



NEUROPATHIC PAIN: A Treatment Challenge for Practitioners

Learning Objectives

After completing this activity, participants should be better able to:

- Determine the difference between nociceptive and neuropathic pain
- Describe common central and peripheral neuropathic pain syndromes
- Implement available assessment tools to evaluate neuropathic pain
- Evaluate specific therapeutic options based on recent published guidelines

Diagnosing Neuropathic Pain

Neuropathic pain is caused by damage to the nervous system, continued inflammatory processes, and cytokine recruitment; importantly, nociceptive input is not required. Neuropathic pain is of higher intensity than the injury would indicate and may be sensed in areas beyond where the injury occurred, in contrast to nociceptive pain, which is proportionate to the receptor stimulus and generally well localized. These characteristics help differentiate neuropathic pain from nociceptive pain. The latter results from the stimulation of mechanoreceptors, thermoreceptors, or chemoreceptors and serves to warn the body that an injury has occurred.

Two prevailing definitions have been composed to describe the phenomenon of neuropathic pain. In 1994, the International Association for the Study of Pain (IASP) proposed that neuropathic pain is “pain initiated or caused by a primary lesion or dysfunction in the nervous system”—peripheral or central—that disrupts impulse transmission and modulation of sensory input.¹ Subsequently, a multidisciplinary expert group collaborating with an IASP task force published a revised definition of neuropathic pain: “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”²

A neuropathic pain condition can occur as a single entity or combined with other acute, chronic, or other neuropathic conditions; determining the contributing painful entities is important to identifying effective treatment(s). A

Neuropathic pain arises from a diverse set of causes, making it a difficult condition to diagnose and treat.

**Are there screening instruments or tools to help accurately identify neuropathic pain?
See page 107**

Neuropathic Pain:

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number of conditions can contribute to the development of neuropathic pain, including surgical procedures that damage nerves, as with postmastectomy pain syndrome (PMPS); chronic metabolic diseases leading to, for example, peripheral diabetic neuropathy (PDN); treatment-related nerve damage, most commonly chemotherapy-induced peripheral neuropathy (CIPN); infection, including HIV/AIDS and postherpetic neuralgia (PHN); and other toxicities, such as poisoning with continued ethanol exposure or heavy metal(s) intake. As there are a diverse group of entities that have the potential to inflict nerve damage and result in neuropathic pain, it is important to consider the setting that a patient's pain is presented in and to determine if there are any pre-existing conditions that may be causing pain.

Neuropathic pain conditions can afflict the peripheral or central nervous system (Table 1). For both, the physiological basis for neuropathic pain is nerve dysfunction. Moreover, the previously listed conditions associated with peripheral neuropathic pain cause nerve injury that results in the mounting of a sustained inflammatory response, including the release of proinflammatory cytokines. These pain facilitators, such as bradykinin, substance P, hydrogen

Table 1. Common Types of Neuropathic Pain

Peripheral Neuropathic Pain	Central Neuropathic Pain	Cancer-Associated Neuropathic Pain
Postherpetic neuralgia	Central poststroke pain	Chemotherapy-induced polyneuropathy
Peripheral diabetic neuropathy	HIV myelopathy	Neuropathy secondary to tumor infiltration or nerve compression
Post-thoracotomy pain	Multiple sclerosis pain	Phantom breast pain
Radiculopathy	Parkinson's disease pain	Postmastectomy pain
Trigeminal neuralgia	Spinal cord injury pain	Postradiation plexopathy and myelopathy
Complex regional pain syndrome	Syringomyelia	
HIV sensory neuropathy		
Carpal tunnel syndrome		
Phantom limb pain		
Peripheral vascular disease		

Adapted from Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. Minneapolis, MN: The McGraw-Hill Companies, Inc; 2000.

ions, interleukin-1 β , nerve growth factor, prostaglandins, histamine, adenosine triphosphate, and tumor necrosis factor, induce the enhanced expression of sodium channels on nerve cell membranes and thereby increase the excitability of neurons.³ This neuronal hyperexcitability then leads to enhanced excitability within the dorsal horn of the spinal cord as well, and therein, second order neurons develop increased expression of calcium channels. These channels are involved in the release of neurotransmitters that promote the transmission of pain impulses in this now pathophysiological state. Overall, this cascade of events results in the remodeling of the nervous system and ultimately the symptom of neuropathic pain. The term “peripheral sensitization” describes the conversion from a healthy peripheral nervous system to one with heightened responses associated with neuropathic pain. Similarly, reorganization within the central nervous system, called central sensitization, can result in neuropathic pain, such as allodynia.³

Allodynia is a painful response to a stimulus that is not normally considered painful, such as the touch of a cotton swab or bed sheets. Other symptoms commonly described in association with neuropathic pain include paresthesia: abnormal spontaneous sensations, such as burning, tingling, pins and needles, or the feeling of “walking on broken glass”; and hyperalgesia: a heightened sensitivity to a stimulus that is normally painful, such as a pinprick. “Numbness” or “painful numbness” is typically used by patients to describe heaviness, weakness, or deadness in their affected body part.

Peripheral Diabetic Neuropathy

Because of the growing epidemic of diabetes, its associated complications are, in turn, on the rise.⁴ A comorbid consequence of diabetes, PDN has escalated to one of the most prevalent neuropathic pain conditions in the United States,⁵ second to PHN.³ An estimated 20% to 24% of individuals with diabetes mellitus will develop PDN.⁴ Certainly, this is a large number of people, considering 24 million people in the United States have diabetes and another 57 million people are prediabetic according to 2007 estimates by the Centers for Disease Control and Prevention.⁶ As diabetes and its complications are exacerbated by poorly controlled blood sugar levels, controlling diet is a critical preventive measure to containing diabetes and reducing the incidence of its comorbidities.⁷ Patient reports with descriptors that include allodynia; sharp, stabbing, or burning pain; and/or painful numbness, as well as pain in a stocking-and-glove distribution, are strong indicators of the development or existence of PDN.⁵ Most commonly with PDN, pain presents in a bilateral distribution to patients’ lower extremities.

The risk factors for developing PDN include duration of diabetes and several potentially modifiable risk factors: raised triglyceride levels (as indicated by the glycosylated hemoglobin value, A1C), elevated body mass index, smoking, and hypertension.⁸ Indeed, cardiovascular disease doubles the risk of developing PDN.⁸

Assessment: Defining Features and Screening Tools

In order to make an accurate diagnosis, the assessment of individuals who may have neuropathic

pain, including PDN, most importantly must involve a detailed history, noting the setting of the pain. The presence of any of the common disease states or conditions (noted earlier) associated with neuropathic pain and its mode of onset and progression can be important indicators that pain is neuropathic in nature. Neuropathic pain also tends to present in the lower extremities first, or along a dermatome. The quality of neuropathic pain often includes a temperature descriptor, such as burning, searing, or freezing. Sometimes patients with neuropathic pain inaccurately describe their symptom as a “spasm,” but rather than a true muscle contraction, further probing reveals instead a “wave of pain.” Another key defining feature of neuropathic pain is the timing: it tends to worsen at night. This constellation of descriptors can provide a strong indication of neuropathic pain, when combined with assessment of whether the pain is constant or episodic, determination of any ameliorating or alleviating factors, and consideration of any other accompanying symptoms. In addition, an accompanying physical examination focuses on assessing for the presence of sensory abnormalities. A brief systemic examination should be conducted as well as a sensory examination, which includes testing with the following stimuli: light touch, pinprick and temperature, deep pressure and vibration (with a 128-Hz tuning fork), as well as assessment of position sense, joint position, and reflexes.

Screening instruments are available to assist with the diagnosis of neuropathic pain. Several tools, such as the self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS), can help differentiate between neuropathic and non-neuropathic pain.⁹ This scale, which was developed in Europe, has a composite cutoff value of 12, below which pain is most likely non-neuropathic. The S-LANSS is best suited as a screening tool for chronic pain patients of all types.^{10,11} The Neuropathic Pain Scale (NPS) is another scale with neuropathic pain discriminatory power. It is self-administered by the patient in order to assess pain intensity using 11 measures including 2 global items (eg, pain unpleasantness), 8 specific items (eg, cold, sensitivity), and 1 item to determine the fluctuation of pain.¹² Items are rated on a 0- to 10-point scale, and higher scores are more indicative of neuropathic pain.¹³ (You can view a sample of the Neuropathic Pain Scale and link to information about how to obtain a user’s agreement at www.practicingclinicians.com/H2_2009/nps.pdf) Throughout the assessment, as well as ongoing during the treatment period, the patient findings and therapy plan should be documented (Table 2).

Treating Neuropathic Pain

For any pain condition, but neuropathic pain in particular, a whole host of dimensions beyond pain intensity must be considered when identifying appropriate treatment. If left untreated, they may worsen the neuropathy and pain. For example, psychiatric comorbidities oftentimes present along with chronic pain. Depression, if untreated, can intensify the experience of pain. A framework for a multidimensional approach to patients with neuropathic pain addresses medical etiology (specific etiology and medical comorbidities); pain mechanisms (neuropathic, inflammatory, myofascial, incidence, etc); psychiatric comorbidity (comorbidities and coping skills); and function and quality of life (QOL) (disabilities,

impaired QOL).¹⁴ For each specific parameter it is important to rate the severity (eg, none, mild, moderate, severe). This approach allows for adjustment to a patient's changing needs and reprioritizing of treatment goals, as needed.

Table 2. Areas and Elements of Patient Care Requiring Documentation

Area	Elements
History and physical evaluation	<ul style="list-style-type: none"> • Medical history • Medication history • Pain history • Substance abuse/addiction history • Screening tool assessments (eg, SOAPP, ORT) if opioids are considered • Pain score/intensity • Physical examination • Results of diagnostic studies
Diagnosis/clinical indication for prescribing opioids	<ul style="list-style-type: none"> • Assumed pathology • Hypothesized pathology
Treatment plan	<ul style="list-style-type: none"> • Treatments, pharmacologic (including type of medication, dosage, quantity, and date prescribed) • Treatments, nonpharmacologic (eg, physical therapy, exercise, behavioral therapy, lifestyle changes) • Treatment goals and anticipated time course • Compliance measures (eg, urine drug screens, pill or patch counts)
Informed consent and agreement for treatment	<ul style="list-style-type: none"> • Informed consent, including discussion of risks and benefits • Agreement specifying patient's responsibilities and clinic policies
Periodic review	<ul style="list-style-type: none"> • Pain score/intensity and perceived analgesia from current medications • Physical, occupational, and overall functioning; family and social relationships; mood; and sleep patterns • Side effects (including severity) • Aberrant drug-taking behaviors • Medication
Consultations and referrals	<ul style="list-style-type: none"> • As appropriate to provide comprehensive care

SOAPP = Screener and Opioid Assessment for Patients with Pain; ORT = Opioid Risk Tool.

Reprinted with permission from Nicholson B, Passik SD. Management of chronic noncancer pain in the primary care setting. *South Med J.* 2007;100:1028-1036.

According to a panel of experts that convened in 2007 under the auspices of the IASP and systematically reviewed the randomized clinical trial evidence in the literature,¹⁵ first-line choices for neuropathic pain include the secondary amine tricyclic antidepressants (TCAs) nortriptyline and desipramine, the selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) duloxetine and venlafaxine, the calcium channel α 2- δ ligands gabapentin and pregabalin, topical lidocaine, and opioids—in certain clinical circumstances.¹⁵ Opioids may be the best first-line option “when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, and for episodic exacerbations of severe pain, acute neuropathic pain, and neuropathic cancer pain.”¹⁵ Opioids can also be a good option when pain persists despite reasonable trials of nonopioid analgesics and adjuvants, or when patient characteristics contraindicate use of other analgesics. Opioids have been recommended for treatment of moderate-to-severe pain associated with chronic ailments ranging from low back pain¹⁶ to neuropathic pain,¹⁵ and for older adult populations, according to the 2009 American Geriatrics Society guidelines.¹⁷

Table 3. Stepwise Pharmacologic Management of Neuropathic Pain

1. Assess and establish the diagnosis of neuropathic pain

- Establish and treat the cause of neuropathic pain
- Identify relevant comorbidities
- Explain diagnosis and treatment plan to patient

2. Initiate symptom treatment with 1 or more of the following:

- Selective serotonin norepinephrine reuptake inhibitor or tricyclic antidepressant
- Calcium channel α 2- δ ligand
- Lidocaine patch 5%
- Opioid analgesic or tramadol—in select clinical circumstances
- Evaluate for nonpharmacologic treatments

3. Reassess pain and health-related quality of life frequently

- If substantial pain relief and tolerable side effects, continue treatment
- If partial pain relief, titrate the initial medication or add another first-line medication
- If no or inadequate pain relief, switch to alternative first-line medication

4. If trial of first-line and second-line medications fails, consider third-line medications or referral to a pain specialist

Dworkin RH, et al.¹⁵

Individualized Treatment

The current pharmacologic guidelines also provide a stepwise approach for managing neuropathic pain (Table 3); however, due to a lack of head-to-head studies, the treatment options cannot be rank-ordered based solely on safety and efficacy profiles. A recent meta-analysis of randomized controlled trials of duloxetine, pregabalin, and gabapentin found comparable efficacy and tolerability of these agents in the treatments for PDN.¹⁸ Rather, in order to determine which option may best fulfill the individual needs of the patient, other characteristics of the medications need to be considered, as well as the entire profile of the patient. For example, many patients who have chronic, painful conditions suffer from depression or anxiety, thereby diminishing their QOL.¹⁹ Duloxetine or a TCA can be a good first option for patients who have comorbid depression, while pregabalin may be more suitable for those who would benefit from an anxiolytic effect. Topical lidocaine can be beneficial for localized pain or when systemic effects are a concern (ie, for older patients taking multiple medications). Indeed, a 4-week, randomized, controlled trial comparing the efficacy and safety of a topical lidocaine patch 5% to pregabalin for the treatment of PHN found comparable efficacy between the 2 agents, but far fewer adverse events and discontinuations with topical lidocaine 5% compared to pregabalin (respectively, 3.9%, 1.3% for lidocaine and 39.2%, 20.3% for pregabalin).²⁰ Furthermore, the lidocaine patch 5% cohort had more responders (62.2% vs 46.5%) and greater improvement in QOL than the pregabalin group.²¹ A longer open-label study established the maintenance of efficacy and safety of the patch for a full year of use in a population over the age of 50 that often requires nonsystemic options due to polypharmacy concerns.²²

Although the efficacy of opioids is well established, due to this drug family's safety and tolerability profile, these analgesics generally are relegated to second-line treatments, except in select clinical circumstances. Nausea and sedation are opioid side effects to which patients habituate with time, while a bowel regimen may be needed for long-term opioid therapy to avoid problems with constipation. Opioid treatment should include setting realistic goals, a collaborative practitioner–patient relationship, patient education, ongoing documentation and reassessments, and a clearly defined exit strategy. Tramadol, a weak μ opioid antagonist as well as an inhibitor of reuptake of norepinephrine and serotonin, has also demonstrated efficacy for treating neuropathic pain but has opioid side effects; therefore, it is recommended as a second-line option.¹⁵

All medications, including analgesics, are initiated on a trial basis until the effects for an individual are established. If after ample time for titration (approximately 3 months) a therapeutic effect has not been established, or in the case of intolerability, third-line agents can be considered. These agents have less evidence of efficacy and/or more variable effects within individuals. They include antiepileptic medications (lamotrigine, topiramate), certain antidepressants (bupropion), mexiletine, N-methyl-D-aspartic acid (NMDA) receptor antagonists (dextromethorphan, amantadine), and topical capsaicin.¹⁵

Dosing adjustments are another way to better individualize patient treatments; guidelines for dosing first- and second-line agents for treating neuropathic pain are provided in Table 4.

Table 4. Recommended Dosing: First- and Second-Line Therapy for Neuropathic Pain

Medication Class	Starting Dosage	Titration	Maximum Dosage	Duration of Adequate Trial
Secondary amine TCAs Nortriptyline, desipramine ^a (use a tertiary amine TCA only if a secondary amine TCA is not available)	25 mg at bedtime	Increase by 25 mg daily every 3-7 days as tolerated	150 mg daily; if blood level of active medication and its metabolite is below 100 ng/mL (mg/mL), continue titration with caution	6-8 weeks with at least 2 weeks at maximum tolerated dosage
SSNRIs Duloxetine	30 mg once daily	Increase to 60 mg once daily after 1 week	60 mg twice daily	4 weeks
Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each week	225 mg daily	4-6 weeks
Calcium channel $\alpha 2$-δ ligands Gabapentin ^a	100-300 mg at bedtime or 100-300 mg 3 times daily	Increase by 100-300 mg 3 times daily every 1-7 days as tolerated	3600 mg daily (1200 mg 3 times daily); reduce if impaired renal function	3-8 weeks for titration plus 2 weeks at maximum dosage
Pregabalin ^a	50 mg 3 times daily or 75 mg 2 times daily	Increase to 300 mg daily after 3-7 days, then by 150 mg/d every 3-7 days as tolerated	600 mg daily (200 mg 3 times or 300 mg twice daily); reduce if impaired renal function	4 weeks
Topical lidocaine Lidocaine patch 5%	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for a maximum of 12-18 h	3 weeks
Opioid agonists^b Morphine, oxycodone, methadone, levorphanol ^a	10- to 15-mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)	After 1-2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (eg, 120- to 180-mg morphine daily; equianalgesic dosages should be used for other opioid analgesics)	4-6 weeks
Tramadol^c	50 mg once or twice daily	Increase by 50-100 mg mg daily in divided doses every 3-7 days as tolerated	400 mg daily (100 mg 4 times daily); in patients older than 75, 300 mg daily	4 weeks

SSNRI = selective serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants. ^aConsider lower starting dosages and slower titration in geriatric patients. ^bFirst-line only in certain circumstances. ^cConsider lower starting dosages and slower titration in geriatric patients; dosages given are for short-acting formulation. From Dworkin RH, et al.¹⁵ Used with permission from the International Association for the Study of Pain.

Table 5. Treatment Selection Considerations for First-Line Medications and Opioid Agonists

Medication Class	Therapeutic Index ^a	Major Side Effects	Precautions	Other Benefits	Cost ^b
Secondary amine TCAs Nortriptyline, desipramine (use a tertiary amine TCA only if a secondary amine TCA is not available)	+	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol	Improvement of depression, improvement of insomnia	\$
SSNRIs Duloxetine ^c	++	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol	Improvement of depression	\$\$
Venlafaxine	+	Nausea	Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation	Improvement of depression	\$/\$\$
Calcium channel $\alpha 2$-δ ligands Gabapentin	++	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, no clinically significant drug interactions	\$/\$\$
Pregabalin ^c	++	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance/ anxiety, no clinically significant drug interactions	\$\$
Topical lidocaine Lidocaine patch 5%	++	Local erythema, rash	None	No systemic side effects	\$/\$\$ (patch) \$(gel)
Opioid agonists^d Morphine, oxycodone, methadone, levorphanol	+	Nausea/vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk, driving impairment during treatment initiation	Rapid onset of analgesic benefit	\$/\$\$
Tramadol	+	Nausea/vomiting, constipation, drowsiness, dizziness seizures	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SSNRI, TCA	Rapid onset of analgesic benefit	\$/\$\$

SSNRI = selective serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant. ^aThe likelihood of pain relief relative to the likelihood of side effects, with “+++” being more favorable. ^bCost varies by region, but is estimated on the basis of availability and cost of generic formulations, with “\$\$\$” being relatively more expensive. ^cLacks long-term clinical experience and safety data because new to market.

^dFirst-line only in certain circumstances. From Dworkin RH, et al.¹⁵ Used with permission from the International Association for the Study of Pain.

In the case where multiple pain etiologies contribute to chronic pain, using analgesics with different physiological mechanisms can help increase pain relief. Furthermore, the overall outcome will be improved if multiple agents are used to activate multiple pathways for pain control. Topical agents can be particularly beneficial for patients who take multiple medications and have a risk of drug-drug interactions. Topical agents have a lower incidence of systemic toxicities and their effects are primarily limited to the site of application.²³

Aging and associated metabolic changes contribute to individual differences in drug distribution, bioavailability, and elimination and can further confound the effective management of neuropathic pain. Consequently, older adults in particular require a tailored treatment plan with modified dosages and frequencies, taking into account any comorbidities and the potential for drug-drug interactions.²⁴ Indeed the potential for drug-drug interactions is an important consideration for all patients who are prescribed multiple systemic medications, as 40% to 50% of all drugs, including opioids, are metabolized by the cytochrome P450 (CYP 450) isoenzymes.²⁵ Exceptions to this include morphine, hydromorphone, and oxycodone, which are *not* metabolized by the CYP 450 enzymes.²⁶ Overall, when treating older patients with chronic pain, it is best to adhere to the sage adage: “Start low and go slow,” using low initial doses and gradual titration. For patients with liver dysfunction, remain vigilant for combination therapies that contain acetaminophen (APAP). Other specific recommendations regarding neuropathic pain treatment tailoring for individual needs and limitations, such as renal insufficiency, are listed in Table 5.

PCEFORUM

It's your turn. Post your comments to this clinical question:



How do you identify drug-seeking behavior in your practice? How do you address this with the patient, and how do you modify the treatment plan?

Post your answer to this question and more on the PCE Forum www.practicingclinicians.com/forumhomestudy

CASE STUDY

A 50-Year-Old Patient With Peripheral Diabetic Neuropathy

Presentation and Context

A 50-year-old female administrative assistant at a financial company complains about pain in her feet along with a burning sensation, both of which flare at night. She recently has begun using reading glasses, she occasionally stumbles when she stands up, and reports some numbness in her feet.

She was diagnosed with diabetes 20 years ago and has been managed with metformin and insulin glargine, as well as advised to exercise and to lose weight. She monitors her blood sugar regularly and tries to follow her diet; however, her lifestyle has continued to be sedentary. Her hobbies are reading and watching television, and she does not exercise regularly, as activity—even walking—is limited by her rheumatoid arthritis (RA). She has a 10-year history of “achy” hand pain, typically scoring a 3 on the 0 to 10 numeric rating scale (NRS), for which she applies topical nonsteroidal anti-inflammatory drug (NSAID) gel and takes acetaminophen (APAP), as needed. She has been treated for hypertension over the last decade and that condition has remained unchanged.



Physical Examination

- Height: 5 ft 6 in
- Weight: 160 lb
- Body mass index: 25.8 kg/m²
- Blood pressure: 130/78 mm Hg
- Heart rate: 78 bpm
- Respiratory rate: 16 breaths per minute
- Eyes: retinal changes; arteriovenous nicking
- Extremities: decreased sensation in her feet; a small open area on her ankle that she did not notice

Laboratory Results

- Complete blood count: within normal limits
- Fasting plasma glucose: 146 mg/dL
- A1C: 9%

- Urine: no ketones
- Electrocardiogram (ECG): normal

Medical History

- RA
- Hypertension

Current Medications

- Angiotensin-converting enzyme (ACE) inhibitor
- Infliximab
- Insulin glargine
- Metformin
- Methotrexate
- Topical NSAID gel
- APAP, as needed

Neuropathic Pain:

A Treatment Challenge for Practitioners

From the examination it is clear that the effects of the patient's diabetes are worsening, and she has several risk factors for developing PDN: a long duration of diabetes, an elevated BMI, an elevated A1C level, and hypertension. Also, the descriptors of her pain, its distribution, and its setting of presentation are archetypal of PDN. The development of decreasing nociceptive thresholds can be assessed through application of von Frey filaments, electromyography (EMG), or by nerve conduction. Hence, an EMG is ordered to assess her nerve conduction status. In addition, using a pain tool such as the NPS can indicate the pain type, clinical characteristics, and information about pain fluctuation; thus the NPS is administered to assess the level of pain in her feet. She scores a 7, indicating that her pain is neuropathic. Her diabetes has been poorly controlled for several years, and she has developed the classic presentation of diabetic foot pain; she is diagnosed with PDN.

Using the multidimensional approach to pain treatment described on page 108, the patient's pain etiology—diabetes—is moderate to severe, as it is seemingly uncontrolled at this point. In addition, other medical conditions are contributing to her diabetes, and RA is another cause of pain. Mechanisms underlying her pain likely include neuropathy and inflammatory processes associated with RA as well as with the nerve injury from diabetes; altogether they are of moderate importance to address at this time. Currently, she has maintained her job and there are no indicators of psychiatric comorbidities; however, her daily function is impaired, such as her reduced ability to

walk, which needs to be addressed. From this analysis, the etiology of her pain is of primary importance to manage immediately, along with providing adequate pain relief in order to improve her functioning. She is put on a sliding scale for insulin; metformin and insulin glargine are continued; and rapid-acting prandial insulin is added. The ACE inhibitor is continued, as are infliximab, methotrexate, and NSAID gel for the RA and associated pain in her hands.

Clinical Decision Point

What medication(s) could be added to address her PDN and flares in pain?

- Calcium channel α 2- δ ligand (gabapentin or pregabalin)
- Duloxetine
- Lidocaine patch 5%
- Tramadol
- Other antiepileptic medication
- Tricyclic antidepressant

Comment

According to the current evidence-based guidelines, all of the above medications are appropriate for treating neuropathic pain.¹⁵ For this particular patient, a multimodal approach is needed to address the multiple aspects of her pain. Both pregabalin and duloxetine have FDA indications for treating PDN, but clinical experience suggests that she may habituate to the side effect of somnolence more quickly with pregabalin than with gabapentin, and gabapentin can require a longer period to titrate up to a therapeutic dose. Thus, pregabalin is chosen for faster onset of pain relief with a starting dose of 50 mg taken twice a day. In addition, given

the patient's pain severity, an opioid is added to address her nightly pain flares. Thus, the "APAP, as needed" is modified to "oxycodone/APAP, as needed" for breakthrough pain. The Opioid Risk Tool (ORT) is administered before prescribing the opioid, and her score of 2 documents her low misuse potential and supports the treatment decision. When opioids are prescribed to treat chronic pain, an ongoing program must be implemented in order to monitor for signs of abuse or misuse, beginning with signing an opioid agreement, performing an opioid risk assessment, and urine toxicology screen. A written opioid treatment agreement helps ensure the patient understands the risks and benefits of opioid therapy and spells out for patient and clinician the specific conditions of its prescription.²⁷ Elements of an agreement should include²⁷:

- Specific information about the medications to be used
- Specific amounts to be dispensed; usually they are small
- A specific refill policy
- The policy for replacement of "lost" medications
- Specifics regarding the frequency of office visits
- The policy for other practitioners prescribing opioid medications: *one* practitioner and *only one* practitioner is a prescriber

When both urine drug testing and behavioral monitoring are utilized, more

patients with inappropriate drug-taking behaviors will be captured than by using either method alone.²⁸ Urine drug testing also provides objective documentation of patients' adherence to their treatment regimen and opioid agreement and supports clinical treatment decisions.²⁹

Comprehensive care for patients with neuropathic pain should include regular exercise in order to maintain functionality. Pool therapy is a possibility for patients who have mobility issues and joint pain, such as the patient in this case. Complementary methods may be helpful, but little research supports their use in patient populations with neuropathic pain. Cognitive-behavioral therapy may be useful for some individuals, especially those with comorbid depression or anxiety.³⁰ It is important for patients to commit to a regular schedule for healthcare and support services to maintain their diabetic regimen and to undergo regular reassessments to ensure the continuing provision of adequate pain relief.

Uncontrolled diabetes coupled with a sedentary lifestyle and significant comorbidities can lead to chronic pain conditions that are very difficult to treat. Treatment for these complex cases requires a multimodal approach and tailoring to the individual's needs. Cases akin to this one are all too common in the United States: only 7% of patients with diabetes achieve simultaneous control of their blood pressure (<130/80 mm Hg), total cholesterol levels (<200 mg/dL), and A1C levels (<7%).³¹

References

1. Task Force on Taxonomy of the International Association for the Study of Pain. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle, WA: IASP Press; 1994.
2. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70:1630-1635.
3. Irving GA. Contemporary assessment and management of neuropathic pain. *Neurology*. 2005;64(12 suppl 3):S21-S27.
4. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clin J Pain*. 2002;18:350-354.
5. Cole BE. Diabetic peripheral neuropathic pain: recognition and management. *Pain Med*. 2007;8(suppl 2):S27-S32.
6. Centers for Disease Control and Prevention. Number of people with diabetes increases to 24 million: estimates of diagnosed diabetes now available for all U.S. counties. *CDC Online Newsroom Press Release*. <http://www.cdc.gov/media/pressrel/2008/r080624.htm>. Accessed May 28, 2009.
7. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. *Phys Ther*. 2008;88:1254-1264.
8. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. *N Engl J Med*. 2005;352:341-350.
9. Bennett MI, Smith BH, Torrance N, et al. Can pain can be more or less neuropathic? Comparison of symptom assessment tools with ratings of certainty by clinicians. *Pain*. 2006;122:289-294.
10. Bennett M. The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain*. 2001;92:147-157.
11. Weingarten TN, Watson JC, Hooten WM, et al. Validation of the S-LANSS in the community setting. *Pain*. 2007;132:189-194.
12. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology*. 1997;48:332-338.
13. Fishbain DA, Lewis JE, Cutler R, et al. Can the neuropathic pain scale discriminate between non-neuropathic and neuropathic pain? *Pain Med*. 2008;9:149-160.
14. Backonja M, Argoff C. Neuropathic pain—definition and implications for research and therapy. *J Neuropathic Pain Symptom Palliation*. 2005;1:11-17.
15. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132:237-251.
16. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147:478-491.
17. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. http://www.americangeriatrics.org/education/financial_recommendations.pdf. Accessed July 6, 2009.
18. Quilici S, Chancellor J, Lothgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol*. 2009;9:6.
19. Gormsen L, Rosenberg R, Bach FW, Jensen TS. Depression, anxiety, health-related quality of life and pain in patients with chronic fibromyalgia and neuropathic pain. *Eur J Pain*. 2009 May 25. [Epub ahead of print]
20. Baron R, Mayoral V, Leijon G, et al. Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. *Clin Drug Investig*. 2009;29:231-241.
21. Baron R, Mayoral V, Leijon G, et al. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin*. 2009; 25:1663-1676.

22. Hans G, Sabatowski R, Binder A, et al. Efficacy and tolerability of a 5% lidocaine medicated plaster for the topical treatment of post-herpetic neuralgia: results of a long-term study. *Curr Med Res Opin.* 2009;25:1295-1305.
23. Argoff CE. Topical treatments for pain. *Curr Pain Headache Rep.* 2004;8:261-267.
24. Milton JC, Hill-Smith I, Jackson SH. Prescribing for older people. *BMJ.* 2008;336:606-609.
25. Rogers JF, Nafziger AN, Bertino JS Jr. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450-metabolized drugs. *Am J Med.* 2002;113:746-750.
26. Kadiev E, Patel V, Rad P, et al. Role of pharmacogenetics in variable response to drugs: focus on opioids. *Expert Opin Drug Metab Toxicol.* 2008;4:77-91.
27. American Academy of Pain Medicine, American Pain Society. The Use of Opioids for the Treatment of Chronic Pain: A Consensus Statement From the American Academy of Pain Medicine and the American Pain Society; 1996.
28. Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth Analg.* 2003;97:1097-1102.
29. Gourlay D, Heit H, Caplan Y. Urine Drug Testing in Clinical Practice: Dispelling the Myths and Designing Strategies. Stamford, CT: PharmaCom Group, Inc.; 2004.
30. Daniel HC, Narewska J, Serpell M, et al. Comparison of psychological and physical function in neuropathic pain and nociceptive pain: implications for cognitive behavioral pain management programs. *Eur J Pain.* 2008;12:731-741.
31. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA.* 2004;291:335-342.

QUESTIONS From Symposium Participants

- Q:** What are some appropriate ways to manage patient expectations regarding neuropathic pain and its treatments?
- A:** From a patient's perspective, since neuropathic pain may not be readily diagnosed and assistance from multiple providers may be sought before a diagnosis is confirmed, the patient may feel as if the condition is untreatable. Although it may not improve the pain levels, sometimes telling the patient the name of the pain condition may provide a sense of comfort and further develop the patient-provider relationship. Begin with the caveat that neuropathic pain is difficult to treat and therefore may require some time to optimize treatment. However, there are several good analgesic options available.
- Q:** How much pain relief should a patient expect from neuropathic pain treatments, and how can progress be monitored?
- A:** It is very unusual to completely alleviate pain. Typically, the target goal is a 30% to 40% reduction in pain, as patients are often satisfied with this level of relief, which, measured by tools such as the Visual Analogue Scale, is equivalent to a 2.0- to 2.7-point reduction on a 10-point scale. However, the functional benefits of providing suitable analgesia, such as increased mobility and activity, are as important as the percent pain reduction.
- Q:** Regarding the development of PHN following a shingles infection, how can acute versus chronic pain be distinguished and how should it be treated?
- A:** PHN is characterized as continued pain 3 months after the resolution of the herpes zoster rash; however, a patient in severe pain requires immediate treatment, even before the diagnosis of PHN is established. First-line therapy with opioids may be appropriate in the situation where a patient is reporting severe pain, but the zoster lesions have not yet healed and therefore are not amenable to topical treatment. In addition, opioids may be suitable for acute treatment of pain while another medication is being titrated up to therapeutic effect. Once the lesions have healed, because PHN pain is well localized, topical treatment, such as a lidocaine patch 5%, can be a good option.

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