ABSTRACT

The recently developed consensus guidelines on the treatment of neuropathic pain reflects our ability to use evidence-based medicine for rational pharmacotherapy in a group of disorders that is often difficult to treat. Neuropathic pain arises from abnormalities in various points in the nervous system and impacts the emotional and psychological status of the affected individual. Because no 2 persons have identical nervous systems, neuropathic pain is a unique disease state for each individual. These guidelines provide a framework, based on published efficacy and safety studies, to provide the healthcare provider with a choice of first-line therapies for neuropathic pain patients. However, as with many areas of medicine, successful outcomes are achieved when both the art and science of medicine are applied. In treating neuropathic pain, the medical “art” may be found in the clinical experience of pain specialists, but may not appear in the published literature. This article is a summary of presentations and discussions by a panel of pain specialists from pain medicine, neurology, anesthesiology, psychiatry, pharmacy, primary care, and nursing. Collectively, the panel members offer their insights into application of these guidelines in real-world clinical experience. The goal is to provide the nonspecialist healthcare team the information and the confidence to treat neuropathic pain with a rational treatment approach and to provide a comprehensive treatment plan aimed at improving clinical outcomes.


PRESENTATION OF NEUROPATHIC PAIN

Although there is no single sign or symptom that is pathognomonic for neuropathic pain, a confident diagnosis can be made from a focused history and a confirming physical examination.

Pain symptoms are first assessed by asking the patient to describe the history of the pain including its location, intensity, quality, duration, frequency, and effect on the patient’s daily activities. Important questions to ask during the examination are listed in the Sidebar (on the next page). Although neuropathic pain has often been described as tingling, burning, lancinating, or shooting pain (as opposed to visceral pain, for example, which “traditionally” has been described as dull, aching, or squeezing), many patients with neuropathic pain also complain of sharp, aching, or throbbing pain as well. It can also be described as an “odd” sensation in an old surgical area, especially with postmastectomy pain.
Neuropathic pain can be spontaneous or elicited. Determining the etiology of the pain or mechanism of injury can also give important clues to understanding the type of pain. For example, a patient with a history of acute herpetic neuralgia 6 weeks prior in the same distribution of the current pain can help lead the clinician to a diagnosis of postherpetic neuralgia. A body diagram may be used by having the patient fill in the painful areas, darker or lighter depending on the severity, so that the extent, quality, and degree of pain can be visualized. Similarly, the type and timing of exacerbations (eg, clothes against the skin) should be noted. The patient should be asked whether or not the pain interferes with sleep, and if so to what extent, and about loss of strength as well as loss of endurance. When questioning the patient about factors/techniques they use to alleviate pain, both pharmacologic and nonpharmacologic measures should be included. It is important to ask about substances that do not require a prescription, as some over-the-counter remedies, including the use of various “supplements,” can interact adversely with prescription medications. These queries will provide important clues to directing treatment plans and help assure the patient that his or her pain is taken seriously.

It is important to ask the patient to rate his or her pain. Use of a pain severity rating may allow the treatment provider to better track the effects of treatment. Pain can only be assessed by subjective self-reports from the patient and pain severity can be measured using one of the several validated rating scales available. Among the several pain rating scales that are available, which have been shown to be reliable measures of pain, the 2 most commonly used in the office setting are the visual analog scale (VAS) and the numeric pain intensity (NPI) scale. The VAS measures pain visually. A 10-cm horizontal is drawn and the patient is told that the left end of the line indicates “no pain” and that the right end indicates “pain as bad as it could be.” The patient is then asked to draw a line intersecting the 10-cm line indicating the intensity of their overall pain. The point at which the patient’s line intersects the line is measured from the “no pain” end in centimeters, thus providing a numerical value to their pain (eg, 8 cm, so the pain score is 8/10). This scale is not commonly used in the clinical setting, but rather, it is more of a research tool. The NPI scale simply asks the patient to rate his or her pain on a scale from 0 (no pain) to 10 (pain as bad as it could be). One real advantage of the NPI scale over the VAS is that patients can label their pain as a number corresponding to a certain level of pain, and relate to their provider using this number in situations without a VAS and ruler being available. The NPI scale has been shown to be both reliable and valid in clinical settings. Other common pain scales are the neuropathic pain scale, the brief pain inventory, and the McGill Pain Questionnaire. These types of assessment tools can be found at www.painEDU.org in the Assessment Tool Kit.

A general physical examination should be performed. Special attention should also be paid to the neurological examination and the musculoskeletal examination. Range-of-motion testing, the presence of tender points or myofascial trigger points, and other musculoskeletal abnormalities need to be assessed. Patients with chronic pain often display exaggerated behaviors while being examined including grunting and groaning, among others; these have been collectively termed pain behaviors and they should be noted if present.

The neurologic examination, following the detailed information on pain, explores somatosensory involvement and includes tests for allodynia, hyperalgesia, myofascial pain, and motor weakness. Allodynia is the term used to describe a normally nonpainful sensation that is experienced as painful, particularly in a neuropathic pain state. Hyperalgesia is the term used to describe a painful stimulus that is experienced as more painful than normal in a patient with neuropathic pain. Testing for allodynia can be done by rubbing a cotton swab on the affected area or placing the cotton swab directly onto the skin. Thermal allodynia can be tested by applying a warm object (eg, a test tube filled with warm or hot water) or cold sensation (eg, a tuning fork, or application of rubbing alcohol on the

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**Clinical Interview Questions of Pain**

- What is the location, quality, and frequency of pain?
- What are the variations and patterns of pain?
- What factors alleviate or worsen the pain?
- How did they work?
- When was the onset of pain?
- What are your physical limitations due to the pain?
- How bad is the pain at its worst? At its best?
- What are your expectations of treatment?
- How do your family/loved ones respond to your pain?
- What other limitations has the pain placed on your life?
skin and then blowing on the affected area). For hyperalgesia, single and multiple pinpricks, a broken sterile cotton swab, or a broken tongue depressor can be used. These tests should be performed on both sides of the body. Videos demonstrating neurologic exams, especially for neuropathic pain syndromes, can be found online or purchased (see Sidebar).1,2

Once the diagnosis is confirmed, psychological and functional assessment are imperative, as these parameters will not only be part of the measures of treatment success but in many ways define treatment success. Neuropathic pain will almost never be completely eliminated even with the most advanced treatment. Sharing this reality with the patient early in therapy sets the stage for goal setting and success of treatment.

The ultimate goal of neuropathic pain management is to reduce pain as much as possible so that disability can lessen and functionality be improved.

Psychological factors may greatly alter pain perception and functionality. Depression and anxiety, in particular, frequently accompany chronic pain. Referral for psychological or psychiatric care is not uncommon, is probably underutilized, and should be discussed as part of the normal pain evaluation and treatment process. Patients with chronic pain commonly experience depression. They experience limitations imposed by their pain on work and social functioning, such that patients may also suffer from a loss of status as family members and members of society. If left untreated, depression and anxiety can result in avoidant behavior, such that patients refrain from participating in any new activity, furthering their sense of isolation and disability, and perhaps resulting in catastrophizing, a coping style of increasingly negative thoughts (eg, “I’ll never be able to do anything again. I’m an awful person”), or even suicide. Even in psychologically healthy individuals, chronic pain can lead to tremendous loss and strained coping abilities.

Psychological and functional assessment can begin with general questions about the patient’s life (How are you sleeping? How are you getting around? How is your job going? How is your energy level?). It is also important to ask about the family’s/loved one’s reactions to the pain as this can have a great impact on treatment success. Family or friends may overcompensate for someone’s pain, contributing to learned helplessness. Conversely, some family members may “punish” the patient by distancing themselves from the patient because they do not believe the pain is real or that the patient is doing anything to help him or herself.

Negative changes in social and occupational functioning are important to consider because the restriction of either can contribute to the loss of sense of purpose. It is critical for all pain care providers to convey and to reinforce the message that the patient’s pain is real, that the patient’s complaints are believed, and that the healthcare team will work with the patient for as long as necessary to achieve the most successful outcomes possible. Table 1 lists several pain severity, functional, and psychological assessment tools commonly used by this panel.

Understanding Neuropathic Pain Treatment Approaches

Pain is defined as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” Nociceptors are specialized nerve endings that can detect noxious stimuli (or those perceived to be noxious), and transform them into pain-producing impulses that travel through sensory neurons to the spinal cord. In general, pain-producing impulses enter the dorsal horn of the spinal cord via sensory axons, which are maintained by the dorsal root ganglion (Figure 1), and are further transmitted to the brain through ascending tracts of nerve fibers, particularly the lateral spinothalamic tract. It is only after these impulses are received and
processed by the brain that pain is perceived. Pain can result from normal nociceptive processes (for example, arising from pain-producing stimuli arising from muscle, joints, skin, or organs), abnormal neuropathic processes (resulting from disease, damage, or dysfunction in the nervous system), or from a combination of these. As described in the guidelines for diagnosing and treating neuropathic pain, dysfunction of the sensory components of the nervous system leading to neuropathic pain can occur from many causes (Table 2) resulting in peripheral nervous system (PNS) or central nervous system (CNS) contributions to neuropathic pain. Damage to peripheral nerves can generate impulses from ectopic or abnormal locations. When nerves are completely cut off from the CNS, deafferentation and hyperexcitability (eg, phantom limb pain) may occur. Centrally, reorganization of synaptic architecture in the spinal cord after peripheral nerve injury such as herpes zoster—referred to as central sensitization—can lead to a permanent state of hyperexcitability. Consequently, it is vital to treat neuropathic pain early before it becomes chronic and to treat the underlying cause of the pain whenever possible.

One of the challenges in managing patients with neuropathic pain is explaining the cause of their pain to them, especially when there is no visible or discernible tissue damage. Simply understanding the cause of the pain can go a long way to improving outcomes as many patients feel ostracized or embarrassed because of their pain (ie, others do not believe them). Panel members offered suggestions on how they explain neuropathic pain to their patients (see Sidebar on the next page). Indeed, this is a critical foundation for the healthcare provider–patient relationship.

“I've had patients walk out of my office when I've given them an explanation for their pain, saying ‘I don't really want to take any medicine for this. I just wanted to know what the problem is. Nobody has ever told me.’ And I am usually not the first physician the patient has seen for the pain problem.”

Randall Brewer, MD

In addition, many clinicians now rely on patient education through Web sites that are professionally written for the patient and peer reviewed by pain experts, such as www.painconnection.org. The information on these Web sites can empower the patient and family with helpful information, and help the clinician to efficiently and effectively treat the patient.

### Table 1. Assessment Tools for Neuropathic Pain

<table>
<thead>
<tr>
<th>Pain Assessment Tools</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>McGill Pain Questionnaire</td>
<td>Assess pain severity and duration</td>
</tr>
<tr>
<td>Neuropathic Pain Scale</td>
<td>Assess distinct pain qualities associated with neuropathic pain</td>
</tr>
<tr>
<td>TOPS</td>
<td>An SF-36 that is modified specifically for chronic pain. Measures objective outcomes in patients during treatment of pain not related to malignancy; used for follow-up</td>
</tr>
<tr>
<td>WOMAC Universities Index</td>
<td>Global measure of pain, stiffness, and disability</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disability Assessment Tools</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roland Morris Disability Questionnaire</td>
<td>Measures disability by evaluating multiple parameters of function (physical and psychosocial)</td>
</tr>
<tr>
<td>Oswestry Disability Index</td>
<td>Measures disability by evaluating multiple parameters of function (physical and psychosocial)—specific for low back pain</td>
</tr>
<tr>
<td>Neck Disability Index</td>
<td>An adaptation of the Oswestry index for patients with neck pain by chiropractic researchers</td>
</tr>
<tr>
<td>Medical Outcomes Study Health Survey Questionnaire SF-36</td>
<td>Assesses functioning and overall health status using 8 health concepts: 1) Limitations in physical activities because of health problems; 2) Limitations in social activities because of physical or emotional problems; 3) Limitations in usual role activities because of physical health problems; 4) Bodily pain; 5) General mental health (psychological distress and well-being); 6) Limitations in usual role activities because of emotional problems; 7) Vitality (energy and fatigue); 8) General health problems</td>
</tr>
<tr>
<td>MPI</td>
<td>Provides a brief but comprehensive assessment of the subjective experience of pain</td>
</tr>
</tbody>
</table>

### Psychological Assessment Tools

| SCL-90-R | Designed to screen for a broad range of psychological problems and symptoms of psychopathology |
| Beck Depression Inventory | Measures presence of depression |
| Beck Anxiety Inventory | Discriminates anxiety from depression in individuals |

TOPS = Treatment Outcomes in Pain Survey; SF-36 = Short Form-36; WOMAC = Western Ontario McMaster; MPI = Multidimensional Pain Inventory; SCL-90-R = Symptoms Checklist 90-Revisited.

Many of the tools can be found at www.painedu.org. Also, the City of Hope (www.cityofhope.org) offers numerous pain assessment tools for nurses.
Our current understanding of the neurobiology of pain provides numerous avenues for intervention to modify pain perception. Figure 2 is a simplified illustration of the nervous system components involved in neuropathic pain and therefore the different targets for pain treatment. Neither specific biochemical markers nor specific or sensitive diagnostic tests exist for most neuropathic pain states. Nevertheless, as in other disorders in which an exact laboratory test may not be available to specifically identify the mechanism of the disorder, such as hypertension or cancer, it is often necessary to use multiple therapies in a rational manner as part of a comprehensive treatment strategy to maximize outcomes.

Multiple therapeutic strategies are effective in neuropathic pain. All of these strategies can be effective and need to be considered by the healthcare provider. Broadly speaking, medical, physical, rehabilitative, interventional, psychological, and surgical approaches need to be considered in neuropathic pain. The therapies can be, and indeed frequently should be, used simultaneously. The medical approaches include a variety of medication classes known to be effective in neuropathic pain (discussed below). Rehabilitation specializes in improving function through physical modalities (eg, transcutaneous electrical nerve stimulation [TENS] units, heat-cold, exercise). Psychological approaches capitalize on the power of the mind to reinterpret the pain. Interventional therapies involve injections of local anesthetics and steroids around the nerves through implanted devices. Surgical approaches are often used in cancer or disc disease. These approaches are frequently called anatomic or ablative procedures and may involve resection of a nerve or neuroma.

The first-line recommended medical treatments for neuropathic pain are gabapentin, the lidocaine patch 5%, opioid analgesics, tramadol, and tricyclic antidepressants. Each drug/class affects at least one target area in the transmission and perception of pain (Figures 1 and 2). The goal of neuropathic pain treatments is to stabilize the nervous system, preventing or limiting aberrant remodeling and thus the potential development of chronic neuropathic pain. Table 3 lists the proposed analgesic mechanisms of action for these first-line therapies.

**GABAPENTIN**

Gabapentin is the first oral medication approved by the US Food and Drug Administration (FDA) for the treatment of postherpetic neuralgia. It is now believed to act as an analgesic primarily as a calcium-channel blocker. It may also enhance gamma-aminobutyric acid turnover in the CNS, attenuating glutamate-mediated excitotoxic neurotransmission as well (Figure 2). It is important to note that the recommended prescribing information in the official package...
insert for gabapentin for the treatment of postherpetic neuralgia is 1800 mg per day total in 3 equally divided doses. Although the package insert indicates that no additional benefit was observed with doses higher than 1800 mg per day in clinical trials, our clinical experience tells us that higher doses can be effective in some neuropathic pain patients, and a dose escalation trial in an individual patient is often worth trying. Gabapentin can be dosed at 600 to 4800 mg per day in 3 to 4 divided doses. (The recommended dosing and titration schedule for gabapentin, as well as the other first-line therapies, can be found in the published guidelines.) Although the neuropathic pain guidelines recommend dosing up to 3600 mg per day and there is no validation by the FDA, some patients may require doses up to 4800 mg per day for a response, as long as gabapentin continues to be well tolerated. The most common side effects with gabapentin include sedation, dizziness, ataxia, weight gain, and peripheral edema. For some patients, however, cost may make use of this drug prohibitive.

Gabapentin is not metabolized and is renally eliminated. Therefore, doses may require adjustment in patients with declining renal function (ie, longer dosing intervals). Although side effects may occur, it is generally well tolerated and has no organ toxicity associated with its use. It has virtually no drug interactions with the exception of antacids, which can inhibit gabapentin absorption from the gastrointestinal tract. The half-life is short (about 5-7 hours) and saturable transport mechanisms limit gastrointestinal absorption of single doses, so divided doses are necessary (eg, 3-4 times daily dosing).

**Lidocaine Patch**

The lidocaine patch 5% is an example of a topical analgesic and the first medication ever approved by the FDA for the treatment of postherpetic neuralgia. Lidocaine blocks sodium channels, thereby decreasing depolarization of nerves, increasing the threshold for excitability, and preventing action potential propagation (Figure 2). The current approved labeling is for up to 3 patches applied once daily directly over the painful site, 12 hours on and 12 hours off. Recent pharmacokinetic and pilot studies suggest that up to 4 patches applied for 18 hours per day are safe, with an adverse effect profile that is not appreciably different from that found when the FDA-approved dosage is used. The lidocaine patch 5% is a topical therapy targeted to the PNS and does not undergo significant systemic absorption (ie, clinically insignificant serum

<table>
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<tr>
<th>Table 2. Possible Underlying Causes of Nervous System Dysfunction Leading to Neuropathic Pain</th>
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<tbody>
<tr>
<td><strong>Case/Source</strong></td>
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<tr>
<td>Infections</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Metabolic abnormalities</td>
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<tr>
<td>Chemotherapy</td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Irradiation</td>
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<tr>
<td>Neurotoxins</td>
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<tr>
<td>Inherited neurodegeneration</td>
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<tr>
<td>Nerve compression</td>
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<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Tumor infiltration</td>
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<tr>
<td>Spinal cord</td>
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</table>

**Figure 2. Treatment Targets in Neuropathic Pain at the Neuronal Level**

A “microscopic” look at the effects of pain treatments on pain impulse conduction. PGE$_2$ = prostaglandin E$_2$; TCA = tricyclic antidepressants; GABA = gamma-aminobutyric acid; AMPA = aminomethylphosphonic acid.
lidocone levels occur with mentioned dosing). As such, there are no significant drug interactions and systemic side effects are unlikely. The most commonly reported, clinically significant side effect may be skin irritation at the site of the patch, but even this occurs infrequently. The lidocone patch should be used only on intact skin to avoid infection. As a topical analgesic, this preparation is active with the skin, soft tissues, and, potentially, superficial branches of peripheral nerves. It may interrupt the pain cycle by diminishing ectopic discharge in the PNS and by reducing CNS excitability.

**Tricyclic Antidepressants**

Tricyclic antidepressants (TCAs) are thought to have multiple analgesic mechanisms of action including potent sodium channel blockade and inhibition of serotonin and norepinephrine reuptake in descending inhibitory pathways. These effects may influence more than one mechanism of neuropathic pain including excitotoxicity, ectopic discharge, central sensitization, and sympathetic involvement. TCAs are absorbed quickly and are widely distributed. Their half-lives range from 5 to more than 37 hours and they undergo significant hepatic first-pass metabolism, mostly through cytochrome P450 2D6. Importantly, because depression is so frequently comorbid with neuropathic pain, and the risk of suicide is always a consideration in chronic pain patients, TCAs should be prescribed with caution in patients who are struggling with diminished function from chronic pain. Continually probing the emotional sequelae of a chronic illness, including chronic pain, is critical, especially with the use of TCAs. The clinician may also consider prescribing “neuropathic pain doses” of TCAs, because the doses used for pain treatment are usually not as high as those required for treating depression. Generally, 50 to 75 mg per day of amitriptyline or its equivalent is adequate for managing neuropathic pain, though patients with increased metabolic capacity may require higher doses.

Patients should also be screened regularly for depression. Patients who are depressed should always be asked if they have suicidal ideation, and if so, if they have plans to act on those thoughts. Depending upon the results of such screening, referral to the appropriate mental health professional may be indicated.

Amitriptyline has historically been the most commonly prescribed TCA for pain treatment. However, it is associated with significantly impairing side effects, namely anticholinergic effects (sedation) and orthostatic hypotension. Pain patients with poor sleep habits may find the sedating effects useful. However, nortripryline and desipramine are less sedating and appear to have equal analgesic benefit.

**Opioid Analgesics**

Opioid analgesics are thought to act through presynaptic blockade of calcium uptake in nerve endings, thus decreasing the ascending transmission of nociceptive information and postsynaptic potassium conductance, which leads to hyperpolarization and depression of neuronal excitability (Figure 2).

Opioids remain one of the most effective classes of agents we have in the management of chronic pain. There has been much controversy, however, on the appropriate use of opiate therapy in neuropathic pain. In the late 1980s and 1990s, physicians believed that neuropathic pain was unresponsive to opiate therapy. Arner and Meyerson treated patients with neuropathic pain, many of whom had been receiving higher doses of

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Proposed Mechanism of Action</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>Calcium-channel blockade, central GABA enhancement</td>
</tr>
<tr>
<td>Lidocone patch 5%</td>
<td>Sodium channel blockade</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Central — CNS opioid receptors inhibit ascending transmission of nociceptive information; activate descending pain control pathways from midbrain</td>
</tr>
<tr>
<td>Peripheral — bind to opioid receptors on peripheral nerves that are “up-regulated” during inflammatory pain states</td>
<td></td>
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<tr>
<td>Tramadol</td>
<td>Weak mu opioid receptor agonist, weak inhibitor of norepinephrine and serotonin reuptake, sodium channel blockade</td>
</tr>
<tr>
<td>TCAs</td>
<td>Local — potent sodium channel blockade</td>
</tr>
<tr>
<td>Central — act on descending pain-modulating pathways, inhibit reuptake of serotonin and norepinephrine in CNS, may relieve pain by other receptors as well (eg, adrenergic)</td>
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</tbody>
</table>

GABA = gamma-aminobutyric acid; CNS = central nervous system; TCAs = tricyclic antidepressants.
opioids, with low-dose opiates, and found that the patients were unresponsive to chronic opiate therapy.\textsuperscript{11} Later, well-controlled trials demonstrated that patients with a variety of neuropathic pain disorders would respond to opiate therapy if dosed appropriately. McQuay et al allowed patients to titrate up their opiate doses using patient-controlled analgesia (PCA). With the PCA method, patients were able to and instructed to administer as much of the opioid as necessary to become pain-free, using a syringe of 10 mg/mL morphine attached to a button that would release the drug solution at rates no faster than 0.5 mL/min. In a small, descriptive study of 22 patients using the PCA method, morphine delivered using the PCA method resulted in a “good response” in 5/13 neuropathic pain patients, a moderate response in 6 patients, and poor response in 2. The results showed that neuropathic pain could be responsive to opioid therapy, but the association was not absolute; other factors are involved in determining opioid sensitivity.\textsuperscript{12} Watson et al demonstrated efficacy with sustained-release oxycodone in 2 double-blind studies of more than 30 patients each (with diabetic neuropathy and postherpetic neuralgia). The results showed that numerous measures of pain and function were significantly improved, such as mean daily pain, steady pain, brief pain, total pain, allodynia, and paroxysmal spontaneous pain, with treatment of up to about 40 mg per day sustained-release oxycodone.\textsuperscript{13,14}

Opioids clearly have a powerful central analgesic effect and because they affect several neurotransmitter systems, their side effects are widespread including constipation (cholinergic), orthostatic hypotension (adrenergic), mood changes (serotonergic), itching (histaminergic), and nausea/vomiting and euphoria (dopaminergic). Opioids can also cause blurred vision/visual changes, diplopia, gastrointestinal irritation, decrease lymphocyte function, and affect smooth muscle contraction (leading to, eg, ureteral or biliary spasm). Opioids also have important effects on sexual hormones and can disrupt menstruation.\textsuperscript{15} Opioids offer the benefit of rapid systemic onset, but also undergo significant hepatic first-pass metabolism, so oral doses are usually 1- to 4-fold higher than equivalent parenteral doses. Hepatic metabolism also renders opioids susceptible to effects by metabolic inhibitors such as fluoxetine or cimetidine, as well as metabolic inducers such as barbiturates.\textsuperscript{16} Opioid-related respiratory depression is an important and potentially lethal side effect that should be taken into consideration in patients naïve to opioids, patients with comorbid respiratory disease (eg, chronic obstructive pulmonary disease), and in patients taking other CNS depressants (eg, benzodiazepines).

Table 4 outlines the equianalgesic doses for the most commonly used opioid analgesics (morphine, hydromorphone, oxycodone, methadone, levorphanol, oxymorphone, and meperidine).\textsuperscript{17} Methadone, in particular, may be a useful alternative to other opioids. It has been shown to be effective in treating neuropathic pain in limited, small trials.\textsuperscript{18,19} Titration is an important aspect of methadone use. The recommended titration schedule is to convert from an equianalgesic dose of the previous agent, then wait 5 to 7 days before adjusting the dose. Single adjustments greater than 10% to 15% of the total daily dose are not recommended, until patient response can be assessed. Because methadone requires about 1 week to reach steady state after a dose change, adjustments should not be made at shorter intervals. In the event that patients experience breakthrough pain while transitioning to methadone from another opioid, short-acting opioids can be used for the first several days until the optimal methadone dose is determined. Methadone is metabolized by cytochrome P450 3A4 (CYP3A4) and

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equianalgesic Dose (mg)</th>
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<tr>
<td></td>
<td>Oral*</td>
</tr>
<tr>
<td>Morphine</td>
<td>30</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4 (acute)</td>
</tr>
<tr>
<td></td>
<td>1 (chronic)</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>--</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300</td>
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</tbody>
</table>

\textsuperscript{*}Starting dose should be lower for older adults.
\textsuperscript{†}These are standard parenteral doses for acute pain in adults and also can be used to convert doses for intravenous infusions and repeated small intravenous boluses. For single intravenous boluses, use half the IM dose. Intravenous doses for children >6 months of age = parenteral equianalgesic dose multiplied by weight (kg)/100.

Reproduced with permission from the American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 5th ed. Glenview, Ill: APS; 2003.\textsuperscript{17}
this has been reported to be associated with QRS prolongation. Tables 5A and 5B list other commonly used drugs that may be inhibit or induce CYP3A4 metabolism and thus may increase the risks associated with methadone treatment.

Perhaps one of the most important aspects of opioid management is the risk of misuse or addiction and potential liability of the clinician. Addiction to opioids in the context of pain treatment occurs less frequently than perceived. Highly publicized cases of prescription opioid addiction covered in the popular media have increased this perception. Such media coverage can translate into fear by patients, rendering them resistant to using opioids when the drug might offer significant if not life-changing benefit, and by clinicians, limiting their therapeutic options to patients and thus never achieving the best possible outcomes. Once again, patient and family education is key to dispelling myths and providing factual information. The Web site www.painconnection.org is a place where this information and answers to questions can be found.

For most healthcare practitioners, prescribing opiate analgesics is associated with concerns regarding the inappropriate use by the patient of such medications. It is important to understand the definition of drug addiction and how it is distinguished from physical dependence, tolerance, and “pseudoaddiction” (see Sidebar on next page).20,21 Addiction is defined as a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its manifestations. It is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. Physical dependence is a state of adaptation manifested by drug class-specific withdrawal syndrome. Physical dependence is not a problem as long as the patient avoids rapid cessation of the drug. Physical dependence is not unique to the use of opiates and may occur with use of many other types of medications. Tolerance is a state of adaptation in which the drug’s clinical effect diminishes over time such that increased doses are required to achieve the desired effect. Importantly, tolerance and physical depen-

<table>
<thead>
<tr>
<th>Class/Subclass</th>
<th>Examples</th>
<th>Degree of Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal agents</td>
<td>Cimetidine</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td>Weak-moderate</td>
</tr>
<tr>
<td></td>
<td>Omeprazole</td>
<td>Weak</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Macrolide antibiotics</td>
<td>Strong</td>
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<tr>
<td></td>
<td>Clarithromycin, erythromycin</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Quinolone antibiotics</td>
<td>Weak-moderate</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin, norfloxacin</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole, itraconazole,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fluconazole, clotrimazole,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>miconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antivirals</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Itraconavir, nelfinavir,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ritonavir, saquinavir</td>
<td></td>
</tr>
<tr>
<td>Psychoactive drugs</td>
<td>SSRI Sertraline, paroxetine</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>Strong</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>Nefazodone</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Mirtazepine, norfluoxetine</td>
<td>Weak</td>
</tr>
<tr>
<td>Hormone therapies</td>
<td>Danazol</td>
<td>Strong</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>Calcium-channel blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diltiazem, verapamil</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Grapefruit juice (flavinoids)</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Cannabinoids</td>
<td>Weak</td>
</tr>
</tbody>
</table>

CYP3A4 = cytochrome P450 3A4; SSRI = selective serotonin reuptake inhibitors.

<table>
<thead>
<tr>
<th>Class/Subclass</th>
<th>Examples</th>
<th>Degree of Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Barbiturates</td>
<td>Weak-moderate</td>
</tr>
<tr>
<td></td>
<td>Phenobarbital, primidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rifampicins</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Rifabutin, rifampin</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>St John’s Wort</td>
<td>Strong</td>
</tr>
</tbody>
</table>

CYP3A4 = cytochrome P450 3A4.
Patients with a history of substance abuse should undergo urine drug screening and referral to a substance abuse treatment program if issues of ongoing substance abuse are identified. Negligible levels of the prescribed medication in the serum, forged prescriptions, early refills, lost or stolen medication, and multiple concurrent prescriptions from multiple healthcare providers may signal drug diversion, which would necessitate the involvement of local law enforcement and DEA agents. However, this aberrant behavior may also signal undertreatment, either due to noncompliance or selling the drug on the street. A pilot study showed wide variations among pain specialists on their perception of the most aberrant drug-taking behaviors (however, frankly illegal behavior was the most common worrisome behavior). For the non-pain specialist who encounters aberrant drug-taking behavior, addiction should be considered but not assumed. A treatment agreement, formerly known as a contract, may be useful in establishing an understanding between the patient and the provider. Instead of being viewed as intrusive, these agreements serve to solidify the provider-patient relationship by reviewing the purpose of opioid treatment and emphasizing that the drugs will be stopped if a benefit is not observed or the patient is not compliant with their use as prescribed. As will be discussed later, this latter point is an important principle of care in treating neuropathic pain. An agreement can also be presented as a means of communication with other healthcare providers about refill schedules when the patient’s healthcare provider is not present. A standard treatment agreement can be found at www.painEDU.org (under Tools).

Given the high profile of opioid abuse, and with more physicians and nurse practitioners obtaining Drug Enforcement Agency (DEA) registration numbers to prescribe opioids in their offices, careful documentation is important. Documentation should include brief focused notes generated by the provider on each visit regarding the reason for treatment with opiates and discussion of the terms and compliance with the opioid agreement. Other documentation tools include the results of serum and urine tests for confirmation of the opioid and exclusion of illicit substances.

<table>
<thead>
<tr>
<th>Identifying Aberrant Drug-Taking Behaviors</th>
<th>Definition</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Addiction</strong></td>
<td>A primary, chronic, neurobiologic disease with genetic, psychological, and environmental factors influencing its manifestations</td>
<td>Characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving</td>
</tr>
<tr>
<td><strong>Physical dependence</strong></td>
<td>A state of adaptation manifested by drug class-specific withdrawal syndrome</td>
<td>Not a problem as long as the patient avoids rapid cessation of the drug; not unique to the use of opiates*</td>
</tr>
<tr>
<td><strong>Tolerance</strong></td>
<td>State of adaptation in which the drug’s clinical effect diminishes over time</td>
<td>Increased doses are required to achieve the desired effect*</td>
</tr>
<tr>
<td><strong>Pseudoaddiction</strong></td>
<td>Patients whose drug-seeking behavior (ie, frequent lost or stolen prescriptions, doctor shopping, frequent trips to the emergency department) appears on the surface to be addictive behavior, but is actually an effort to achieve pain relief</td>
<td>Signals undertreatment; can be distinguished from addiction if the drug-taking aberrant behaviors resolve with treatment</td>
</tr>
</tbody>
</table>

*Tolerance and physical dependence alone do not suggest addiction in chronic pain patients taking opioids.
the type of test used. Von Seggern et al elegantly reported a case study of false-negative results with an immunoassay for oxycodone testing. Through this experience, they realized that there are several substance testing options, which vary based on expense, sensitivity, and specificity. If the healthcare provider is going to pursue urine drug screening, 3 factors are required: honest communication with the patient regarding the goals of opioid therapy and the importance of laboratory testing for monitoring, open communication with the laboratory regarding the clinical questions being asked by the practitioner and the type of test the laboratory will perform, and an understanding of the drug testing procedures.

Urine drug screening is commonly used in the management of pain. It helps healthcare providers determine that the drug being prescribed is present in the urine and that no illicit drugs are present. Although not perfect, it does help assure that the drugs are not being diverted or traded for illicit substances. Urine toxicology does not determine doses of drugs, however, and it is still possible for patients to sell portions of their prescription and have a “normal” urine toxicology screen.

**TRAMADOL**

Tramadol acts as an analgesic by mu opioid receptor agonism and weak inhibition of descending serotonin and norepinephrine systems (Figure 2). It is rapidly absorbed, not affected by food intake, and metabolized in the liver to an active metabolite and excreted via renal elimination (30% unchanged drug). It has a relatively short half-life (6-7 hours) but it may accumulate in the elderly, and in those with renal insufficiency and cirrhosis. Tramadol is contraindicated in those with previous tramadol hypersensitivity, monoamine oxidase inhibitor (MAOI) use, and acute alcohol or opioid intoxication. Important warnings with tramadol use are increased seizure risks with doses above 400 mg per day, concomitant use of selective serotonin reuptake inhibitors (SSRIs), TCAs, opioids, MAOIs, neuroleptics, or other drugs that reduce seizure threshold, in patients with epilepsy or history of seizures, and with administration of naloxone due to overdose. Clearly, if polypharmacy is to be used for treating neuropathic pain, careful assessment of drug-drug interactions with tramadol is required. Tramadol has known drug interactions with carbamazepine, the first anticonvulsant to be approved by the FDA for neuropathic pain in the treatment of trigeminal neuralgia.

Tramadol has a very low abuse potential, with less than 0.75 abuse cases per 100 000 patients. It may induce psychic and physical dependence with withdrawal symptoms if it is discontinued abruptly. Ninety-seven percent of cases of abuse or physical dependence to tramadol were in patients with histories of alcohol and drug abuse. Tramadol, as with analgesic opioids, can probably be used safely in appropriate patients.

**Choosing a First-Line Medication**

The safety profiles for each of the recommended therapies vary widely and will thus help to determine which medication would be a useful first-line agent. Table 6 summarizes safety issues with the first-line agents, while Table 7 summarizes the pros and cons of each drug/class. It is up to the clinician to make a careful assessment of the best first-line treatment based on the presenting symptoms, the patient’s emotional and functional status, concomitant medications, comorbidities, and the provider-patient relationship.

**Choosing a Second-line Medication**

The 5 first-line therapies from the guidelines were chosen based on a careful analysis of the literature and the availability of randomized controlled trials. However, pharmacotherapy for neuropathic pain involves both the art and science of medicine; partial relief is the expected outcome in many cases of neuropathic pain. It is important to establish goals of therapy at the outset. As with other disease states, there are different ways of achieving a positive outcome, many of which may not be found in the published literature but are based on clinical experience.

Gabapentin has the most clinical experience among the anticonvulsants in treating neuropathic pain. However, as discussed in the guidelines, lamotrigine and carbamazepine have also been studied with several types of neuropathic pain and the limited results are encouraging. Lamotrigine has been shown to be effective for treating HIV sensory neuropathy, painful diabetic neuropathy, central poststroke pain, and perhaps a subgroup of patients with incomplete spinal cord lesions. The required slow and careful titration and risk of severe rash and Stevens-Johnson syndrome prohibit it from being a first-line therapy, but it can and should be tried in patients who do not respond to or are unable to take gabapentin.
Carbamazepine has a formal indication for trigeminal neuralgia and may be useful for peripheral diabetic neuropathy, but the results are not conclusive. Topiramate has been shown to be particularly effective for migraine headache treatment, but the data for other forms of neuropathic pain are very limited. Only one very small pilot study (n = 3) offered inconclusive results for the treatment of trigeminal neuralgia, but the limited positive effect warrants larger trials. Other anticonvulsants such as levetiracetam, oxcarbazepine, tiagabine, and zonisamide have limited if any published data; however, these drugs share many of the mechanistic properties of the proven antiepileptic agents. One of the newer drugs may be considered if gabapentin is not effective or well tolerated. Topiramate and zonisamide, in particular, may be useful for patients who are overweight as these drugs have anorexic effects.

Other commercially available topical analgesics including capsicain and the eutectic mixture of 2.5% lidocaine/2.5% prilocaine are often used to treat neuropathic pain when first-line agents fail to produce sufficient analgesia; however, none have randomized trials showing efficacy. Compounding pharmacies can custom make gels or creams containing various medications either alone or in combination, including anticonvulsants, local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, clonidine, ketamine, and TCAs. These preparations are active with the skin, soft tissues, and, potentially, superficial branches of peripheral nerves, and they may interrupt the pain cycle by diminishing ectopic discharge in the PNS and reduce CNS excitability. They appear to pose a lower risk of side effects due to the low systemic absorption and lower serum levels. The clinician is subject to the potential variability in pharmacy compound preparations and the lack of data from controlled trials. The clinician may pursue use of these agents in patients who have not responded to other commercially available drugs, whose concomitant medications prohibit many of the first-line drugs, or who wish to pursue non-oral drug treatments for their pain.

The first generation of non-TCA antidepressants focused on inhibition of SSRIs. They have not been extensively studied in neuropathic pain, but the limited reports in the published literature indicate that their

### Table 6. Safety Issues with First-Line Neuropathic Pain Treatments

<table>
<thead>
<tr>
<th></th>
<th>GI</th>
<th>Renal</th>
<th>Cardiac</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Lidocaine patch 5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GI = gastrointestinal; CNS = central nervous system; TCAs = tricyclic antidepressants.

### Table 7. Pros and Cons of First-Line Neuropathic Pain Treatments

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Well tolerated; virtually no drug interactions</td>
<td>May cause sedation (caution with tasks requiring alertness); cost</td>
<td>Indicated for use in PHN</td>
</tr>
<tr>
<td>Lidocaine patch 5%</td>
<td>Easy to administer; may be useful in those afraid or unwilling to take pills; no systemic side effects or drug interactions, targeted therapy</td>
<td>Possible reaction to patch; some patients may not feel comfortable with patch technology; cost</td>
<td>Indicated for use in PHN</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Rapid onset; effective analgesia; systemic action</td>
<td>Risk of activating addiction, of diversion and of abuse in some; many drug interactions</td>
<td>Pain with peripheral and central mechanisms</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Rapid onset; multiple mechanisms of action</td>
<td>Drug interactions; increased seizure risk</td>
<td>Those unable to tolerate gabapentin or anticonvulsants</td>
</tr>
<tr>
<td>TCAs</td>
<td>Multiple mechanisms of action; improvements in insomnia, anxiety, and depression</td>
<td>Risk of suicide; potentially serious side effects; highly metabolized</td>
<td>Concomitant depression; only applies to certain TCAs</td>
</tr>
</tbody>
</table>

PHN = postherpetic neuralgia; TCAs = tricyclic antidepressants.
analgesic effect for neuropathic pain conditions is at best modest, and most often not evident. The newest antidepressants inhibit uptake of serotonin and norepinephrine (SNRIs) in the CNS, yet avoid many of the problematic side effects with TCAs including dry mouth, sedation, constipation, weight gain, cardiotoxicity, and risk of overdose. SNRIs include bupropion, escitalopram, and venlafaxine. Bupropion lacks the sexual side effects of the SSRIs and has shown efficacy in one randomized, neuropathic pain trial. However, more extensive and thorough study of these medications for neuropathic pain conditions is needed before they can be formally recommended. For now, it is up to the physician’s discretion to use these as second- or third-line medications on an empiric basis for treating neuropathic pain.

PRINCIPLES OF PHARMACOLOGIC MANAGEMENT OF NEUROPATHIC PAIN

Realistic treatment goals are an essential part of neuropathic pain management. These should be discussed at the very beginning of pain treatment and reassessed frequently with the patient. As discussed earlier, complete remission of pain is rare, so both patient and provider must focus on realistic pain relief, improvement in patient functioning, and providing hope and encouragement of a better life through pain management. As such, there are several principles of pain management that must be borne in mind by the treating healthcare team:

1. Regardless of the published studies, all drug treatment should be based on the strongest available evidence that is shown in the first-line drugs; however, as with any complex disease, achieving optimal drug treatment is often trial and error. Trials must be systematic so that firm conclusions can be reached as to whether the patient is benefiting from the treatment.
2. Polypharmacy means that partial relief with one agent represents a treatment success, rather than a treatment failure. Such medications should be kept as part of the treatment regimens; other medications can then be systematically added to produce further pain relief.
3. The choice of subsequent medications generally involves choosing medications with complementary or synergistic mechanisms of action. Combining drugs from different classes may address multiple underlying mechanisms of pain.
4. Side effects may be the major reason for failure of therapeutic trials of analgesics. Start with low doses, escalate slowly, and aggressively identify and manage any side effects that arise. Patients must be warned in advance that this is not an overnight process, and that most side effects will either subside on their own or can be controlled.
5. The need to coprescribe medications, alter timing of medications, or switch to sustained-release preparations to manage side effects produced by the primary analgesic treatment is common. Patients need to be made aware of this.
6. Medications that do not work should be tapered and withdrawn. Patients may feel they have a “right” to a certain pain medication, which is most frequently seen in opioid prescriptions, but medications that are not working only complicate treatment plans and can be detrimental to achieving the best possible outcome. Not uncommonly, benefits from a particular drug are not acknowledged until tapering is attempted.
7. Do not underestimate the value of information provided by family members; they are an indispensable source. Balancing pain relief and side effects is tricky and the information provided by the family can help the clinician make treatment decisions earlier.

PSYCHOTHERAPIES

Long-term, intense psychotherapy is clearly beyond the scope of the healthcare providers who treat pain patients. Healthcare providers should seek support from psychosocial providers when the scope or the time required is beyond their capabilities. All practitioner encounters, however, should be “psychotherapeutic” for the patient, in the sense of providing information, validation, and realistic hope in a supportive, gentle, and kind environment. This healing interaction is often the most cherished part of an office visit by patients and serves to neutralize the remnants of conditioned fears often left over from previous negative encounters with the healthcare system. Cognitive-behavioral therapy (CBT) is used to help patients realize the relationship between their thoughts, their emotions, their perception of pain,
and their pain behaviors in various contexts. CBT therapy focuses on changing patients’ thought patterns to have realistic yet positive expectations for outcomes and to teach coping skills. Family therapy focuses on the family unit and the dynamics involved in determining treatment success or failure. Group therapy and support groups are important for addressing the isolation with neuropathic pain. These should be led by competent lay persons or a mental health professional in order to keep the discussions focused on changing thought patterns and providing realistic expectations. Patient-led groups should be carefully researched by the clinician. Advocacy groups that distract patients’ focus from improved function to disability and dissatisfaction with treatments/providers may perpetuate disability and psychosocial dysfunction. Clinicians should also review the validity of any information patients are exposed to on the Internet and provide reliable sources when necessary. Spiritual or religious support can be very helpful, depending on the role faith plays in the patients’ lives. This can be a useful avenue to explore for coping skills and support.22

**INTERVENTIONAL TREATMENTS**

Although interventional treatments are the domain of pain specialists, it is important for all healthcare providers to be aware of the technologies available, such as nerve blocks, spinal cord stimulation, and intrathecal drug delivery.

Neural blockade is used for both diagnosis and treatment of neuropathic pain. For diagnostic purposes, neural blockade can help to confirm whether a particular nerve (or the nerve distribution) is the source of pain. However, diagnosis with neural blockade is not foolproof, possibly affected by placebo effect, spread of drug to surrounding areas, any systemic effect of the local anesthetic, and of course the technical proficiency of the drug administrator.42,43 For therapeutic purposes, different types of nerve blocks may be helpful, especially if used early in the course of the neuropathic pain process. Nerve blocks used in treating neuropathic pain target either local blockade of the peripheral nerve or blockade of the sympathetic chain. Ironically, although nerve blocks are almost uniformly recommended in textbooks, there are almost no outcomes data to support their use. Also, the odds of long-term relief are low, but a small percentage benefit long term from this type of treatment.42

Spinal cord stimulation and peripheral nerve stimulation augment descending pain inhibitory pathways through stimulation of the dorsal column of the spinal cord or peripheral nerves, respectively. These modalities may be particularly helpful when other more conservative therapies have failed to provide sufficient relief. Patients typically undergo a 7-day trial period followed by the implantation of a pulse generator if the trial is successful. Spinal cord stimulation has emerged as a successful treatment option in patients with neuropathic pain due to failed low back surgery syndrome, complex regional pain syndrome, and post-herpetic neuralgia.44

Intrathecal drug delivery devices can also be implanted to infuse high-dose opioids and other nonopioid analgesic medications directly into the cerebrospinal fluid when systemic therapy is effective but not well tolerated. Drugs that have been tested for the treatment of neuropathic pain when delivered intrathecally include morphine, clonidine, sufentanil, ziconotide, and adenosine. Specific recent studies include a comparison of intrathecal versus intravenous delivery of adenosine for 7 patients with chronic neuropathic pain and intrathecal ziconotide for the treatment of refractory pain in patients with cancer or AIDS.45,46 Adenosine delivered intrathecally caused blockade in 5 of 7 patients for 6 hours, reducing alldynia and pain from stimulation of the allodynic area; intravenous adenosine was ineffective.45 In a double-blind, randomized, placebo-controlled study, ziconotide or placebo were evaluated in 111 patients with pain and cancer or AIDS. Moderate to complete pain relief was observed in 53% of the treatment group, compared with 17.5% of the placebo group. Five patients in the treatment group achieved complete pain relief.46 These examples of robust analgesic results with intrathecal delivery, even in complex, heterogeneous, treatment-refractory patients, support its use in the treatment of challenging cases of neuropathic pain.

Epidural steroids are used to treat mononeuropathies, neuromas, and certain radiculopathies. They are perhaps the most common interventional therapy for neuropathic pain. As with neural blockade, epidural steroids are thought to stop ectopic discharge, in this case from neuromas. This is a widely accepted treatment for pain resulting from nerve compression, despite the paucity of well-controlled studies. In fact, many orthopedic and neurosurgeons refer patients for this procedure as a first step to avoiding surgery.47
COMPLEMENTARY STRATEGIES

TENS and acupuncture directly stimulate peripheral nerves, altering pain sensations. TENS involves applying low-voltage current to large nerve fibers. As with spinal cord stimulation, patients receiving TENS report a buzzing or tingling sensation that replaces painful sensations. Acupuncture has also been used but with questionable long-term benefit. In 1997, the National Institutes of Health issued a consensus statement on acupuncture:

“...There are other situations such as addiction, stroke rehabilitation, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis, low back pain, carpal tunnel syndrome, and asthma for which acupuncture may be useful as an adjunct treatment or an acceptable alternative or be included in a comprehensive management program. Further research is likely to uncover additional areas where acupuncture interventions will be useful.

Findings from basic research have begun to elucidate the mechanisms of action of acupuncture, including the release of opioids and other peptides in the central nervous system and the periphery and changes in neuroendocrine function. Although much needs to be accomplished, the emergence of plausible mechanisms for the therapeutic effects of acupuncture is encouraging.

The introduction of acupuncture into the choice of treatment modalities readily available to the public is in its early stages. Issues of training, licensure, and reimbursement remain to be clarified. There is sufficient evidence, however, of its potential value to conventional medicine to encourage further studies.

There is sufficient evidence of acupuncture’s value to expand its use into conventional medicine and to encourage further studies of its physiology and clinical value.”

FOLLOW-UP

As with other chronic conditions commonly treated in primary care settings (eg, hypertension, diabetes), regular follow-up is essential with any drug trial to ascertain if the treatment is working and whether it is being tolerated. Just as a diabetic patient reports blood sugar results after starting a new drug, the neuropathic pain patient should follow up to assess pain and function with each change in treatment. As with any other disease, all aspects of therapy must be addressed early (emotional, social support, functional, and medical), to maximize patient outcomes.

Reassessing patient beliefs about their treatment is also important, as they may lose hope with successive treatment failures, or may draw false hope from information gathered by well-meaning friends and family or on the Internet. Too often, medical misinformation in the lay press is easily dismissed by the healthcare providers, making the patient feel stupid or embarrassed, or leaving him/her with the feeling that they or their pain are not taken seriously. These reactions will often prevent the patient from sharing their experiences with alternative medicines and other complementary medical approaches with his/her doctors and nurses, thus undermining the provider-patient relationship and potentially complicating the care being delivered by the healthcare team. Once again, referring the patient to a reliable, peer-reviewed, noncommercial Web site will help dispel myths and answer questions, as well as help the patient ask more informed questions when they visit the doctor.

A more successful way to approach this situation is to acknowledge that medicine is an inexact science, the placebo response can be substantial, and there are cases of inexplicable remission of symptoms and disease. For the patient, consider whether the alternative or complementary treatment they are trying is dangerous or expensive. If the answer is no to both, perhaps cautious encouragement is the best strategy, because it allows patients to experiment with a treatment in which they hold some belief of efficacy, it keeps the provider aware of new therapies, and it allows the practice of more traditional medicine while maintaining the often fragile balance that patients with chronic pain achieve in living with their condition.

A COMPREHENSIVE APPROACH

The consensus guidelines illustrate, and clinical experience confirms, that no single agent is likely to provide complete benefit for a patient with neuropathic pain. Thus, the clinician must choose the appropriate therapies based on the signs and symptoms of neuropathic pain and the individual patient. There are few, if any, data that formally examine the rationality of polypharmacy or the role of truly integrated care in neuropathic pain management. Nonetheless, an integrated approach offers the highest chance of treatment success. A recent open-label, 2-week study showed that a combination of lidocaine patch 5% with gabapentin as rational therapy resulted
in significant improvement in quality of life in patients with postherpetic neuralgia, painful diabetic neuralgia, and low back pain.49

Figure 3 is a proposed algorithm to guide the clinician through management of neuropathic pain. Typically, by the time a patient is seeing the clinician for pain, NSAIDs, physical approaches, and alternative therapies have been tried unsuccessfully. The primary care doctor should know that there is limited rationale for using an NSAID for neuropathic pain. The next step is to offer one of the first-line drugs, with possible topical therapy to address specific problem areas or indications (eg, postherpetic neuralgia). First-line drugs should be chosen with special attention to efficacy, safety, cost, and ease of use of the agent. Neuropathic pain may have an underlying cause that can be treated (eg, diabetic neuropathy). Even with adequate pain treatment, the underlying cause needs to be addressed and continuously re-evaluated. Patients should also be screened for any underlying psychological complicating factors, such as depression and/or anxiety, as they may impede treatment success. If the pain becomes chronic and intolerable, alternative approaches should be considered, such as long-term opioid therapy in appropriate patients, TENS, or interventional approaches. Psychological/family therapy is critical at this stage.

CONCLUSION

For neuropathic pain, as with many other common chronic disorders, there are established treatments and useful algorithms for comprehensive management. For the non-pain specialist, neuropathic pain can be treated in the same rational manner as diabetes or hypertension, given the appropriate diagnostic tools and therapeutic strategies. The ultimate goal of neuropathic pain management is to reduce pain and disability and improve quality of life.

REFERENCES


Figure 3. A Proposed Algorithm for Integrated Treatment of Neuropathic Pain

NMDA = N-methyl-D-aspartate; IT = intrathecal; TENS = transcutaneous electrical nerve stimulation; IV = intravenous; TCAs = tricyclic antidepressants. This “algorithm” is more a metaphor for typical approaches to neuropathic pain management. It is often appropriate to start with more conservative therapies (eg, NSAIDs, nonpharmacologic approaches) and continue up the “ladder.” However, considerable clinical judgement is used in managing any neuropathic pain patient, due to the complexity of neuropathic pain etiology and confounding factors on pain intensity and responsiveness to particular therapies. For example, there are certain cases in which epidural steroids might be considered a first- or second-line approach. The overarching concept, however, is to start with conservative therapies, and proceed to more complex or sensitive approaches if first-line treatments are ineffective or only partially effective.


