Peripheral Diabetic Neuropathy

Cost effectiveness should be an important consideration

By Whitney Cobb, PA-C, and Laura Lee, MHE, PA-C

Learning Objectives

1. Discuss the presentation, incidence and etiology of peripheral diabetic neuropathy.
2. Describe how to develop treatment regimens based on a holistic approach.
3. Explain the risks associated with not treating peripheral diabetic neuropathy.
4. Discuss treatment guidelines for peripheral diabetic neuropathy.

Peripheral neuropathy is a complication of diabetes mellitus characterized by a loss of sensation in the extremities, typically in a stocking-and-glove pattern. Recent reports suggest that peripheral neuropathy affects 16% of patients with diabetes, but 12.5% of them don’t report the symptoms. Untreated peripheral diabetic neuropathy (PDN) can be disabling, greatly affecting quality of life with specific effects on functionality, mood and sleep patterns.

The American Society of Pain Educators released a consensus guideline on the treatment of peripheral neuropathy in 2006, but it does not provide guidance about tier 1 agents, which are usually generic drugs with lower out-of-pocket costs to patients. Although the American Academy of Neurology (AAN) published treatment recommendations in 2011, the document incorporates medication cost as an independent factor rather than a priority in treatment decision making. To enhance adherence to therapy, factors such as affordability, comorbidities, treatment goals, current medications and side effect profile should be considered. These factors independently contribute to the suitability of a regimen for a particular patient.

Diagnosis

Multiple criteria and recommendations have been made about the screening and diagnosis of peripheral diabetic neuropathy, but no consensus has emerged. Current clinical modalities for screening include monofilament, vibratory and ankle reflex testing. According to Jayaprakash et al, the current gold standard for the diagnosis of peripheral neuropathy is vibration perception threshold (VPT). VPT is measured using a neurothesiometer at the hallux; a result of 25 volts or higher is classified as abnormal.

The indicator test can also be used to test for neuropathy. In this test, blue plaster is applied to the soles of the feet, below the first and second toes. Color change of the plaster shows the results. If the plaster turns pink, no nerve damage is present. If it remains blue or partially changes to pink after 600 seconds, nerve damage is present.

Both the indicator test and the VPT are sensitive for neuropathy, but one study...
found that sensitivity is higher with the indicator test (97.8% vs. 78.9%). Specificity is higher with the VPT test (85.9% vs. 67.2%). This study concluded that the indicator test would be a good additional diagnostic tool for detecting neuropathy.

**Patient Presentation**
The patient presentation associated with diabetic neuropathy is similar to the symptoms and historical findings of type 2 diabetes. The hyperglycemic component is responsible for complications associated with diabetes, such as diabetic neuropathy. In type 2 diabetes, this component occurs insidiously. Therefore, it is not unusual for patients to develop peripheral neuropathy soon after being diagnosed with diabetes. Symptoms specific to diabetic peripheral neuropathy can be identified by pattern of sensation loss, characteristics of pain and timing of pain (Table 1).

Physical examination may reveal bilateral, symmetrical sensory involvement associated with dulled perceptions of vibration, pain and temperature. Patients may experience pain described as tingling, burning or superficial aching with nighttime exacerbations. The exam may also reveal allodynia, hyperalgesia and paresthesia. Denervation of the small muscles of the foot result in clawing of the toes and anterior displacement of the submetatarsal fat pads. Joint and connective tissues alter the biomechanics of the foot, leading to increased plantar pressure. Other physical findings include lacerations, diminished dorsalis pedis pulses and an ulcer at the point of increased pressure.

**Treatment**
A staggering percentage (39%) of diabetic peripheral neuropathy is untreated. Although pharmacologic and nonpharmacologic agents are available to treat peripheral neuropathy, ongoing management is a concern that stymies treatment initiation. Treatment should not only focus on therapeutic effectiveness; it should also reflect accessibility and affordability. Accessibility is influenced by health plans in the form of prior approval requirements. Prior approvals are designed to decrease...
the number of expensive medications dispensed, thus decreasing costs to healthcare plans.8 If the medication requires a prior approval, it may be accepted or denied by the insurance company. If denied, an alternative mediation will be dispensed at lower cost to healthcare plans.8 Without a prior approval in place, the more costly medication is prescribed without consideration of a less expensive agent.8

Table 2 provides an overview of pharmacologic treatment choices for peripheral diabetic neuropathy.9

### Anticonvulsants
Several anticonvulsants are recommended for the treatment of peripheral diabetic neuropathy. The two agents compared in this article display the fewest side effects.2 The AAN guidelines recommend pregabalin as a first-line agent due to its effectiveness in pain reduction, its ability to improve quality of life and its ability to reduce sleep interference.2,3 This recommendation is supported by Level A evidence. Level B evidence supports gabapentin as an alternative option.2 While pregabalin is superior in terms of pharmacokinetics, gabapentin is superior in terms of affordability.

The potential for cost savings with pregabalin is low due to small market share and lack of a significant monetary difference between pregabalin and commonly substituted agents.2 Pregabalin may cause sedation, confusion, constipation, headache and/or weight gain.1,3 Common side effects of gabapentin are dizziness, somnolence, dry mouth and fatigue.3

### Antidepressants
Antidepressants are also recommended based on Level B evidence for the treatment of peripheral diabetic neuropathy.2 Amitriptyline, a tricyclic antidepressant (TCA), is recommended as a first-line agent.1,3 This drug is effective and affordable, and it is available through some low-cost generic programs. Amitriptyline may be combined with pregabalin for an increased response, but it should not be combined with duloxetine because this combination can increase the toxic effects of amitriptyline and lead to serotonin syndrome.1 Common side effects experienced with this agent are dry mouth and somnolence.1,3

Venlafaxine and duloxetine are serotonin norepinephrine reuptake inhibitors (SNRIs). Duloxetine has a rapid onset and provides sustained pain improvement specifically at night, producing substantial symptom improvement within a week of use. Common side effects of duloxetine are nausea, somnolence, dizziness, decreased appetite and dry mouth.3 Venlafaxine can be combined with pregabalin for an increased response.2 Common side effects of venlafaxine include nausea and somnolence.3

Due to lack of sufficient head-to-head comparison studies, one antidepressant cannot be recommended over another for the treatment of PDN.2 As a result, consider selecting these agents based on cost and side effects. Some evidence shows that the SNRIs are better tolerated than TCAs and have fewer drug interactions.1

### Opioids and Opioid-Like Medications
Opioids have been suggested for the treatment of peripheral diabetic neuropathy, but long-term use can lead to tolerance and potential dependence.2,3 Opioid use can also lead to novel pain syndrome and should be reserved for patients who do not respond to other therapies.2

Dextromethorphan, morphine sulfate, oxycodone and tramadol can reduce peripheral neuropathy pain by 27%.2 Tramadol should be avoided in patients with epilepsy, since it may lower the seizure threshold. However, compared with the other opioids, it has the lowest risk of dependence.2,3

### Topical Agents
The AAN uses an evidence classification system that provides four tiers to rate five areas: therapeutic, diagnostic, prognostic, screening and causation. Class I indicates strong evidence, and Class IV indicates weak evidence. The AAN also used four levels of recommendation (A, B, C and U). A is considered effective, B is probably effective, C is possibly effective, and U means that evidence is inadequate or conflicting.10

Levels of recommendation can be translated to class. Level A requires two consistent Class I studies, and B requires one Class I study or two consistent Class II studies. C requires one Class II study or two consistent Class II studies. Level U is for studies that do not meet criteria for Class I through III. Class I evidence is based on a randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent. Class II evidence is based on a randomized, controlled clinical trial with masked or objective outcome that lacks one of the criteria in Class I. Class III evidence reflects all other controlled trials in a representative population, in which outcome is independently assessed or independently derived by objective outcome measurement.10

According to the AAN, Class I and Class II evidence support the use of capsaicin cream in the treatment of PDN.1,2 Capsaicin can produce notable side effects such as burning pain upon contact with warm water or hot weather.2 Class III evidence suggests that lidocaine cream improves pain scores and may be used in the treatment of PDN.2

### Combination Approaches
Treating pain associated with PDN can be challenging, since some patients may not experience a response with a single agent.1 In these instances, agents should be combined to augment the effects of individual agents.1,11 Data support the addition of topical and nonpharmacologic agents to any of the classes of agents
recommended to treat PDN at any point of the treatment course. An alternative method of combination approaches is to adjunctively use an agent from a different class. An example of this is the use of gabapentin with morphine sulfate, which results in an additive effect to increase the absorption and decrease the clearance of gabapentin. Although combination approaches may be required, experts recommend exhausting monotherapy first due to the complexity of the agents used to treat PDN. In patients with comorbidities, review medication lists because the following agents may interact with PDN therapies: statins, beta blockers, sulfonylureas, levethoxyxine, warfarin and loop diuretics.

Risk of Nontreatment
If left untreated, peripheral neuropathy can lead to substantial complications, including lower extremity amputation. Lower extremity amputations in patients with diabetes are often necessary secondary to peripheral vascular disease, peripheral neuropathy or chronic foot ulcers. Diabetes mellitus accounts for more than 60% of lower extremity amputations in the United States. Suboptimal glycemic control is associated with increased risk for infection, impaired wound healing and long-term diabetes complications such as neuropathy and peripheral vascular disease. These complications, as well as risk factors such as hypertension, high cholesterol, cigarette smoking, male gender and increasing age, raise the risk for lower extremity amputations in this population.

Proper management of chronic pain is a difficult task. More than 100 million Americans are affected by chronic pain, 50% are undertreated, and 25% to 39% are not treated at all. For patients who experience chronic pain refractory to nonopioid treatment, opioids may be considered. Prescribing opioids to alleviate pain resulting from chronic conditions may lead to severe adverse reactions, tolerance, dependence and death. However, the risks of not treating PDN may include depression and disruption of daily life activities and overall quality of life. On the other hand, not treating pain costs an estimated $635 billion each year in lost productivity and medical treatment.

**Recommendations**

Two sets of treatment guidelines for peripheral neuropathy have been published, one in 2011 by the American Academy of Neurology and one in 2006 by the American Society of Pain Educators in conjunction with the American Academy of Family Practice.

The AAN guideline on neuropathy is based on extensive evidence-based medicine reviews, which recommend agents that decrease pain and improve quality of life. However, these guidelines fail to consider affordability as a main concern. In clinical practice, the AAN recommendations offer a variety of agents that are supported by levels of evidence. In contrast, the guideline recommended by the American Society of Pain Educators in conjunction with American Academy of Family Practice provides a stepwise approach to treatment that reflects a more holistic approach. This guideline provides clear first- and second-line treatment options that includes consideration of side effects, costs and drug interactions. These are useful for NPs and PAs who are unfamiliar with this disease process and its complex management requirements.

References

15. Institute of Medicine. Relieving pain in America:

Table 2

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PA = prior authorization required by some insurance companies
Tier 1, low copay; Tier 2, moderate copay; Tier 3, high copay
2 discounts available at some pharmacies
3 differing price based on dosage
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Questions

1. A 45-year-old black man with known diabetes mellitus presents with numbness and tingling in his feet. His HbA1c is 9%. You suspect peripheral neuropathy. Which test is the current gold standard and will most likely support your diagnosis?
   a. Neuropad
   b. MRI
   c. Vibration perception test
   d. Needle EMG

2. Which of the following classes of medications is used in the treatment of diabetic neuropathy?
   a. Anticonvulsants
   b. Anesthetics
   c. Benzodiazepines
   d. NSAIDs

3. A 33-year-old man with a known history of opioid abuse and past medical history significant for diabetes mellitus and diabetic neuropathy presents to your office and reports foot pain that he ranks 7/10. This patient is a self-pay. Which treatment would be most appropriate?
   a. Dextromethorphan
   b. Lidocaine, topical
   c. Pregabalin
   d. Amitriptyline

4. A patient presents to your office complaining of a burning sensation when stepping out into the sun, which he correlates to the use of medicine X, prescribed to treat his PDN. Medicine X is most likely...
   a. Capsaicin cream
   b. Lidoderm patch
   c. Bengay cream
   d. TENS

5. Which one of the following agents approved to treat PDN requires a prior approval?
   a. Amitriptyline
   b. Pregabalin
   c. Gabapentin
   d. Dextromethorphan

6. Which treatment option is recommended in conjunction with any of the regimens at any point during the treatment course?
   a. Antidepressants
   b. Anticonvulsants
   c. Topical agents
   d. Opioids

7. What percentage of people with diabetic neuropathy goes untreated every year?
   a. 50%
   b. 39%
   c. 19%
   d. 10%

8. What is the most common cause of nontraumatic lower extremity amputation in this country?
   a. Gangrene
   b. Peripheral vascular disease
   c. Accidents
   d. Diabetes mellitus

9. A 32-year-old man with a diagnosis of diabetic neuropathy presents to your office complaining of unbearable pain in his right lower extremity. You discover he has recently completed a drug rehab program and lives in a group home. What medication should you prescribe in addition to amitriptyline?
   a. Oxycodone
   b. Ibuprofen
   c. Capsaicin cream
   d. Duloxetine

10. Your patient is taking amitriptyline for peripheral neuropathy and you are considering adding an agent due to insufficient pain relief. What medication should you NOT consider due to potential side effects between classes?
    a. Venlafaxine
    b. Oxycodone
    c. Pregabalin
    d. Lidoderm 5% patch

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Evaluation

1. The educational objectives were achieved.
   a. strongly disagree
   b. disagree
   c. neutral
   d. agree
   e. strongly agree

2. Based on what you learned in this article, will you make changes in your practice?
   a. yes
   b. no
   If yes, please describe the changes you intend to make: ________________________________

   What barriers to change do you anticipate? ________________________________

   What strategies or mechanisms will you apply to overcome these barriers? ________________________________

   3. The information in the article was fair, balanced, free of commercial bias and supported by scientific evidence.
   a. yes
   b. no
   If no, describe the nature of the issue: ________________________________

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