constipation, hyperhidrosis, anorexia	60 mg once daily; 60 mg every 12 h also safe and effective	60 mg/d (maximum 120 mg/d)	Contraindicated in patients with glaucoma and those taking MAOIs; recent US FDA approval for use in diabetic neuropathy
Venlafaxine	Metabolism by CYP450 2D6 and 3A4	Hypertension, ataxia, sedation, insomnia, nausea, hyperhidrosis, dry mouth, constipation, anxiety, anorexia	37.5 mg once daily; increase dose weekly by 37.5 mg/d	150-225 mg/d (maximum 375 mg/d)	Dose adjustment in patients with renal dysfunction; contraindicated in patients taking MAOIs
Anticonvulsants					
Carbamazepine (CBZ)	Metabolism by CYP450 3A4, 1A2 and 2C8; inducer of CYP450 1A2, 2C and 3A	Sedation, ataxia, rash, diplopia, hyponatremia, agranulocytosis, nausea, diarrhea, hepatotoxicity, aplastic anemia, Stevens-Johnson syndrome	100-200 mg/d, in divided doses every 6-8 h; increase dose weekly by 100-200 mg/d	600-1200 mg/d (maximum 1600 mg/d); for trigeminal neuralgia, controlled-release CBZ every 8-12 h, with short-acting CBZ every 4 h for rescue	First-line therapy for trigeminal neuralgia only; contraindicated in patients with porphyria or atrioventricular block and in those taking MAOIs; monitor CBC, liver function test results and blood levels
Gabapentin	Simple antacids reduce bioavailability	Sedation, ataxia, edema, weight gain, diplopia, nystagmus	300-900 mg/d, in divided doses every 8 h; increase dose weekly by 300 mg/d	1200-2400 mg/d (maximum 3600 mg/d)	Dose adjustment in patients with renal dysfunction
Pregabalin	None documented to date	Sedation, ataxia, edema, diplopia, weight gain, dry mouth	50-150 mg/d, in divided doses every 8-12 h; increase dose weekly by 50-150 mg/d	300-600 mg/d (maximum 600 mg/d)	Dose adjustment in patients with renal dysfunction
Opioids					
Tramadol	Metabolism by CYP450 2D4; risk of serotonin syndrome with SSRI co-administration	Respiratory depression, ataxia, sedation, constipation, seizures, nausea, orthostatic hypotension	50 mg/d, in divided doses every 12 h; increase dose weekly by 50 mg/d	200-400 mg/d (maximum 800 mg/d)	Use with caution in patients with epilepsy
Morphine (or alternative opioid with appropriate dose conversion)	Potentiates other sedatives	Respiratory depression, sedation, nausea, constipation, cognitive dysfunction	5-15 mg (short-acting) every 4 h as needed; after 1-2 wk convert to long-acting preparation and continue dose titration as needed	Benefits of daily morphine equivalents > 180 mg/d have not been established	Screen patients for alcohol/substance abuse and consider "opioid contract"; co-administer pre-emptive stool softeners and antiemetics

Note: CYP450 = cytochrome P450 enzyme, MAOI = monoamine oxidase inhibitor, SNRI = mixed serotonin-noradrenaline reuptake inhibitor, FDA = Food and Drug Administration, CBC = complete blood count, SSRI = selective serotonin reuptake inhibitor.

*This is a nonexhaustive list that includes medications recommended in Fig. 3.

tated by the risk of acetaminophen-related hepatotoxicity (i.e., < 4000 mg acetaminophen).

Although supportive evidence is limited, polypharmacy may be helpful. Therefore, in the event of a partial response to any single drug, one could add an alternate drug. If none of the above tried treatments is effective or tolerated, referral to a pain clinic is warranted for consideration of third-line drugs, interventional treatments and pain rehabilitation programs.

Prescribing considerations

Table 2 provides basic information on drugs recommended in Fig. 3. Given the potential for drug interactions,¹³⁰ a thorough review of the patient's current medications is warranted before prescribing any drugs for neuropathic pain. Given the potential for overdose toxicity with opioids and tricyclic antidepressants, suicide risk should be evaluated before prescribing. Some patients need reassurance that analgesia with antidepressants and anticonvulsants does not necessarily imply a diagnosis of depression or epilepsy. Because the central nervous system is depressed by most tricyclic antidepressants, anticonvulsants and opioids, gradual drug dose titration over weeks, toward a maximal tolerated dose, allows for accommodation to adverse effects while reaching an effective dose. Because of this need for gradual dose titration, the physician and patient need to recognize that onset of pain relief will be gradual. If possible, nursing resources should be devoted to weekly patient contact to guide dose titration. Since tricyclic antidepressants are rapidly metabolized in some patients, plasma tricyclic antidepressant levels should be measured if no analgesic or adverse effects are observed at maximal doses so as to safely guide further dose increases.¹³¹ In elderly people, drug treatment should be started at the lowest possible dose and be increased very slowly (i.e., longer titration period) to minimize the risk of falling and related trauma.

Conclusion

Neuropathic pain is a devastating chronic condition that generally can be diagnosed by history and findings on physical examination. For some neuropathic pain syndromes, available treatments are tolerable and afford meaningful relief to a considerable proportion of patients. Nevertheless, many patients report intractable and severe pain, and better treatment strategies are desperately needed.¹³² The field of neuropathic pain research and treatment is in the early stages of development, with many goals yet to be achieved. In particular, future laboratory, clinical and epidemiologic^{3,9} research into pathogenesis,^{64,136} treatment^{2,18,118,137,138} and prevention¹³³⁻¹³⁵ of neuropathic pain is expected as well as improved dissemination of new information to health professionals and the public. Over the years to come, many upcoming advances are expected in the basic and clinical science of neuropathic pain as well as in the implementation of improved therapies for patients who continue to experience these devastating conditions.

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