Understanding and Managing Neuropathy: Advances in Diagnosis and Treatment—Part 2

PN's complex challenges have led to myriad new studies and potential new solutions.

BY JEAN CHEN-VITULLI, DPM, MS AND ANASTASIOS MANESSIS, MD, FACE, ECNU, ABOM

Objectives

1) Early diagnosis of neuropathy will help save limbs from ulcers and potential complications.

2) Social determinants of health are a risk factor for diabetes neuropathy.

3) According to the American Diabetes Association, individuals with Type I diabetes mellitus for five years or longer, and those with Type II diabetes mellitus should be assessed for diabetes neuropathy annually.

4) The most common causes of peripheral neuropathy include diabetes, metabolic, traumatic, compressive, infection, toxic chemicals, and alcohol.

5) Clinicians should be aware of conditions that mimic polyneuropathy.

6) Symptoms of polyneuropathy can be categorized as sensory, motor, or autonomic.

7) A thorough history and physical exam are warranted when peripheral neuropathy is suspected.

8) When initial laboratory testing, history, and physical examination findings are unrevealing, referral to a neurologist should be considered, especially when the symptoms are rapidly progressing.

9) Intensive treatment of hyperglycemia in patients with T1DM leads to a lower incidence of neuropathy, whereas it has a minimal effect on preventing neuropathy in patients with T2DM.

10) Nerve conduction study remains the method of choice for detecting large fiber neuropathy in people with diabetes. A gold standard for the detection of small nerve neuropathy has yet to be internationally accepted.

Welcome to Podiatry Management's CME Instructional program. Podiatry Management Magazine is approved by the Council on Podiatric Medical Education as a provider of continuing education in podiatric medicine. Podiatry Management Magazine has approved this activity for a maximum of 1.5 continuing education contact hours. This CME activity is free from commercial bias and is under the overall management of Podiatry Management Magazine.

You may enroll: 1) on a per issue basis (at $35.00 per topic) or 2) per year, for the special rate of $299 (you save $51). You may submit the answer sheet, along with the other information requested, via mail, fax, or phone. You can also take this and other exams on the Internet at podiatrym.com/cme.

If you correctly answer seventy (70%) of the questions correctly, you will receive a certificate attesting to your earned credits. You will also receive a record of any incorrectly answered questions. If you score less than 70%, you can retake the test at no additional cost. A list of states currently honoring CPME approved credits is listed on pg. 100. Other than those entities currently accepting CPME-approved credit, Podiatry Management cannot guarantee that these CME credits will be acceptable by any state licensing agency, hospital, managed care organization or other entity. PM will, however, use its best efforts to ensure the widest acceptance of this program possible.

This instructional CME program is designed to supplement, NOT replace, existing CME seminars.** The goal of this program is to advance the knowledge of practicing podiatrists. We will endeavor to publish high quality manuscripts by noted authors and researchers. If you have any questions or comments about this program, you can write or call us at:* ***516-521-4474 or e-mail us at bblock@podiatrym.com.

*Following this article, an answer sheet and full set of instructions are provided (pg. 100).—**Editor***

Part 1 of this article (Nov./Dec. 25) discussed the prevalence and identification of peripheral neuropathy (PN), along with a thorough examination of its many causes and symptoms. The article also offered insights into how to address the condition with patients, including history taking, making decisions about testing, and when to refer patients to specialists. In part 2 (the present article) the author deals with the many possible treatments for PN and DPN, takes a look at emerging trials, and presents a detailed case study of a patient who presented to Endocrine Associates of West Village (NY) in 2024.

Continued on page 94

Neuropathy (from page 93)

Treatment

Patients with diabetes mellitus should be monitored for adherence to treatment with nutritional and lifestyle changes.[7] Proper foot hygiene, appropriate footwear, weight loss, physical therapy and gait training can help improve symptoms.[19] Intensive glycemic control reduces DPN incidence in T1D 78%[23]; in T2D 59%.[23] Aerobic and resistance exercise can prevent and reverse DPN.[23] The Diabetes Prevention Program showed small fiber reinnervation is possible in participants with T2D or metabolic syndrome.[23]

Address nutritional neuropathies by correcting nutritional deficiencies while medication-induced neuropathies need medication adjustments.[7]

Few patients achieve more than a 50% pain reduction with monotherapy.[10] Patients should be counseled that the goal is to reduce pain.[10,23] Guidelines recommend calcium channel α_2-δ ligands (gabapentin and pregabalin) and antidepressants that inhibit reuptake of serotonin and noradrenaline as first line treatment.[2,10,20,23] Opioids can provide short-term relief.[10,20] Opioids and opioids combined with SNRIs increase the risk for dependence and serious adverse effects.[10] Cannabis-based medicines are investigational.[10] If monotherapy fails, try combination first-line medications with adjunct topical therapy such as capsaicin or transdermal lidocaine.[10,20]

Pregabalin and gabapentin[2,8,11,19,20,21,22,23,25] bind to the calcium channel Î±2-Î´ subunit with decreased central sensitization and nociceptive transmission.[2] Pregabalin has faster onset of action and the starting dose of 150mg/day may be increased to 300mg/day after one to two weeks, up to 600 mg/day[2] An adequate trial duration to assess efficacy is four weeks.[2]

Gabapentin is initiated at 300mg on day one and increased by 300 mg/day every for two to three days, up to a total daily dose of 1800-3600mg.[2,20,22] Titration should not exceed 1800mg/day at the end of week one, 2400mg/day at the end of week two, and 3600mg/day at the end of week three.[2,19,20] An adequate trial is between five and 10 weeks with at least two weeks at the maximum tolerated dose.[2]

In older adults, Pregabalin and gabapentin can cause somnolence, dizziness, ataxia and fatigue.[2] Peripheral edema and weight gain from these medications may also limit use. Both have a risk of increased suicidal ideation and requires dose adjustment in renal impairment.[2]

Tricyclic antidepressants (TCAs) inhibit norepinephrine reuptake in the spinal dorsal synapses and acts at sodium channels.[2,20,21,22,23,25] Nortriptyline and desipramine are preferred in older patients or in those likely to experience adverse effects including somnolence and anticholinergic effects.[2] TCAs are contraindicated in patients with glaucoma, prostate hypertrophy or certain cardiac conduction disturbances.[20] Starting dose is 10-to-25mg/day up to 75mg/day.[2] Analgesic effect is observed after two to four weeks but may take up to six to eight weeks.[2,20] Secondary amines are better tolerated than tertiary amines.[20]

Few patients achieve more than a 50% pain reduction with monotherapy.

Serotonin norepinephrine reuptake inhibitors (SNRIs)[2,8,11,20,21,22,23,25] block the presynaptic serotonin and norepinephrine. Duloxetine inhibits both neurotransmitters. In contrast, venlafaxine inhibits only serotonin at 150 mg/day but inhibits serotonin and norepinephrine at higher doses.[2] Both medications are associated with increasing blood pressure and cardiac conduction abnormalities.[2,21] Duloxetine is usually dosed at 60-120mg but start at 30 mg/day to decrease the incidence of nausea.[2] Duloxetine-induced anorexia may benefit individuals with obesity. Older patients may experience more severe side effects and are recommended to start at a low dose then titrate slowly.[2] Duloxetine had a high evidence of pain reduction compared with venlafaxine in DPN.[2] Venlafaxine is dosed between 150 and 225mg/day and can lower the seizure threshold.[2] An adequate trial of venlafaxine is four to six weeks.[2] When discontinuing either medication, taper down the dose gradually to prevent withdrawal symptoms.[2]

Carbamazepine showed similar effects as venlafaxine in 257 patients with DPN and pregabalin in improving scores for sleep, mood, and work interference.[25]

Oxacarbazepine has also been reported to be effective in improving DPN pain, but evidence for treating DPN is low and can have serious adverse effects.[25]

Metformin studies suggested its anti-inflammatory effect on DPN. In-vitro and animal studies have shown Metformin in preventing peripheral neuropathy, but results remain conflicting.[11]

Opioids and Combination Therapies

Opioid and opioid-like drugs are not recommended as first-line therapy for neuropathic pain due to risk of diversion, misuse, overdose, morbidity and death.[2,17,20,21,23,25] They should be avoided in those with a history of substance abuse.[2,20]

Tramadol inhibits norepinephrine and serotonin reuptake with a lower risk for abuse compared to other opioids. It is still limited by its abuse potential.[2,20]

Tapentadol also inhibits noradrenaline reuptake and is the only FDA-approved opioid for the management of neuropathic pain associated with diabetic peripheral neuropathy.[21] Its abuse potential is currently unknown.[2]

Cochrane reviews found low or very low-quality evidence in using strong opioids in the treatment of NP. Gaskell et al. in 2016 reported that three out of the five studies showed a 30% reduction in pain, and no study reported a 50% reduction in pain with oxycodone.[2] There is no evidence for or against the use of hydromorphone, fentanyl, morphine or buprenorphine in the treatment of NP.[2,17]

The American Diabetes Associa-

Continued on page 95

Neuropathy (from page 94)

tion (ADA) reports that pharmacotherapy is necessary to control symptoms from NP.[2] The ADA supports the use of pregabalin and duloxetine to treat NP in patients with diabetes.[2] The ADA does not recommend the use of opioids as first- or second-line therapies for NP in patients with diabetes.[2]

The American Society of Clinical Oncology supports a moderate recommendation for the use of duloxetine in patients living with CIPN due to treatment with oxaliplatin or paclitaxel therapy.[2]

Combination therapies are often used in patients with NP who have either failed to have a response or only had a partial response to monotherapy.[2,10] Studies on the use of combination therapies have found mixed results.[2,10] A meta-analysis of two studies did find that a combination of gabapentin with an opioid was superior to monotherapy or placebo, but the combination of the two medications were associated with higher adverse effects.[2] A large study that focused on comparing duloxetine and pregabalin at high doses as monotherapy to lower doses in combination did not show any difference in efficacy.[2] Currently, there is not much available evidence that supports specific combinations of medications for NP.[2]

Studies on the use of combination therapies have found mixed results.[2,10]

Topicals, Vitamins, Supplements, and Cannabinoids

Finnerup et al. recommended topical treatments such as capsaicin, lidocaine, and botulinum toxin type A as second- or third-line therapies for peripheral neuropathy pain.[2,21] Topical therapies may be considered first-line therapies for elderly patients[2] who may have altered drug metabolism and elimination.[2] Topical capsaicin gel of 0.025% and 0.075% capsaicin lotion were not superior to placebo in relieving painful DPN.[25] Capsaicin 8% patches can reduce pain for up to 12 weeks. However, it must be applied by a healthcare provider in a clinic.[2,19,20] Repeated applications can result in a long-lasting effect.[2] The long-term safety of repeated applications has not been established.[2] Creams must be applied multiple times per day and can cause pain for the first few weeks of therapy.[2]

Lidocaine patches 5% in combination with other analgesic drugs have low systemic absorption to enhance quality of life.[20] Lidocaine reduces spontaneous ectopic nerve discharge.[21]

Botulinum toxin type A subcutaneous injection is a third line of pain treatment used in refractory cases.[2,21] Evidence is limited, but small trials of its use in patients with postherpetic neuralgia, trigeminal neuralgia and diabetic neuropathy showed positive results.[2,21]

Cannabinoid, another third-line agent for the treatment of NP pain, is associated with dizziness, sedation, dry mouth, oral discomfort, and gastrointestinal adverse effects.[2] Do not prescribe in patients with a history of heart disease or psychiatric disorders, and controversy about their long-term use exists.[2]

Alpha lipoid acid (ALA) decreases oxidative stress and improves endothelial function in patients with metabolic syndrome with diabetic neuropathy.[3,25,27] Treatment for three weeks with 600 mg TID orally, five weeks with 600 mg ALA orally QD, BID, and TID, as well as six months using oral ALA 600 mg BID, reduced the pain, paresthesia, and numbness.[3,20] In the NATHAN 1 trial involving 460 patients with diabetes, after four years of ALA treatment using 600 mg daily, neuropathic deficits were improved.[3,20] but nerve conduction did not improve.[3] The primary indication for ALA includes pain, paresthesia and numbness.[3] Additionally, a meta-analysis of 448 patients with a daily intravenous dose of 600 mg for three weeks showed sustained pain relief through one year.[25]

Vitamins B1 (thiamine), B6 (pyridoxine), and B12 (cyanocobalamin) can reduce the severity and duration of neuropathic pain[27] and increase nerve fiber density and 2-point discrimination.[27] A combination of these vitamins are more effective in decreasing pain compared to when taken separately.[27] Vitamin B12 (500 mg three times a day) facilitates myelinogenesis and nerve regeneration.[27]

Benfotiamine is a lipid-soluble derivative of vitamin B1 and prodrug of thiamine that blocks three major pathways of hyperglycemia-induced microvascular damage. Neuropathic symptoms improved after six weeks of treatment using a dose of 300 mg BID.[3,27] It is indicated for both painful and nonpainful neuropathy symptoms of DPN.[3]

Vitamin E 200 mg twice daily did not improve neuropathic symptoms over one year in people with DPN. However, in post hoc subgroup analyses, it suggests it reduced lancinating pain among people with HbA1c levels > 8% and normal homocysteinemia after one year.[3]

Acetyl-L-carnitine (ALC) promotes the expression of nerve growth factors and peripheral nerve regeneration and conduction.[27] Patients with chronic DPN treated with ALC (500-1000 mg three times a day) manifested improvements in pain and vibration perception in fingers and toes. There is also an increase in the number of nerve fibers after 52 weeks of treatment. Moreover, in a randomized study, ALC reduced pain in antiretroviral-induced (HIV) neuropathy.[27]

Vitamin D deficiency may be an independent and modifiable risk factor in DPN.[27] Vitamin D deficiency up-regulates inflammatory mediators (IL-13 and IL-17) in diabetes and DPN.[27]

Interventional, Psychotherapeutic, and Acupuncture Treatments

Interventional therapies, such as spinal cord stimulation, are an option for patients who experience chronic nerve pain for greater than six months despite standard treatments and responded to trial spinal cord stimulation by a specialist.[2,23] Other interventional therapies include transcutaneous electrical nerve stimulation, sym-

Continued on page 96

Neuropathy (from page 95)

pathetic nerve blocks, and steroid injections.[2] Evidence on quality of life is limited. Most studies were short-term, and spinal cord stimulation with serious adverse events were reported.[5]

Nonpharmacological treatments may decrease pain, decrease the use of medications, increase function, and improve QOL.[2] Several small trials suggest exercise may improve muscle strength, functional ability, and fatigue.[2,12,18]

A Cochrane review found insufficient evidence on the efficacy or safety of psychotherapy for NP.[2] A Johns Hopkins review of evidence for cognitive behavioral therapy and acupuncture was insufficient; no exercise or physical therapy trials met inclusion criteria.[5]

Emerging treatment using of stem cell therapy seems promising and under investigation for patients with NP.[2] Others are exploring personalized pain therapy to provide patients with the most effective treatment for NP by targeting phenotype-based classification systems and mechanisms responsible for NP, rather than etiology.[2] Specific phenotypes have been associated with positive response to certain treatments.[2]

Transcutaneous electrical nerve stimulation (TENS) is suitable as preliminary or adjunct therapy for NP.[18,25] It induces the release of endogenous opioids.[25] When low-frequency TENS (≤10 Hz) was applied to 19 patients suffering from mild-to-moderate symptomatic DPN, pain decreased compared to placebo.[25] When traditional TENS (80 Hz) or acupuncture-like TENS (2 Hz) was applied to five patients suffering from DPN, significant pain relief occurred in all, but it lacks a control.[25] In addition, in a study comparing micro-TENS (2 Hz) and placebo in 41 diabetic patients, micro-TENS did not show significant improvement in pain relief.[25] No adverse reactions were reported in patients treated with TENS.[25]

Review from John's Hopkins found frequency-modulated electromagnetic stimulation was more effective than sham electromagnetic stimulation in the short-term neuropathic pain relief but does not persist long-term.[5] Spinal cord stimulation was more efficacious for pain management.[5] Martinez et al. recommended transcutaneous electrical nerve stimulation, spinal cord stimulation, and cognitive behavioral therapy as effective non-pharmacologic interventions to treat neuropathic pain.[18]

Physiotherapy is necessary to prevent or reverse changes in tropism, disuse atrophy, subsequent contractures, and deformities, preventing ankylosis and deconditioning.[18] Psychological assessment for anxiety, depression, worsening sleep, and QOL, followed by appropriate psychotherapy, is suggested.[18]

Martinez et al. recommended the use of acupuncture to treat post-herpetic neuralgia and TENS for localized peripheral neuropathic pain treatment, and spinal cord stimulation for chronic postoperative lumbar back pain with predominant radiculopathy.[18]

In Taiwan, Traditional Chinese medicine (TCM) was used as an adjunctive treatment to ameliorate diabetes-associated chronic complications.[6] Patients who received TCM for DN had significant lower cumulative risks of hospitalization and mortality compared to patients who did not receive TCM. However, further prospective studies are needed.[6] One study showed that the use of TCM treatment can improve blood circulation of Type II diabetes, thereby alleviating ischemia and hypoxia of nerve tissue.[6]

One study evaluated the effect of acupuncture in DPN pain reported pain relief in 45 subjects, compared with placebo. However, the study lacks robust outcome measures; hence, it is not approved as a treatment of DPN.[20]

Chetty et al. Emphasized a multidisciplinary approach in neuropathic pain management integrating non-pharmacologic treatment, psychotherapy, TENS, and physiotherapy. They further recommend deep brain stimulation for neuropathic pain refractory to pharmacological and non-pharmacological interventions.[18]

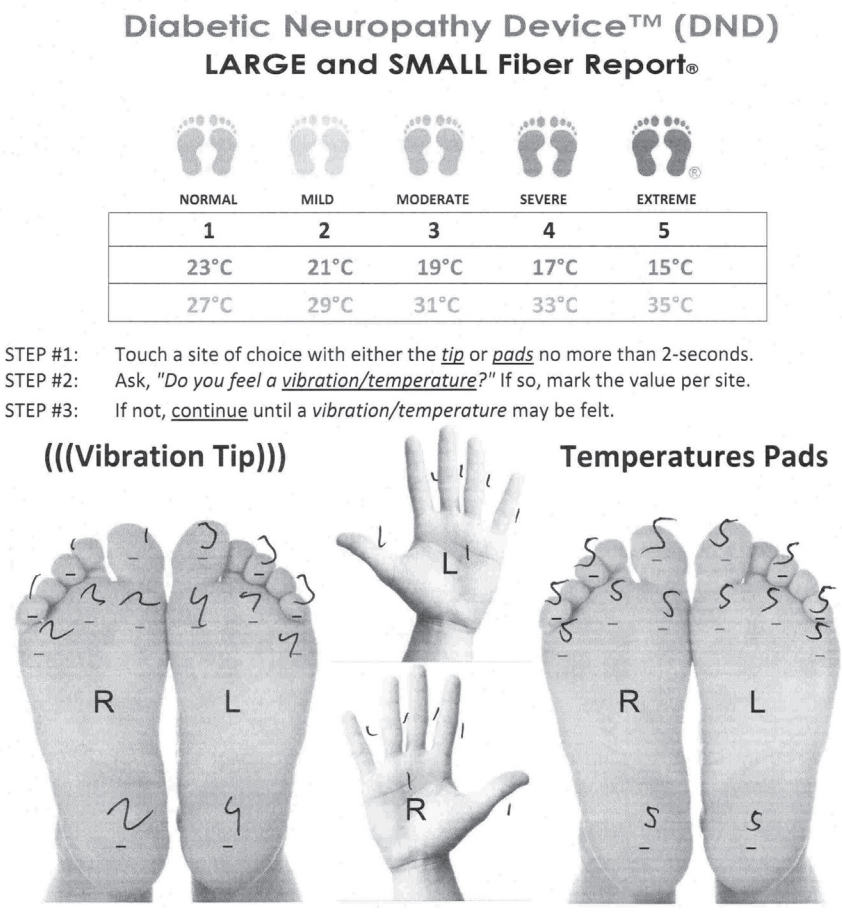

Figure 1: Dynamic nerve testing showed polyneuropathy

Continued on page 97

Neuropathy (from page 96)

Emerging Trials

Ketamine, memantine, and N-methyl-d-aspartate receptor (NMDAR) antagonists have been investigated in several preclinical and clinical studies for the treatment of neuropathic pain; however, they are not approved by the FDA for this indication.[21] Several clinical studies also highlighted the efficacy of *Cannabis sativa* derivatives in the modulation of neuropathic pain, particularly a mixture (1:1) of the Δ-9-THC and cannabidiol (CBD) in an oromucosal spray formulation (Sativex®; GW Pharma Ltd, Salisbury, UK). It is approved for spasticity symptom improvement in multiple sclerosis and has beneficial effects on multiple sclerosis central pain (NCT01604265; NCT00391079), neuropathic pain after peripheral injury (NCT00711880; NCT00710554), and diabetic neuropathy (NCT00710424).[21]

Noninvasive transcranial brain stimulation techniques have emerged as a therapeutic option in patients with refractory neuropathic pain. These include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).[21] A study of phantom limb pain in landmine victims (NCT01872481) showed high frequency rTMS (10 Hz) reduces the pain significantly for up to 15 days after treatment. Likewise, clinical trial NCT00443469 showed that the use of repetitive spinal magnetic stimulation (SMS) in patients with intractable neuropathic pain of the lower limbs had immediate analgesic effect, with residual effect observed up to four days post-treatment. Another trial NCT00337324 investigated the effects of frequency-modulated electromagnetic stimulation (FREMS) in patients with diabetic neuropathy. The treatment reduced pain with improved microvascular blood flow. Additionally, tDCS stimulation using electric current of 1–2 mA, has shown a beneficial effect in the treatment of neuropathic pain associated with diabetes, traumatic spinal cord injury, and fibromyalgia syndrome.[21]

IMPRESSIONS:
This study is abnormal.
There is electrophysiologic evidence suggestive of chronic axonal pathology affecting lumbar L5 - S1 nerve root levels bilaterally.

Note: NCV findings
Left/ right Sup Peron Sensory and right/left Sural Sensory showing no response due to the swelling secondary the bilateral kidney transplants.

There was no electrophysiologic evidence of additional focal nerve pathology, proximal nerve, plexus or polyneuropathy, myopathy or motor neuron pathology.

Figure 2: Patient's EMG report

IMPRESSION:
1. Cystic mass with mild papillary projections in the pelvis, suspicious for ovarian neoplasm. Gynecologic consult is recommended.
2. No suspicious lymphadenopathy or peritoneal nodule.
3. The uterus is within normal limits. Bilateral normal ovaries are not well seen.
4. Right lower quadrant transplant kidney, within normal limits.
5. Atrophic left lower quadrant transplant.

Figure 3: MRI report suspicious mass

Dorsal column stimulation or spinal cord stimulator (SCS) is an invasive technique that involves stimulation of spinal cord dorsal columns in patients who are not responsive to standard treatment. Approximately 50% of patients experienced pain relief. It works by stimulation of the large-diameter fibers in the dorsal column to induce paresthesia.[21] A new technique of SCS is burst stimulation with significant reduction of pain in patients' diabetic neuropathy.[21] Van Beek M et al. showed that in around 50% of patients, SCS treatment reduced chronic pain symptoms in the lower extremities up to five years of follow-up; 80% of patients with PDPN still use their SCS device after five years.[25] The FDA approved SCS devices for the treatment of painful DPN in 2022.[25]

Recent research in treatment of DPN has shifted toward elucidating the molecular pathways and identifying potential therapeutic targets for disease-modifying strategies instead of symptomatic treatment.[24] Key areas include oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, and central sensitization mechanisms.[24] Novel pharmacological agents, including sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and ion channel blockers, have shown promising neuroprotective and pain management effects.[24]

Other experimental animal studies for neuropathic pain studies include metformin, Simvastatin, organoselenium compound p,p´-methoxyl-diphenyl diselenide ((OMePhSe)2), neuropeptide SP, antioxidant and anti-inflammatory compound from Chinese medicine called Puerarin and Gastrodin.[21]

Discussion

Effective management of neuropathic pain involves a multidisciplinary approach. Although significant research in pharmacological management exists, a paucity of literature on physical medicine and rehabilitation management is available. Optimal strategy involves coordinated care between multi-specialties to improve pain management. Furthermore, regular exercise to improve glucose control may prevent the progression and possibly even the onset of DPN.[20,24]

Case Study

A 69-year-old female with insulin-dependent Type II diabetes mellitus presented to Endocrine Associates of West Village on January 31, 2024, with HbA1c >14% and no recent corticosteroid use. Her history includes hypertension, systemic lupus erythematosus (SLE), and bilateral kidney transplantation. Medications included insulin degludec, insulin lispro, mycophenolate, prednisone, and metoprolol. She was allergic to cephalexin and erythromycin. She is a former smoker and occasional alcohol user.

She reported neuropathic foot pain, gait instability, and recent falls,

Continued on page 98

Neuropathy *(from page 97)*

requiring a cane, and she had been referred to podiatry, cardiology, and vascular surgery. PVR/ABI and arterial duplex showed obstructive PAD in the right dorsalis pedis artery and moderate non-obstructive plaque in the right CFA. *Note: Patient provided verbal consent to share her case.*

Timeline

By July 1, 2024, she reported bilateral leg heaviness, nocturnal pain (4/10), and swelling. She applied Bengay and Nervacol for relief and followed a low-sodium diet. Stress echocardiogram was unremarkable; renal transplant function remained stable.

On July 15, 2024, she returned with worsening leg pain and stiffness, now requiring a wheelchair. Vascular surgery deemed circulation adequate. X-rays were negative. A venous duplex ruled out DVT. Paresthesia worsened, and she had difficulty rising from a seated position. Referred to physical therapy.

By August 26, 2024, she experienced unintentional weight loss. Her insulin regimen was adjusted following a hypoglycemia-related ER admission. Dynamic nerve testing showed polyneuropathy (Figure 1). She began dynamic nerve supplements.

On September 10, 2024, she was placed on medical leave from her job due to limited mobility. Labs (from August 29) showed declining renal function: eGFR 59, BUN 42–43, Cr 1.02.

On September 30, 2024, she reported no strength improvement despite PT and increased left leg swelling. HbA1c had improved to 7.3%.

By October 28, 2024, she reported worsening sleep and was referred to neurology. The patient's EMG report showed evidence suggestive of chronic axonal pathology (Figure 2). An MRI was ordered on November 12 by a neurologist who suspected a hip etiology.

On November 18, 2024, she had poor appetite, nausea, and persistent quadriceps weakness despite therapy, with continued weight loss.

On January 20, 2025, an MRI revealed a large pelvic mass, likely uterine in origin. (Figure 3). She was referred to gynecology and oncology. Gabapentin 100 mg at bedtime was initiated (up to 200 mg/day) for neuropathic pain exacerbated by lying down.

By February 10, 2025, HbA1c improved to 7.1%, but she was fully walker-dependent with muscle wasting. Nutritional support included protein powder and dietary protein increase.

On March 17, 2025, her condition was unchanged; HbA1c rose slightly to 7.5%.

By March 26, 2025, she was advised not to ambulate without a walker due to weakness and fall risk. She expressed frustration and was referred for counseling. Gynecology/oncology evaluated the pelvic mass. A vascular study was abnormal and she was referred to a vascular surgeon (Figure 4).

On April 26, 2025, she presented for endocrine clearance before scheduled laparoscopic surgery.

On May 16, 2025, she underwent successful laparoscopic excision of the pelvic mass, which was confirmed benign on pathology. **PM**

References

[1] https://www.ccjm.org/content/85/10/801

[2] https://pharmaceutical-journal.com/article/research/treatments-for-neuropathic-pain

[3] https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(23)00527-2/fulltext

[4] https://www.ingentaconnect.com/content/ben/cds/2021/00000016/00000001/art00003

[5] https://pure.johnshopkins.edu/en/publications/non-pharmacologic-treatments-for-symptoms-of-diabetic-peripheral-

[6] https://journals.lww.com/joms/fulltext/2024/44040/study_on_the_prognosis_effect_of_traditional.1.aspx

[7] https://www.racgp.org.au/afp/2015/march/paraesthesia-and-peripheral-neuropathy

[8] https://onlinelibrary.wiley.com/doi/10.1111/jdi.13711

[9] https://www.e-enm.org/journal/view.php?doi=10.3803/enm.2016.31.2.230

Continued on page 99

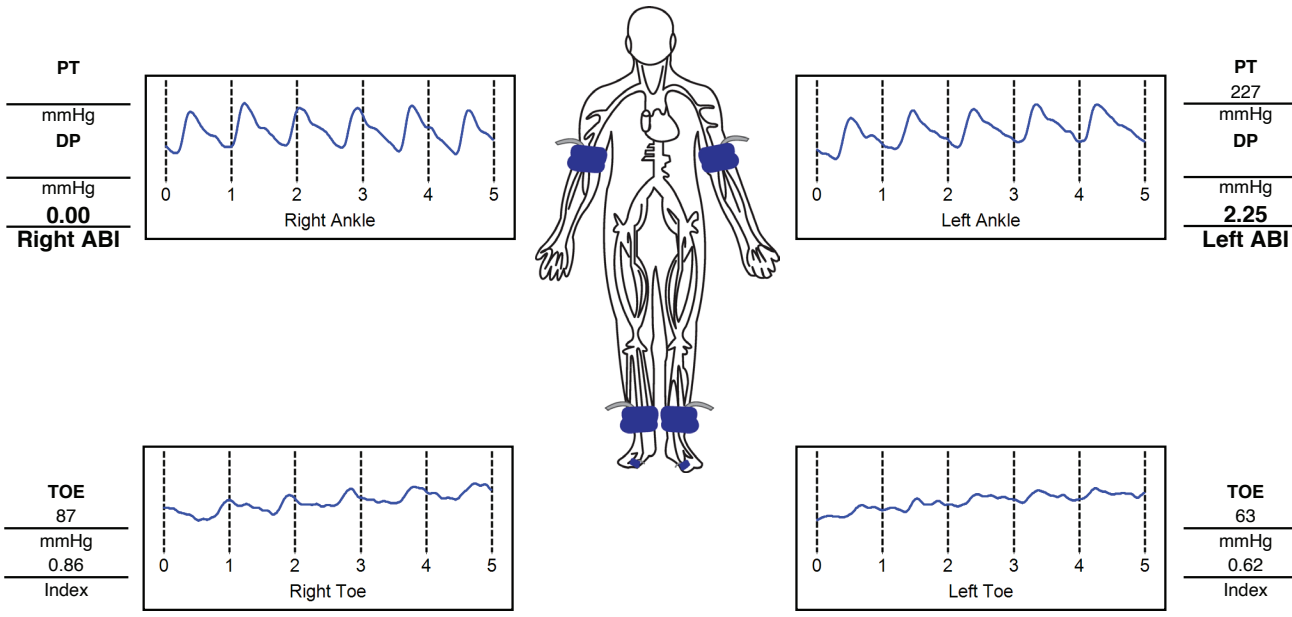

Figure 4: Vascular study was abnormal and referred to vascular surgeon.

Neuropathy (from page 98)

[10] https://www.cmaj.ca/content/195/6/E227
[11] https://www.researchgate.net/publication/369385685_Peripheral_Neuropathy_A_review_of_mechanism-based_treatments_with_a_focus_on_metformin_as_a_possible_choice_Journal_of_Clinical_Images_and_Medical_Case_Reports
[12] https://link.springer.com/article/10.1007/s11916-021-00971-2
[13] https://practicalneurology.com/diseases-diagnoses/neuromuscular/diagnosis-and-treatment-of-vasculitic-neuropathy/32110/
[14] https://www.researchgate.net/publication/369230307_Peripheral_Neuropathy_a_review
[15] https://diabetesjournals.org/care/article/40/1/136/37160/Diabetic-Neuropathy-A-Position-Statement-by-the
[16] https://link.springer.com/article/10.1007/s40122-017-0085-2
[17] https://www.nature.com/articles/s41572-019-0092-1
[18] https://www.mdpi.com/2075-4418/11/1/74
[19] https://www.aafp.org/pubs/afp/issues/2020/1215/p732.html
[20] https://onlinelibrary.wiley.com/doi/10.1111/jphp.13241
[21] https://journals.sagepub.com/doi/10.1177/2058738419838383
[22] https://link.springer.com/article/10.1007/s40122-020-00210-3
[23] https://www.annualreviews.org/content/journals/10.1146/annurev-med-043021-033114
[24] https://www.nature.com/articles/s41392-025-02175-1
[25] https://e-dmj.org/journal/view.php?doi=10.4093/dmj.2023.0018
[26] https://neurolrespract.biomedcentral.com/articles/10.1186/s42466-020-00064-2
[27] https://pmc.ncbi.nlm.nih.gov/articles/PMC9138404/
[28] https://pmc.ncbi.nlm.nih.gov/articles/PMC9966617/

Dr. Jean Chen-Vitulli is a podiatrist who specializes in wound care and limb salvage. She obtained her master's degree from Roswell Park Cancer Institute. Dr. Chen-Vitulli trained under Anastasios Manessis, MD to become a certified diabetic educator and is involved in interdisciplinary research. She also enjoys mentoring NYCPM students in interdisciplinary research and is actively involved with the American Podiatric Medical Association.

Dr. Manessis is a double-board-certified physician at Endocrine Associates of West Village PC in Murray Hill, Manhattan, and Long Island City, NY, specializing in endocrinology, diabetes, and metabolism and obesity medicine. Dr. Manessis has an endocrine certification in neck ultrasounds and has extensive experience in diagnosing, treating, and managing endocrine disorders, including diabetes, thyroid disorders, hormonal dysfunction, and obesity. Dr. Manessis earned his medical degree from the State University of New York at Buffalo and completed a combined residency in internal medicine and pediatrics at New York Medical College at Saint Vincent's Hospital in New York. Following a year as chief medical resident, he completed a two-year clinical fellowship in endocrinology, diabetes, and metabolism, where his research interest, among others, involved the use of insulin pumps in patients with Type II diabetes.

CME EXAMINATION

SEE ANSWER SHEET ON PAGE 101.

1) Multidisciplinary approach to management of painful neuropathy should include:
- **A) Neurologist**
- **B) Physical therapist**
- **C) Psychologist/psychiatrist/counsellor**
- **D) A, B, and C**

2) Which of the following is false?
- **A) Ketamine is approved by the FDA for the treatment of neuropathic pain.**
- **B) Memantine is not approved by the FDA for the treatment of neuropathic pain.**
- **C) N-methyl-d-aspartate receptor antagonist is not approved by the FDA for the treatment of neuropathic pain.**
- **D) Ketamine, Memantine, and N-methyl-d-aspartate receptor antagonists are currently being studied in clinical trials of neuropathic pain.**

3) Which of the following is false regarding spinal cord stimulator?
- **A) Spinal cord stimulator is an FDA-approved non-invasive technique in the treatment of neuropathic pain.**
- **B) Can be considered in patients who do not respond to standard treatments.**
- **C) Approximately 50% of the patients experience pain relief.**
- **D) It induces paresthesia.**

4) Which of the following regarding research into treating painful peripheral neuropathy is false?
- **A) Research is looking at molecular pathways and identifying therapeutic targets for modifying the disease.**
- **B) Research is only interested in symptomatic relief of painful neuropathy.**
- **C) Experimental animal studies are looking into metformin and simvastatin for neuropathic pain treatment.**
- **D) Chinese medicines such as Puerain and Gastrodin are being evaluated for their antioxidant and anti-inflammatory properties in the treatment of peripheral neuropathy.**

5) Aside from a multidisciplinary approach to management of diabetes, for peripheral neuropathy patients:
- **A) exercise is not encouraged, as it may lead to falls**
- **B) exercise is encouraged to improve glucose control**
- **C) improved glucose control may prevent the progression and possibly the onset of diabetic peripheral neuropathy**
- **D) B & C**

Continued on page 100

Continuing Medical Education

CME EXAMINATION

(Continued from page 99)

6) Treatment of neuropathic pain does NOT include:
- **A) gabapentin**
- **B) heroin**
- **C) spinal cord stimulator**
- **D) Pregabalin**

7) Potential therapeutic targets for treatment of peripheral neuropathy include areas of:
- **A) oxidative stress and mitochondrial dysfunction**
- **B) chronic low-grade inflammation**
- **C) central sensitization strategies**
- **D) All of the above**

8) CBD oil is helpful in treatment of:
- **A) Painful spasm from multiple sclerosis**
- **B) Diabetic neuropathy pain**
- **C) Pain from nerve injury**
- **D) All of the above**

9) Treatment of neuropathic pain should include all of the following except:
- **A) Letting patients know the goal of treatment is to reduce pain.**
- **B) Guidelines recommend calcium channel α_2-δ ligands (gabapentin and pregabalin) and antidepressants that inhibit reuptake of serotonin and noradrenaline as first-line treatment.**
- **C) If monotherapy fails, try combination first-line medications with adjunct topical therapy.**
- **D) Since it is a difficult condition to treat, patients living with diabetes should comfort themselves with as much carbohydrates as they want to eat.**

10) In elderly patients with peripheral neuropathy pain:
- **A) Pregabalin and gabapentin can cause somnolence, dizziness, ataxia, and fatigue.**
- **B) Topical therapies may be considered first-line therapies for elderly patients who may have altered drug metabolism and elimination.**
- **C) A & B**
- **D) Older patients do not experience more severe side effects compared to younger individuals; hence, there is no need to start a medication such as duloxetine at a low dose before titrating slowly.**

SEE ANSWER SHEET ON PAGE 101.

The author(s) certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

PM's CME Program

Welcome to the innovative Continuing Education Program brought to you by *Podiatry Management Magazine*. Our journal has been approved as a sponsor of Continuing Medical Education by the Council on Podiatric Medical Education.

Now it's even easier and more convenient to enroll in PM's CE program!

You can now enroll at any time during the year and submit eligible exams at any time during your enrollment period.

CME articles and examination questions from past issues of *Podiatry Management* can be found on the Internet at podiatrym.com/cme. Each lesson is approved for 1.5 hours continuing education contact hours. Please read the testing, grading and payment instructions to decide which method of participation is best for you.

Please call 516-521-4474 if you have any questions. A personal operator will be happy to assist you.

Each of the 10 lessons will count as 1.5 credits.

The* Podiatry Management Magazine *CME Program is approved by the Council on Podiatric Medical Education as a provider of continuing education in podiatric medicine.* Podiatry Management Magazine *CME has approved this activity for a maximum of 1.5 Continuing Education Contact Hours for each exam successfully completed.

PM's privacy policy can be found at podiatrym.com/privacy.cfm.

This CME is valid for CPME-approved credits for three (3) years from the date of publication.

Enrollment/Testing Information and Answer Sheet

Continuing Medical Education

Note: If you are mailing your answer sheet, you must complete all info. on the front and back of this page and mail with your credit card information to: **Program Management Services, 12 Bayberry Street, Hopewell Junction, NY 12533.**

TESTING, GRADING AND PAYMENT INSTRUCTIONS

(1) Each participant achieving a passing grade of 70% or higher on any examination will receive an official computer form stating the number of CE credits earned. This form should be safeguarded and may be used as documentation of credits earned.

(2) Participants receiving a failing grade on any exam will be notified and permitted to take one re-examination at no extra cost.

(3) All answers should be recorded on the answer form below. For each question, decide which choice is the best answer, and circle the letter representing your choice.

(4) Complete all other information on the front and back of this page.

(5) Choose one out of the 3 options for testgrading: mail-in, fax, or phone. To select the type of service that best suits your needs, please read the following section, "Test Grading Options".

TEST GRADING OPTIONS

Mail-In Grading

To receive your CME certificate, complete all information and mail with your credit card information to: **Program Management Services, 12 Bayberry Street, Hopewell Junction, NY 12533. PLEASE DO NOT SEND WITH SIGNATURE REQUIRED, AS THESE WILL NOT BE ACCEPTED BY THE RECEIVER.**

There is **no charge** for the mail-in service if you have already enrolled in the annual exam CME program, and we receive this exam during your current enrollment period. If you are not enrolled, please send $35.00 per exam, or $299 to cover all 10 exams (thus saving $51 over the cost of 10 individual exam fees).

Facsimile Grading

To receive your CME certificate, complete all information and fax 24 hours a day to 1631-532-1964. Your test will be dated upon receipt and a PDF of your certificate of completion will be sent to the Email address on file with us. Please allow 5 business days for the return of your certificate. This service is available for $2.95 per exam if you are currently enrolled in the 10-exam CME program, and can be charged to your Visa, MasterCard, or American Express.

If you are *not* enrolled in the 10-exam CME program, the fee is $35 per exam.

Phone-In Grading

You may also complete your exam by using the toll-free service. Call 516-521-4474 from 10 a.m. to 5 p.m. EST, Monday through Friday. Your CME certificate will be dated the same day you call and mailed within 48 hours. There is a $2.95 charge for this service if you are currently enrolled in the 10-exam CME program, and this fee can be charged to your Visa, Mastercard, American Express, or Discover. If you are not currently enrolled, the fee is $35 per exam. When you call, please have ready:

1. Program number (Month and Year)
2. The answers to the test
3. Credit card information

In the event you require additional CME information, please contact PMS, Inc., at **516-521-4474**.

ENROLLMENT FORM & ANSWER SHEET

Please print clearly...Certificate will be issued from information below.

Name _____ Email Address_____
Please Print: FIRST MI LAST

Address_____

City_____ State_____ Zip_____

Charge to: _____Visa _____ MasterCard _____ American Express

Card #_____Exp. Date_____ Zip for credit card_____

Note: Credit card is the only method of payment. Checks are no longer accepted.

Signature_____ Email Address_____ Daytime Phone_____

State License(s)_____ Is this a new address? Yes_____ No_____

Check one: _____ I am currently enrolled. (If faxing or phoning in your answer form please note that $2.95 will be charged to your credit card.)

_____ I am not enrolled. Enclosed is my credit card information. Please charge my credit card $35.00 for each exam submitted. (plus $2.95 for each exam if submitting by fax or phone).

_____ I am not enrolled and I wish to enroll for 10 courses at $299.00 (thus saving me $51 over the cost of 10 individual exam fees). I understand there will be an additional fee of $2.95 for any exam I wish to submit via fax or phone.

Over, please

ENROLLMENT FORM & ANSWER SHEET *(continued)*

EXAM #3/26
Understanding and Managing Neuropathy: Advances in Diagnosis and Treatment—Part 2 (Chen-Vitulli and Manessis)

Circle:

1.	**A**	**B**	**C**	**D**	**6.**	**A**	**B**	**C**	**D**
2.	**A**	**B**	**C**	**D**	**7.**	**A**	**B**	**C**	**D**
3.	**A**	**B**	**C**	**D**	**8.**	**A**	**B**	**C**	**D**
4.	**A**	**B**	**C**	**D**	**9.**	**A**	**B**	**C**	**D**
5.	**A**	**B**	**C**	**D**	**10.**	**A**	**B**	**C**	**D**

Medical Education Lesson Evaluation

Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]

1) This CME lesson was helpful to my practice ____

2) The educational objectives were accomplished ____

3) I will apply the knowledge I learned from this lesson ____

4) I will makes changes in my practice behavior based on this lesson ____

5) This lesson presented quality information with adequate current references ____

6) What overall grade would you assign this lesson?

A B C D

7) This activity was balanced and free of commercial bias.

Yes _____ No _____

8) What overall grade would you assign to the overall management of this activity?

A B C D

This CME has been certified by a psychometrician as taking a minimum of 1.5 hours to complete.

What topics would you like to see in future CME lessons? Please list :

_____

_____

_____

_____

_____

_____