Management of Neuropathic Pain in Hospitalized Patients

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KEYWORDS

• Neuropathic pain • Allodynia • Hyperalgesia • Painful diabetic peripheral neuropathy
• Hospitalized patient

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Neuropathic pain is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". It can arise from either the peripheral or central nervous system.
2. Attempt to identify the underlying disease process that supports the diagnosis of neuropathic pain.
3. Invasive testing (nerve conduction, electromyography, and so forth) and neuroimaging are rarely indicated in the hospital setting. If the diagnosis is uncertain or thought to be secondary to another confirmed diagnosis (malignancy, Parkinson, and so forth), then the respective specialist should be involved in care.
4. Neuropathic pain can be difficult to treat in the hospital setting. Assess pain severity and establish realistic expectations of treatment.
5. Identify comorbidities (eg, renal disease, cardiovascular disease, and other prescribed medications) that could be affected by treatment.
6. Initiate appropriate treatment with first-line agents, bearing in mind the side effect profiles and rate of onset.
7. Acute neuropathic pain can quickly be alleviated with opioid receptor agonists. Opioids can rapidly be titrated to effects and alleviate neuropathic pain of many causes. However, side effects and abuse potential can limit use.
8. Topical lidocaine is effective for localized neuropathic pain and has a rapid rate of onset, few systemic side effects, and can limit the doses of additional medications.
9. Tricyclics, other antidepressants, and gabapentin can take weeks to titrate to effect.

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Hosp Med Clin 2 (2013) e587–e602
http://dx.doi.org/10.1016/j.ehmc.2013.04.007
2211-5943/13/$ – see front matter

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10. Combination treatment can produce greater relief than maximal treatment with a single agent.
11. If a trial of maximized first-line therapy and combination therapy fail, then consultation with a pain specialist is warranted.
12. Close communication with the patient's primary care physician can assist with difficult to manage pain situations and is essential for coordinating therapy following discharge.

1. What is Neuropathic Pain?

Defining neuropathic pain (NP) and distinguishing it from nociceptive pain (ie, pain that is protective to the organism) has proved challenging. The definition of NP was recently updated to be "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". In this definition, disease refers to an identifiable disease process such as inflammatory or autoimmune conditions, and lesion refers to macroscopically or microscopically identifiable damage.[1]

2. What is the pathophysiology of NP?

NP can be classified as either arising in the central nervous system (damage to brain or spinal cord) or the peripheral nervous system (damage to a peripheral nerve, plexus, dorsal root ganglion or root; **Fig. 1**).

Multiple mechanisms have been implicated in peripheral NP. Pain can be classified as stimulus-independent pain (spontaneous) or stimulus-evoked pain. With spontaneous pain nociceptor C and large myelinated A fibers are thought to be involved, with nociceptor C responsible for burning pain and A fibers associated with paresthesias. Stimulus-evoked pain has 2 common components: hyperalgesia (increased sensitivity to pain) and allodynia (pain experienced from a typically nonpainful stimulus).

Alterations of sodium channel function are thought to play a major role in NP. Axonal injury, either traumatic or toxic, causes sodium channel accumulation in the area of injury, which results in areas of hyperexcitability and ectopic action potential discharges.[2] The development of ectopic activity is thought to be important in the development of hyperalgesia, allodynia, and ongoing pain associated with nerve injury. However, the exact mechanisms that cause the changes in sodium channel expression are unclear. Additional voltage-gated channels, including calcium channels, have also been implicated.[3]

Changes in anatomic organization can also occur, such that neurons that normally receive high-threshold input begin to interpret low-threshold signals as nociceptive. Central sensitization can occur and cause pain beyond the territory of the affected nerves. This process is mediated by the *N*-methyl-D-aspartate (NMDA) receptors, and central sensitization can be blocked with NMDA antagonists to reduce hypersensitivity in those with NP.[3,4]

Different mechanisms may have varying importance in different patients with the same underlying disease process (eg, postherpetic neuralgia). In addition, NP caused by one disease may operate via similar mechanisms as another disease process. As an alternative, the same symptom in two different patients could be caused by different mechanisms.[4]

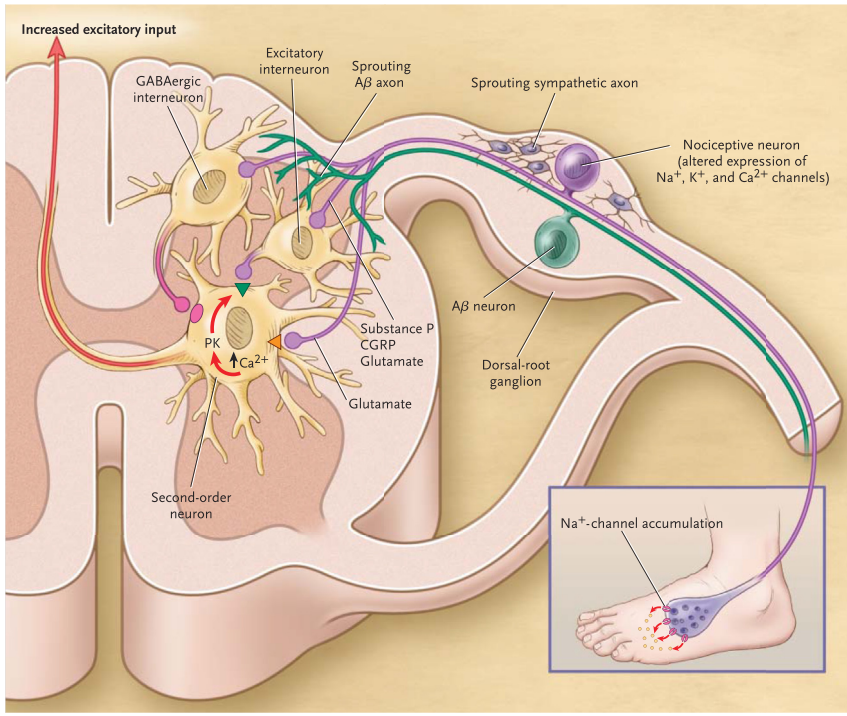

Fig. 1. Pathways of peripheral NP and potential sites of pharmacologic intervention. GABA, gamma-aminobutyric acid; CGRP, calcitonin gene–related peptide. (*From* Mendell JR, Sahenk Z. Painful sensory neuropathy. N Engl J Med 2003;348(13):1243–55; with permission. Copyright © 2003, Massachusetts Medical Society.)

3. What are common causes of NP?

There are many different causes of NP, as listed in **Table 1**.

There are few data describing the epidemiology of NP in hospitalized patients. Identification of one of the diseases in **Table 1** affecting the location of a patient's pain would be considered supportive but not diagnostic of the pain being neuropathic.

4. What features of the history help in diagnosing NP?

Many historical features are helpful in establishing a diagnosis of NP. The history should include descriptions of the pain location, distribution, intensity, quality, and time course. In addition, it is important to consider whether the patient has an underlying disease known to cause NP (eg, long-standing diabetes, as per **Table 1**) or whether there is a clearly identifiable lesion in the nervous system (eg, nerve root compression on imaging). Patients with NP often describe pain as burning, shooting, vicelike, squeezing, or tightening of the skin.[5] Some describe allodynia, which is defined as pain elicited by normally nonpainful stimuli, such as light touch.

Additional features related to small nerve fiber damage include burning, sharp pain, shooting pain, and aching in the toes and feet. Peripheral nerve pain is frequently exacerbated at night, but is also described by some patients to be worse with standing or walking.[6]

Table 1
Common types of NP

Peripheral NP	Central NP
Carpal tunnel syndrome	Central poststroke pain
Chemotherapy-induced polyneuropathy	Multiple sclerosis pain
Complex regional pain syndrome	Spinal cord injury pain
Herpes zoster pain	Syringomyelia
Human immunodeficiency virus sensory neuropathy	
Idiopathic sensory neuropathy	
Neuropathy secondary to tumor-related infiltration or compression of nerve	
Painful diabetic neuropathy	
Phantom limb or breast pain	
Postherpetic neuralgia	
Spinal radiculopathy	
Traumatic neuropathy, including after surgery (such as postmastectomy pain)	
Trigeminal neuralgia (tic douloureux)	

Data from O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics 2009;27(2):95–112.

Another helpful way to classify historical features of NP is by negative and positive features (**Table 2**). Negative symptoms include a decrease in perception of mechanical or vibratory stimuli or loss of noxious or thermal perception. Positive symptoms include allodynia; paresthesias; spontaneous ongoing pain; and shooting, electric shock–like sensations.[7]

5. What features are present on physical examination that help diagnose NP?

Clinical examination is helpful in the diagnosis of NP, but there is no gold standard to label a patient's pain as neuropathic. Instead, physical examination is performed to identify abnormalities that may be related to a lesion of the somatosensory system (see **Table 2**). Sensory testing to assess touch, vibration, pinprick, cold, and warmth are the most important and should be done at the bedside before any invasive or more sophisticated sensory testing.[8]

6. What features are present on diagnostic tests that help diagnose NP?

There is no single diagnostic test for NP, although there are some tests that can confirm or exclude underlying diseases. Peripheral nerve function can be assessed with nerve conduction testing and electromyography, but they do not test the smaller nerve fibers carrying pain and temperature information. Magnetic resonance imaging (MRI) can be useful in assessing the anatomy of the brainstem, sensory cortex, spinal cord, and other areas that contribute to central NP, but many lesions on MRI are not accompanied by pain.[9,10]

7. What are the goals of therapy in hospitalized patients?

In general, the goals of managing NP are to reduce suffering and to maximize patients' quality of life and function.[11] In addition to aggressively relieving pain, it is appropriate

to help patients maximize their ability to perform activities of daily living, so early assessment and ongoing treatment by occupational therapy and physical therapy are also warranted. An example of this need is an elderly patient with postherpetic neuralgia. Among hospitalized patients, reducing length of stay and the risk of rehospitalization are also important goals.

Cost of treatment is a factor in both the inpatient and outpatient settings. Several studies have estimated that different types of NP contribute at least a few thousand US dollars in excess health care costs per patient over the course of a year.[11,12] However, these studies were performed in ambulatory patients. The cost per day of hospitalization in the United States was recently estimated to be nearly $4000 (in 2011 dollars).[13] Because NP likely contributes to longer lengths of stay, loss of functional ability, additional homecare needs, and a higher risk of rehospitalization, it is expected that the costs attributable to NP among inpatients are substantially higher. In addition to the costs related to direct medical expenses, societal costs also include the loss of productivity associated with NP, both for patients and for their caregivers.[11]

8. What are the best pharmacologic treatment options?

The management of NP in hospitalized patients is challenging. There are numerous gaps in the medical literature regarding the management of NP in general, and no randomized clinical trials focusing on management in the hospital setting. Given the lack of specific evidence-based recommendations for hospitalized patients, this article emphasizes existing evidence-based guidelines for outpatient management and extrapolates, where applicable, to hospitalized patients.

Most systemic pharmacologic treatments tend to take a few weeks or more for full effect, which is not optimal for hospitalized patients with NP. Opioid receptor agonists are important exceptions to this, and they are typically the best option for rapid treatment of NP. However, opioid therapy commonly produces significant side effects, some of which can be associated with additional morbidity and prolonged hospitalization; in addition, long-term opioid therapy for noncancer pain should be avoided when possible.[14] Topical lidocaine may also have a rapid onset and can be useful when opioid side effects are problematic, but it may be less efficacious than opioids.[15]

Each of the recommended medications is discussed in more detail later and a stepwise approach to treatment is shown in **Box 1**.

ANTIDEPRESSANTS

Tricyclic antidepressants are inexpensive, have established efficacy, and are considered first-line treatment of NP.[14–17] Side effects, including the classic antimuscarinic effects of dry mouth, constipation, urinary retention, and blurry vision, are common, but can be minimized by using the secondary amine tricyclics (nortriptyline and desipramine) rather than the tertiary amines (amitriptyline and imipramine).[14,17]

Their analgesic effect occurs via inhibition of the reuptake of norepinephrine and serotonin, and they may also improve depression and insomnia. Cardiac toxicity, myocardial infarction, and sudden death have been raised as possible concerns with the use of tricyclics[18,19]; however, currently available evidence suggests that they are not associated with significant cardiac toxicity in dosages of less than 100 mg per day.[17,19]

Tricyclics (nortriptyline, desipramine, and amitriptyline) are typically started at 25 mg nightly and increased by 25 mg every 3 to 7 days. The maximum recommended dose is 150 mg daily. Before use, an electrocardiogram should be obtained in patients more

Table 2
Definition and assessment of negative and positive sensory symptoms or signs in NP

Symptom/Sign	Definition	Assessment	Expected Response
Negative Signs and Symptoms			
Hypoesthesia	Reduced sensation to nonpainful stimuli	Touch skin with painter's brush, cotton swab, or gauze	Reduced perception, numbness
Pall hypoesthesia	Reduced sensation to vibration	Apply tuning fork to bone or joint	Reduced perception threshold
Hypoalgesia	Reduced sensation to painful stimuli	Prick skin with single-pin stimulus	Reduced perception, numbness
Thermohypoesthesia	Reduced sensation to cold or warm stimuli	Touch skin with objects at 10°C (metal roller, glass of water, coolants like acetone) Touch skin with objects at 45°C (metal roller, glass of water)	Reduced perception
Spontaneous Sensations/Pain			
Paresthesia	Nonpainful ongoing sensation (ant crawling)	Grade intensity (0–10) Area in cm^2	—
Paroxysmal pain	Shooting electrical attacks for seconds	Number per episode Grade intensity (0–10) Threshold for evocation	—
Superficial pain	Painful ongoing sensation, often of burning quality	Grade intensity (0–10) Area in cm^2	—

Evoked Pain			
Mechanical dynamic allodynia	Normally nonpainful light-pressure moving stimuli on skin evoke pain	Stroking skin with painter's brush, cotton swab, or gauze	Sharp, burning, superficial pain in the primary affected zone, spreading into unaffected skin areas (secondary zone)
Mechanical static allodynia	Normally nonpainful gentle static pressure stimuli on skin evoke pain	Manual gentle mechanical pressure to the skin	Dull pain in the area of affected (damaged or sensitized) primary afferent nerve endings (primary zone)
Mechanical punctate or pinprick hyperalgesia	Normally stinging, but not painful, stimuli evoke pain	Manual pricking of the skin with a safety pin, sharp stick, or stiff von Frey hair	Sharp superficial pain in the primary affected zone, spreading into unaffected skin areas (secondary zone)
Temporal summation	Repetitive application of identical single noxious stimuli is perceived as increasing pain sensation (wind-up–like pain)	Pricking the skin with safety pin at <3-s intervals for 30 s	Sharp superficial pain of increasing intensity
Cold allodynia	Normally nonpainful cold stimuli evoke pain	Touch skin with objects at 20°C (metal roller, glass of water, coolants like acetone) Control: touch skin with objects at skin temperature	Painful, often burning, temperature sensation in the area of affected (damaged or sensitized) primary afferent nerve endings (primary zone)
Heat allodynia	Normally nonpainful heat stimuli evoke pain	Touch skin with objects at 40°C (metal roller, glass of water) Control: touch skin with objects at skin temperature	Painful burning temperature sensation in the area of affected (damaged or sensitized) primary afferent nerve endings (primary zone)
Mechanical deep somatic allodynia	Normally nonpainful pressure on deep somatic tissues evokes pain	Manual light pressure at joints or muscle	Deep pain in joints or muscles

Data from Baron R. Mechanisms of disease: neuropathic pain – a clinical perspective. Nat Clin Pract Neurol 2006;2(2):95–105.

Box 1
Stepwise pharmacologic management of NP

Step 1

Assess pain and establish the diagnosis of NP[8,9]; if uncertain about the diagnosis, refer to a pain specialist or neurologist.

Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP cause, refer to appropriate specialist.

Identify relevant comorbidities (eg, cardiac, renal, or hepatic disease; depression; gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy.

Explain the diagnosis and treatment plan to the patient, and establish realistic expectations.

Step 2

Initiate therapy for the disease causing NP, if applicable.

Initiate symptom treatment with 1 or more of the following:

- Antidepressant medication: either secondary amine tricyclic antidepressant (TCA) (nortriptyline, desipramine) or selective serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine).
- Calcium channel alpha-2–delta ligand: either gabapentin or pregabalin.
- For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first-line therapies.
- For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies.

Evaluate patient for nonpharmacologic treatments, and initiate if appropriate.

Step 3

Reassess pain and health-related quality of life frequently.

If substantial pain relief (eg, average pain reduced to $\leq$3/10) and tolerable side effects, continue treatment.

If partial pain relief (eg, average pain remains $\geq$4/10) after an adequate trial (see **Box 1**), add one of the other 4 first-line medications.

If no or inadequate pain relief (eg, <30% reduction) at target dosage after an adequate trial, switch to an alternative first-line medication.

Step 4

If trials of first-line medications alone and in combination fail, consider second-line medications or referral to a pain specialist or multidisciplinary pain center.

Data from Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132(3):237–51.

than 40 years of age. In addition, they should generally be avoided in patients with cardiac arrhythmias and congestive heart failure, and should be used with caution in elderly patients.[14,20]

The serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine have shown efficacy for the treatment of peripheral NP. Duloxetine has only been studied in painful diabetic peripheral neuropathy, but is US Food and Drug Administration (FDA) approved for that indication. Three separate randomized clinical trials showed

the efficacy of duloxetine 60 mg and 120 mg daily for painful diabetic peripheral neuropathy and showed separation from placebo at 1 week. The most common side effect is nausea, and discontinuation of treatment because of side effects was more common when patients received 120 mg daily (60 mg twice a day), in part because of orthostatic hypotension and tremor.[21–23] Venlafaxine has shown efficacy in painful diabetic peripheral neuropathy and painful polyneuropathy but not in postherpetic neuralgia.[14,17] The most common side effects include somnolence and nausea.[24]

CALCIUM CHANNEL LIGANDS

Gabapentin binds to the alpha-2–delta subunit of voltage-gated calcium channels. It is commonly used in the treatment of painful diabetic peripheral neuropathy and is one of 2 medications FDA approved for treatment of postherpetic neuralgia. It is less expensive than pregabalin and effective at relieving symptoms of allodynia, burning pain, shooting pain, and hyperesthesia with dosages ranging from 1800 mg to 3600 mg daily. Dosing can be started at 900 mg daily, given in 3 divided doses, and titrated every few days to the maximum of 3600 mg daily or to the maximum tolerated dose. Adverse effects include dizziness, somnolence, and confusion.[25,26]

Gabapentin must also be dose adjusted for patients with renal dysfunction and those requiring hemodialysis.[27] With worsening renal function, the side effects become more pronounced, particularly myoclonus and altered mental status, and dosages should be carefully and slowly titrated. Gabapentin must be discontinued if myoclonus develops and symptoms normally resolve in 4 to 15 days.[28]

Pregabalin is FDA approved for the treatment of both painful diabetic peripheral neuropathy and postherpetic neuralgia. It binds to the alpha-2–delta subunit of voltage-gated calcium channels and decreases calcium influx. A recent Cochrane Review concluded that dosages of pregabalin between 300 mg and 600 mg daily were efficacious in postherpetic neuralgia, painful diabetic peripheral neuropathy, and central NP.[29] Dosages less than 150 mg daily do not consistently show efficacy. Dosing should start at 150 mg daily and be titrated to 300 mg daily in 1 to 2 weeks. At the higher end of the dose spectrum, dizziness and somnolence were more prevalent. Additional side effects such as ataxia, sedation, weight gain, and edema may also occur.

Pregabalin has excellent gastrointestinal absorption, can be given twice daily, and seems to have an onset of less than 2 weeks.[30] As with gabapentin, dosing must be reduced for patients with a creatinine clearance less than 60 mL/min to avoid toxicity. Pregabalin is also cleared rapidly by hemodialysis and should be replaced after each dialysis session.[31]

OPIOID RECEPTOR AGONISTS

Opioid analgesics provide analgesia by inhibiting noxious stimuli in peripheral, presynaptic, and postsynaptic opioid receptors in the dorsal horn and in sites within the brain. Oral opioids have been shown to be superior to placebo for several different types of NP. Intravenous opioids have also shown efficacy for some components of central pain.[15] Opioids are particularly appealing for the management of hospitalized patients because they produce powerful analgesia immediately, unlike the other systemic pharmacotherapeutic options. However, opioids are limited by their side effects, including somnolence, constipation, and nausea; in elderly and medically complex patients they can also cause delirium and gait instability.[32,33] Early in a patient's course, a short-acting opioid should be titrated aggressively to effect. After the 24-hour daily opioid requirement has been established, then conversion to a long-acting opioid is recommended.[14,17]

Tramadol is a mu-receptor agonist that also inhibits the reuptake of serotonin and effectively decreases pain in dose ranges of 200 mg to 400 mg daily. It has similar side effects to pure opioids.[34,35] However, tramadol can also lower the seizure threshold and can precipitate the serotonin syndrome (the triad of altered consciousness, autonomic dysfunction, and neuromuscular excitability), particularly when used with serotonin reuptake inhibitors.[36]

TOPICAL AGENTS

The 5% lidocaine patch has shown efficacy in peripheral NP with allodynia, and its onset of analgesia is typically within the first 8 hours of application. Topical lidocaine is well tolerated: minor local skin reactions are the most common adverse effect, and systemic side effects are rare because of the low rate of systemic absorption. The cost of the patch can be prohibitive, but less expensive topical preparations exist, including a 5% gel.[17] Topical lidocaine seems to have less overall efficacy than tricyclic antidepressants and opioids,[15] but it does have a role for localized NP in hospitalized patients because it is so well tolerated and it has a rapid onset of action. Patients for whom topical lidocaine monotherapy is insufficient may still benefit from partial analgesia, which may help limit the dosages of the other analgesics required (eg, opioids) and may spare patients some side effects.

Capsaicin is of limited use in the treatment of NP. One review of multiple randomized controlled trials focusing on neuropathic conditions (diabetic neuropathy, postherpetic neuralgia, and chronic postoperative pain) concluded that capsaicin is better than placebo for the treatment of chronic NP, but a separate Cochrane Review was inconclusive because of the lack of data supporting the use of capsaicin cream in NP.[37] Local adverse advents are common, with approximately one-third of those treated reported a burning sensation after application.[38]

COMBINATION TREATMENT

There is evidence that combination pharmacotherapy can produce greater pain relief than maximally tolerated dosages of a single agent.[39,40] Although side effects of both drugs were experienced by patients taking the combination, patients achieved greater analgesia on lower dosages of the component drugs than patients who received monotherapy. Combination therapy is expected to be most effective and best tolerated using agents with different mechanisms of action and different side effect profiles (eg, a tricyclic antidepressant and an opioid).

9. Are there other types of treatments that should be considered?

NP can be challenging to treat. However, patients who do not respond well to standard pharmacologic treatment, whether because of inadequate analgesia or intolerable side effects, are not rare. There are a large number of invasive and noninvasive treatment alternatives that have been tried in refractory NP, but for nearly all of them there is comparatively little evidence to support their use. Some of the better studied and more promising treatments relevant to hospitalized patients are summarized later.

Injections with an epidural steroid and local anesthetic combination seem to have efficacy in patients with herpes zoster pain,[41–44] although the dosing and protocol have varied among these randomized trials. We recommend reserving injections for patients whose pain is difficult to manage with oral or topical treatment.

Epidural steroid injections have shown efficacy for the treatment of lumbar radicular pain.[45] We recommend reserving their use for patients with pain refractory to traditional pharmacotherapy.

Spinal cord stimulation has been found to have efficacy for patients with refractory complex regional pain syndrome, type I.[46,47] Its role seems to be more for chronic, outpatient therapy than for acute management in hospitalized patients.

Two separate studies examining botulinum toxin in postherpetic neuralgia and diabetic NP showed improvement in pain severity and the quality of sleep. In the case of postherpetic neuralgia, a reduced opioid need compared with lidocaine was seen at day 7 and 3 months after treatment.[48,49] A third randomized, double-blind, placebo-controlled study of 61 patients with chronic NP showed persistent effects on pain intensity at 2 and 14 weeks after injection, with concurrent improvement in allodynia to brush and decreased pain thresholds to cold.[50] Again there is a lack of data with larger sample sizes, but these initial studies suggest that botulinum toxin could be used as an adjunct therapy or for those who do not tolerate, or are refractory to, typical pharmacologic therapies.

No randomized controlled trials were found regarding the role of acupuncture in NP. Further trials are warranted with larger sample sizes, randomized control, and assessment of long-term effects. The same is true for physical therapy or other physiologic treatments because these potential therapies have not been studied in the context of NP.

10. When should consultation be sought?

Because the management of NP is different than other types of pain, it is important to accurately diagnose pain as neuropathic or not neuropathic. Consultation with a neurologist may be warranted if the diagnosis is not clear or if further testing, such as nerve conduction studies, is being considered. Other possible testing includes somatosensory testing, neuroimaging, skin biopsy, blood, and possible cerebrospinal fluid analysis, and is best directed by physicians with expertise in NP diagnosis. In addition, certain suspected or confirmed diagnoses such as malignancy, multiple sclerosis, Parkinson disease or epilepsy should usually prompt the involvement of the appropriate specialist.

Patients who do not respond well to pharmacotherapy may benefit from consultation with a pain specialist who can guide further adjustments to pharmacotherapy, help confirm the diagnosis (if it is in question), and also can guide consideration of the use of invasive treatments in particularly refractory cases.

If an underlying disease process causing or contributing to the NP is not well controlled (eg, depression or diabetes), then consultation with the appropriate specialist (eg, psychiatry or endocrinology) should be considered.

11. Can certain types of NP be prevented?

Few studies have been conducted to assess the prevention of NP, and this is an area in which future research is needed. However, it is widely recognized that central sensitization can be prevented by early pain relief. Although ketamine does seem to decrease immediate postoperative pain after thoracotomy, there was no difference in measured pain between ketamine and placebo at 4 months after surgery.[51] A different study found that preoperative and intraoperative thoracic epidural anesthesia, using bupivacaine and morphine, produced a reduction in pain incidence and intensity at 6 months compared with a group receiving intravenous patient-controlled analgesia.[52]

Several treatments have been evaluated in efforts to reduce the incidence of phantom limb pain or postamputation pain. Combinations of ketamine, epidural bupivacaine, morphine, and memantine have failed to produce statistically significant reductions of phantom pain or acute central sensitization. However, studies have shown a small improvement in the immediate postoperative pain period when epidural medications were administered before surgery.[53–56] The same is largely true for complex regional pain. One double-blind study found that taking vitamin C after a wrist fracture, 500 mg daily for 50 days, reduced the incidence of postfracture complex regional pain syndrome.[57]

The Shingles Prevention Study showed that vaccination against herpes zoster reduced the incidence of postherpetic neuralgia as well as the average severity of the illness of those who developed herpes zoster.[58] The vaccine is typically not offered in the hospital setting, but it could be discussed with patients in the hospital, to be administered later by a primary care physician.

12. Clinical Practice Guidelines

There are no clinical practice guidelines specifically for the management of hospitalized patients. However, there are 3 international guidelines for the pharmacologic management of NP. The different guideline committees, representing the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP), the Canadian Pain Society, and the European Federation of Neurologic Sciences, produced similar recommendations (**Table 3**). These practice guidelines

Table 3
Comparison of NP treatment guidelines, excluding trigeminal neuralgia. Only medications considered first or second line in one of the guidelines are presented

Medication Class	NeuPSIG Guidelines	CPS Guidelines	EFNS Guidelines
Tricyclic antidepressants	First line	First line	First line for PPN, PHN, CP
Calcium channel alpha-2–delta ligands (gabapentin and pregabalin)	First line	First line	First line for PPN, PHN, CP
SSNRIs (duloxetine and venlafaxine)	First line	Second line	Second line for PPN
Topical lidocaine	First line for localized peripheral NP	Second line for localized peripheral NP	First line for PHN if small area of pain/allodynia
Opioid analgesics	Second line except in select circumstances[a]	Third line	Second/third line for PPN, PHN, CP
Tramadol	Second line except in select circumstances[a]	Third line	Second/third line for PPN, PHN

Abbreviations: CP, central pain; CPS, Canadian Pain Society; EFNS, European Federation of Neurologic Societies; NeuPSIG, Neuropathic Pain Special Interest Group; PHN, postherpetic neuralgia; PPN, painful polyneuropathy; SSNRIs, selective serotonin and norepinephrine reuptake inhibitors.

[a] Opioid analgesics and tramadol were considered first-line options in the following circumstances: for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.

Data from O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 2009;122:S22–32.

all consider tricyclic antidepressants, gabapentin, and pregabalin to be first-line agents.

Each of the guidelines gives a less strong recommendation for opioids and for tramadol, because of concerns about the long-term use of opioids for chronic noncancer pain, with tolerance, abuse, diversion, and tolerability concerns all contributing. For these reasons, we suggest that, when opioids or tramadol are used for hospitalized patients, a first-line treatment is also started and gradually titrated up; after the first-line treatment has been titrated to an effective dose, tapering off the opioids, either later in the hospitalization or as an outpatient, should be attempted if possible.

Topical lidocaine also deserves greater emphasis in hospitalized patients with peripheral NP that is localized because of its rapid onset of analgesia and favorable risk profile. A trial of topical lidocaine early in a patient's hospital course is reasonable, although, if it does not seem to produce significant analgesia for a particular patient, then it should be discontinued.

The management of NP is often challenging. Often trial and error is needed to find an effective regimen for a particular patient. Coordination with a patient's primary care provider and appropriate specialists well before hospital discharge is recommended.

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