CME A Review of Neuropathic Pain Treatments for the Older Adult

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Neuropathic pain (NP) results from injury or dysfunction in the processing of sensory information in the nervous system. It occurs in a wide array of disease processes and may involve complex management strategies. A comprehensive approach utilizing proven pharmacologic and nonpharmacologic therapies can be used to return function and improve quality of life that has been lost because of pain. In the older population, age-related physiologic and pharmacodynamic alterations, coexisting diseases, and the prevalence of polypharmacy must be considered when selecting therapies for neuropathic pain.

Key words: *neuropathic pain, older adults, neuropathy, pain, analgesics*

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Introduction

The International Association for the Study of Pain defines pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Neuropathic pain (NP) "arises as a result of a lesion or dysfunction of the nervous system."[1] The most common causes of neuropathic pain in the older adult include low back pain (LBP), postherpetic neuralgia (PHN), and diabetic peripheral neuropathy (DPN) (Table 1). In patients without a known diagnosis, a thorough diagnostic evaluation or neurologic referral may be necessary to elucidate the cause of the pain.

Clinical Features

Across the various disorders, the description of neuropathic pain by individuals is quite similar. Patients complain of burning, tingling, itching, stabbing, or electric sensations. Numbness and other neurologic deficits may also be present. There may be pain from innocuous stimuli such as sheets or clothing (allodynia), or an exaggerated response to mildly painful stimuli (hyperalgesia).

Pathophysiology of Neuropathic Pain

The normal transmission of painful impulses is summarized in Figure 1. Significant advances have been made in our understanding of the pathophysiology underlying neuropathic pain.[2] The principal theme is the development of abnormal sensory processing within the central and peripheral nervous system. Altered gene expression, upregulation of excitatory neurotransmitter receptors, downregulation of inhibitory neurotransmitter receptors, neuron-glial interactions, and neuroplastic changes within the nervous system have been described as potential mechanisms contributing to the development of NP (Figure 2).

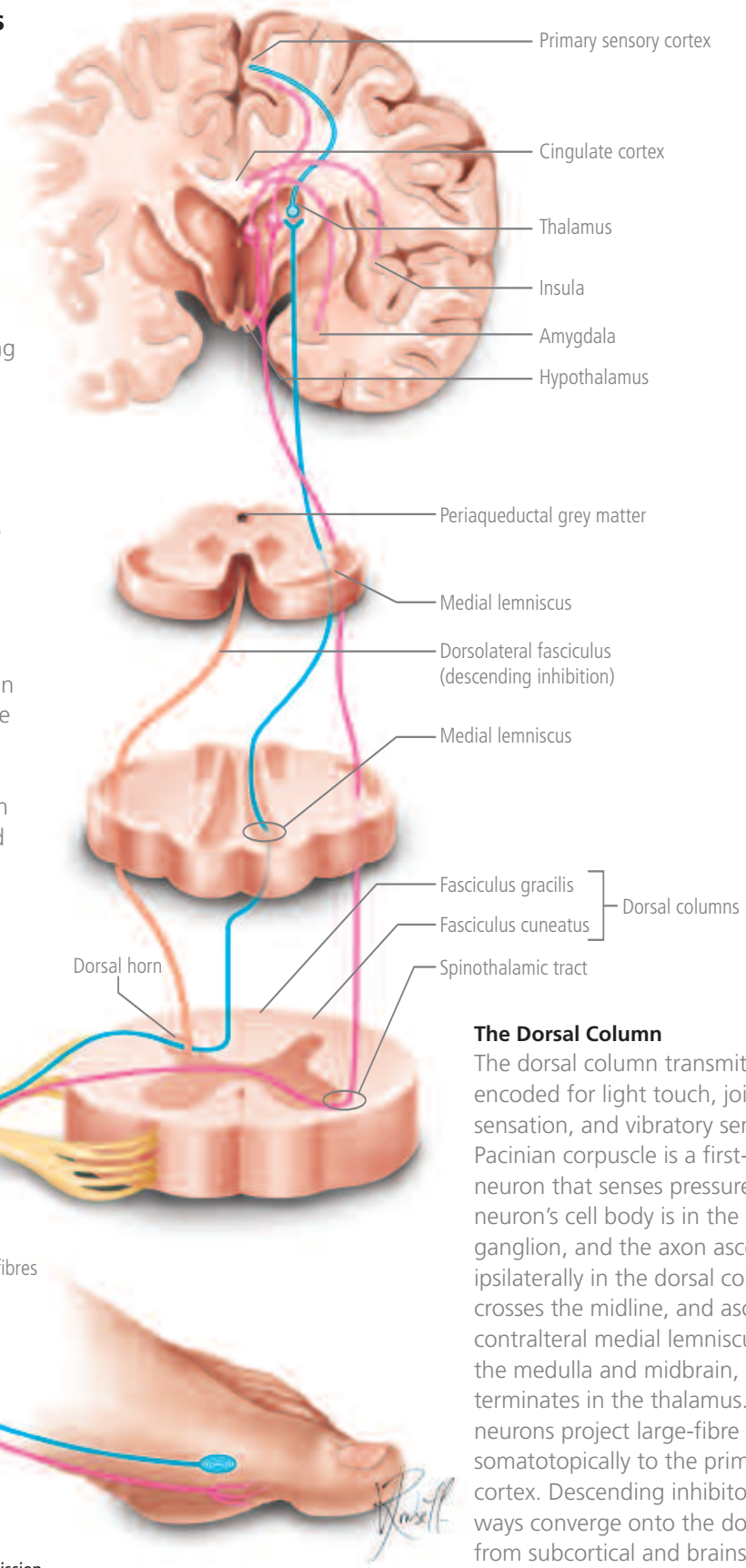
Physiologic Changes in the Older Adult

Changes in the older adult population that may result in altered responses to drugs include decreased lean body mass, gastrointestinal motility, cardiac output, renal clearance, protein binding, and increased central nervous system (CNS) effects of drugs.[3] The net effect is susceptibility to constipation, delayed redistribution and clearance of drugs, increased availability of active drugs, and increased CNS side effects. Physicians must keep these physiologic changes in mind when placing patients on medication trials for NP.

Table 1: Common Conditions Associated with Neuropathic Pain in the Older Adult

Painful diabetic neuropathy
Postherpetic neuralgia
Cancer-associated neuropathic pain
Idiopathic sensory neuropathy
Lumbar spondylosis (neuropathic low back pain)
Spondylotic radiculopathy

Figure 1:
Normal Sensory Pathways



The Spinothalamic Tract
The spinothalamic tract transmits input encoded for pain and temperature. The free nerve ending of an A delta fibre or a C fibre senses pain and temperature and has its cell body in the dorsal root ganglion. This synapses in the dorsal horn with a second-order neuron that eventually crosses the midline and ascends on the contralateral side in the spinothalamic tract. The axons of the second-order neuron terminate in the hypothalamus and thalamus. In the thalamus, some projections are made directly to the primary sensory cortex, whereas others project to the limbic system, which includes the insula, amygdala, and cingulate cortex.

The Dorsal Column
The dorsal column transmits input encoded for light touch, joint position sensation, and vibratory sensation. The Pacinian corpuscle is a first-order neuron that senses pressure. This neuron's cell body is in the dorsal root ganglion, and the axon ascends ipsilaterally in the dorsal column, crosses the midline, and ascends in the contralteral medial lemniscus through the medulla and midbrain, and terminates in the thalamus. Thalamic neurons project large-fibre sensation somatotopically to the primary sensory cortex. Descending inhibitory pathways converge onto the dorsal horn from subcortical and brainstem nuclei.

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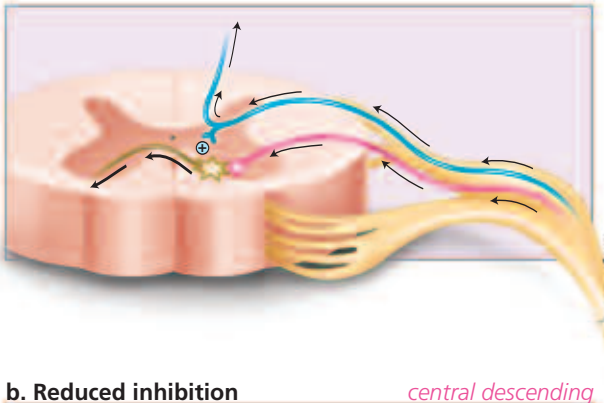
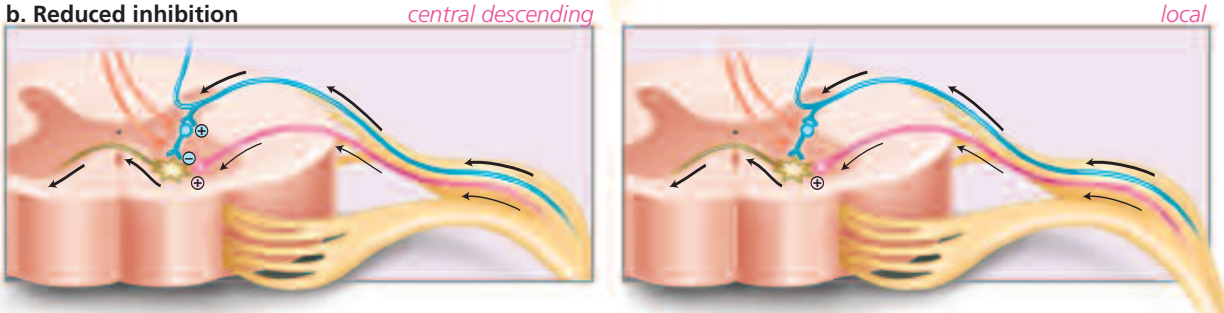
Figure 2:
Mechanisms of Neuropathic Pain and Therapeutic Options

a. Central sensitization



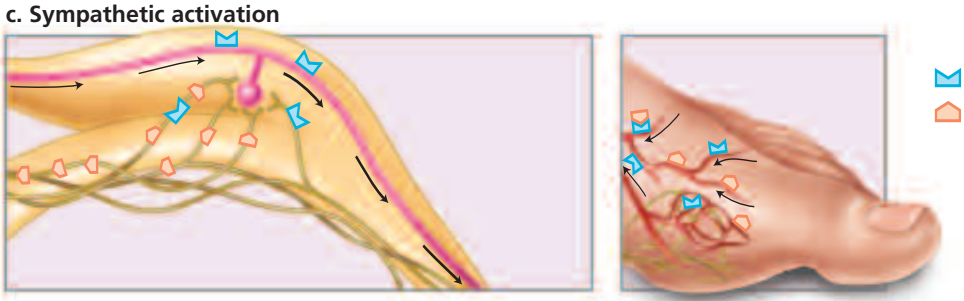
mechanism: Overactivity of a second-order neuron in the dorsal horn leads to enhanced pain transmission. It is characterized by a lowered threshold for activation and expanded receptive fields, leading to the activation of key excitatory amino acid receptors such as the N-methyl-D-aspartate receptor.
therapeutic options: Ca^{2+} channel antagonists, NMDA receptor antagonists, glutamate antagonists

b. Reduced inhibition



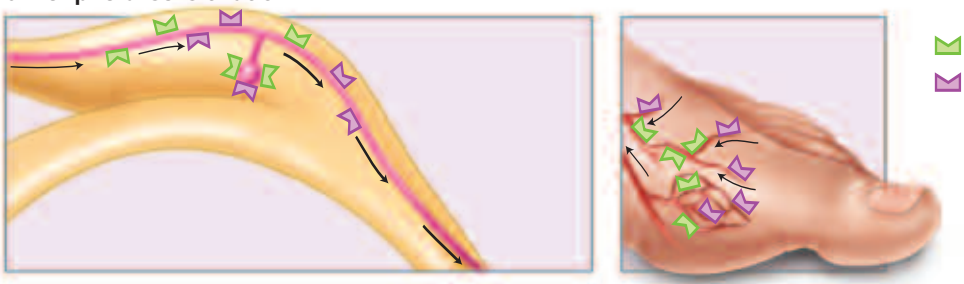
mechanism: Reduced activation of key central inhibitory inputs from the dorsolateral fasciculus through endogenous opioid, serotonin, and norepinephrine pathways may result in neuropathic central pain. Disinhibition may also result from loss of local inhibitory pathways from an interneuron.
therapeutic options: central alpha-receptor agonists, NE reuptake inhibition, 5-HT reuptake inhibition, GABA agonists, TENS, SCS, opioids

c. Sympathetic activation



mechanism: Sympathetic nerve endings sprout from nearby blood vessels towards the site of injury and can enhance signal transmission in the dorsal root ganglion. Catecholamine release and upregulation of adrenergic receptors on free nerve endings and neuronmas contribute to sympathetically mediated pain.
therapeutic options: central alpha-receptor agonists, peripheral alpha receptor agonists, sympathetic nerve blocks, systemic sympatholytics

d. Peripheral sensitization



mechanism: Injury to peripheral nerves may lead to hyperexcitability of peripheral nerve terminals, or nociceptors, that are normally responsible for the transduction of painful stimuli. This may be a result of altered expression of Na^+ channels, Ca^{2+} channels, and adrenergic receptors in the peripheral nerves and dorsal root ganglia.
therapeutic options: Na^+ channel antagonists, Ca^{2+} channel antagonists

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Analgesics are now the second most frequent new class of medications prescribed to older patients.[4] Dosing starts at the minimum dosage and is allowed to reach steady state before further upward titration commences. Delayed redistribution may result in slower achievement of steady state concentration. Care should be taken to monitor for cognitive dysfunction. Furthermore, disease-specific relative contraindications for particular analgesics and the increased susceptibility of many older adults to systemic side effects must be carefully considered in the selection of medications. For example, opioids and tricyclic antidepressants (TCAs) both delay micturition and may have synergistic effects in patients with bladder outlet obstruction. Opioids, gabapentin, or TCAs alone or in combination can impair bowel motility and worsen constipation or obstipation. TCAs can also induce arrhythmias and should be avoided or used very judiciously in older adults.[5]

First-Line Treatments

Based upon the evidence from randomized trials, first-line medications for NP have been recommended. These include TCAs, gabapentin, tramadol, and opioids. The Food and Drug Administration (FDA) has also approved topical lidocaine as a first-line therapy, but it is currently not approved for use in Canada.[6,7,8] Medications used to treat NP in older adults are summarized in Table 2.

Antidepressants

TCAs influence NP symptoms by sodium channel blockade and serotonin/norepinephrine reuptake inhibition. Tertiary amines (amitriptyline) inhibit H1-histaminergic,

Table 2: Pharmacotherapy for Neuropathic Pain in the Older Adult

Pharmacologic Mechanism(s)	Drug (Class)	Dosing Starting mg/d	Maintenance mg/d	Frequency	Most Common Side Effects
Na+ channel blockade	Topical lidocaine (5%)†* (local anesthetic) (not approved in Canada)	1–4 patches	1–4 patches	12–24 hrs	Local erythema, pruritus
Serotonin-norepinephrine reuptake inhibition, Na+ channel blockade	Nortriptyline† (tricyclic antidepressant)	10–25	50–100	Once daily	Orthostasis, xerostomia, urinary retention, blurry vision, anxiety, constipation, weight gain, sedation
Serotonin-norepinephrine reuptake inhibitor	Duloxetine*§ (antidepressant) (not approved in Canada)	20–30	60	Once or twice daily	Nausea, somnolence, dizziness, constipation, dry mouth, sweating, decreased appetite
Calcium channel (α2d subunit) antagonist	Gabapentin†* (antiepileptic)	100–300	900–3,600	Every 8 hours	Ataxia, nausea, fatigue, dizziness, somnolence, peripheral edema
Calcium channel (α2d subunit) antagonist	Pregabalin*§ (antiepileptic) (not approved in Canada)	50–100	150–600	Every 8 hours	Dizziness, somnolence, peripheral edema, blurry vision, xerostomia
Opioid μ-receptor agonist	Opioids†	15–30 (oral morphine equivalents)	30–300	Every 4–6 hours; 1–3 times daily (extended release)	Sedation, nausea, vomiting, pruritus, constipation, cognitive dysfunction
Nonopioid μ-receptor agonist serotonin-norepinephrine reuptake inhibitor	Tramadol† (synthetic μ-receptor agonist)	37.5–50	200–400	Every 6–8 hours	Sedation, seizures, constipation, confusion

†Recommended as first-line therapy; *FDA approved for PHN , §FDA approved for DPN

α1-adrenergic, and muscarinic-cholinergic receptors, which explains the side effects experienced in older persons. TCAs may be lethal in overdose, an important consideration in depressed patients. Secondary amines (nortriptyline) tend to have fewer side effects without sacrificing efficacy. Nightly dosing is especially desirable in patients with nocturnally exacerbated pain and insomnia. Amitriptyline is not recommended for use in persons older than 65 years.[8]

One study has suggested efficacy of bupropion (dopamine, norepinephrine reuptake inhibitor) for the treatment of NP.[9] Bupropion may assist smoking cessation, is generally nonsedating, and causes fewer sexual side effects. Selective serotonin/norepinephrine reuptake inhibitors venlafaxine and duloxetine have an improved side effect profile over the TCAs. In one placebo-controlled crossover study of imipramine and venlafaxine for treatment of painful polyneuropathy, venlafaxine showed similar efficacy to imipramine in reduction of pain scores.[10] Duloxetine is approved in the U.S. but not Canada for the treatment of pain caused by DPN at doses of 60mg and 120mg daily.[8] It is awaiting approval by Health Canada only for its use in major depression and stress urinary incontinence.

Antiepileptics

Gabapentin is effective for the treatment of PHN and DPN. Its most common side effects are sedation, fatigue, and incoordination. Recently approved for DPN and PHN, a related compound, pregabalin, has a side effect profile similar to that of gabapentin. It is also effective for the treatment of depression and anxiety, common symptoms accompanying NP. [11]

Carbamazepine is a potent inhibitor of sodium channel activation. It is considered first-line therapy in treating paroxysmal attacks in trigeminal neuralgia (TN) and is effective in DPN and PHN.[12] Except for TN, the serious adverse event profile of the drug has tempered its use as a first-line agent in the older adult. A carbamazepine analog, oxcarbazepine, has a more favourable pharmacokinetic profile and is effective in DPN.[13] Lamotrigine is effective in TN, HIV neuropathy, and poststroke pain.[11] Encouraging preliminary data exist for topiramate, levetiracetam, zonisamide, and tiagabine.

Topical Agents

Topical agents are favoured in older adults because of their low systemic toxicity, drug-drug interactions, and CNS side effects. The topical lidocaine patch is approved in the U.S. but not Canada for the treatment of PHN. Research has suggested benefit of the drug in the treatment of pain associated with PDN and low back pain.[14]

Tramadol

The mu-receptor agonist tramadol is effective in NP and is recognized as a first-line agent.[6] Tramadol may interact with serotonin reuptake inhibitors, such as TCAs. It has low abuse potential but occasionally causes confusion in the older patient.

Opioids

Research has demonstrated opioids to be effective in treating NP with efficacy and tolerability comparable to TCAs and gabapentin.[15,16] Opioids block A-delta and C-fibre–mediated pain, and contribute to endogenous inhibition and pain perception. Methadone antagonizes the NMDA receptor, suggesting potential modulation of opioid tolerance and central sensitization. However, comparative trials with methadone and other opioids are lacking. The unique pharmacokinetic and pharmacodynamic profile of methadone requires caution during initiation of therapy.[17] The weak opioid propoxyphene, a drug commonly utilized in older adults, undergoes renal excretion of the active metabolite norpropoxyphene. The accumulation of this metabolite in the older patient with renal impairment may cause CNS side effects (seizures). Propoxyphene is thus not recommended as long-term therapy in the aging.

Nonpharmacologic and Complementary Therapies

Complementary therapies can greatly abate the patient's experience of NP. Sleep hygiene can be improved by reducing caffeine, limiting naps, encouraging physical activity, and scheduling sedating drugs at night. Physical therapists are utilized to improve strength, range of motion, and muscle tone, and may initiate a trial of transcutaneous electrical nerve stimulation (TENS). Occupational therapy may help the patient gain functional independence. Psychosocial impairments may benefit from cognitive-behavioural therapy or biofeedback training.[18] Acupuncture, acupressure, and aromatherapy are sought by many patients and may assist with pain relief and stress reduction. Herbal remedies and other nontraditional therapies may be utilized by older patients and should be reviewed by the treating physician.

Pain Medicine Consultation

If there is little success with first-line NP medications, consultation with a pain medicine specialist may be necessary. Specialists may assist with recommendations for second-line therapies or perform specific interventions. For example, early consultation is suggested for the treatment of complex regional pain syndrome (CRPS). Sympathetic blockade (stellate ganglion or lumbar sympathetic blocks) may be useful to facilitate maximal participation in physical therapy.

Epidural steroid injections (ESI) are among the most common interventions performed for NP. They are most useful in treating radicular arm or leg pain.[19] If conservative therapy is not beneficial or well tolerated, the primary care physician may consider consultative referral for ESI as a complement to medical and nonpharmacologic approaches. Partial success in alleviating symptoms with ESI may improve function, reduce drug dependence, and reduce side effects.

The goal of therapy for implantable devices or neurolytic techniques is to provide maximal analgesia and cognitive function simultaneously. At the end of life, considerable effort is made to eliminate pain, increase periods of pain-free alertness, and optimize the quality of life. Interventional techniques for NP cancer pain include epidural therapies (tunneled catheters), radiofrequency, phenol or alcohol neurolysis, and intrathecal drug delivery. The type and route of intervention will vary according to the clinical condition of the patient. Intrathecal opioids are used for intractable pain with opioid intolerance. Delivery of opioids into the cerebrospinal fluid may reduce systemic side effects and improve quality of life. If the duration of intrathecal infusion is expected to be longer than three months, an implantable intrathecal delivery system is more economical than an exteriorized temporary catheter.[20] Occasionally, intrathecal opioids are necessary in the older opioid-intolerant patient with nonmalignant NP.

Conclusion

Neuropathic pain is prevalent and often challenging to treat in the older population. An approach that encompasses nonpharmacologic and pharmacologic interventions provides the greatest chance of reduced pain and improved function. Pharmacotherapy should be undertaken balancing the safety, efficacy, and tolerability of approved or recommended drugs with the known comorbidities and physiologic changes present in the older adult. Nonpharmacologic and alternative approaches are often recommended to improve function and reduce the need for systemic medications. The primary care physician or geriatrician should carefully review each therapy, focusing on the most appropriate treatment goals for the individual. Consultation with a pain medicine specialist may be required in refractory cases or if specific interventions are necessary. ◆

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