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The Use of Transcutaneous Electrical Nerve Stimulation for the Treatment of Painful Diabetic Neuropathy

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ABSTRACT

Diabetic Peripheral Neuropathy (DPN) is the most common complication of diabetes affecting approximately 50% of people with diabetes in the United States. Painful diabetic neuropathy (PDN), the clinical scenario of neuropathic pain arising as a direct consequence of DPN, affects from 16% to 33% of people with diabetes. Patients with PDN have higher health care costs, higher rates of work and activity impairment and more frequent hospitalizations compared to patients with diabetes that do not have PDN. Several changes have been described in central neurons as well as peripheral nerves which help explain the development of neuropathic pain. Treatment has centered on controlling risk factors known to exacerbate DPN such as hyperglycemia and cardiovascular risk factors. In addition, symptom control with reduction in pain is a key component of the therapeutic approach. Unfortunately, complete resolution of pain is rare regardless of the type of therapy used and pharmacologic therapies are associated with potential side effects. Transcutaneous electrical nerve stimulation, the delivery of electricity across the intact surface of the skin to activate underlying nerves has been shown to provide symptomatic relief from various forms of pain, such as chronic pain due to PDN. This monograph reviews the available medical literature on the use of transcutaneous electrical nerve stimulation for the treatment of PDN. The sum total of the literature supports its use for the treatment of PDN.

EPIDEMIOLOGY

Diabetic Peripheral Neuropathy (DPN), the most common complication of diabetes, is defined as a symmetrical, length-dependent distal sensorimotor polyneuropathy attributable to metabolic and microvascular alterations. Painful diabetic neuropathy (PDN) is the clinical scenario of neuropathic pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with DPN.¹ While the description of the pain is variable among patients, a number of terms are consistently used (see Table 1). A hallmark of PDN is that this pain is usually not exacerbated by walking but rather

is worse at night when the patient is off their feet and their feet are elevated.² This finding is in contrast to musculoskeletal pain or vascular insufficiency which is usually exacerbated by activity and relieved with rest. The prevalence of DPN in the United States is approximately 50% of patients with type 1 and type 2 diabetes.³ PDN affects from 16% to 33% of people with diabetes. The estimates of how often it occurs vary depending on how PDN is defined and the nature of the population studied.⁴⁻⁶ Regardless, PDN is clearly a common problem. Pain severity has been shown to affect the health outcomes of patients with PDN. Patients with severe PDN have annual health care costs of \$17,000 compared to \$11,000 and \$9,000 for those with moderate or mild pain

PDN can cause significant distress to patients with diabetes. Other complications of diabetes such as mild retinopathy and nephropathy are painless and do not impact on the patient's quality of life early in their course. PDN sends the patient a clear message that diabetes is having a negative impact on their well-being.

respectively. Those patients with severe PDN also had higher rates of work and activity impairment.⁷ Patients with PDN are hospitalized 2.5 times more frequently and the cost of caring for these patients is nearly \$6,000 more per year compared to patients without PDN.⁸

PDN can cause significant distress to patients with diabetes.

Table 1. Frequently used descriptions of PDN

- tingling
- burning
- lancinating
- shooting
- increased sensitivity (allodynia)
- pain on walking - 'walking barefoot on marbles' or 'walking barefoot on hot sand'
- sensations of heat or cold in the feet
- persistent achy feeling in the feet
- cramping sensations in the legs

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Other complications of diabetes such as mild retinopathy and nephropathy are painless and do not impact on the patient's quality of life early in their course. PDN sends the patient a clear message that diabetes is having a negative impact on their well-being. In addition, living with chronic pain from PDN has been shown to have a negative impact on patients' quality of life. A recent study identified PDN as having a substantial impact on the quality of life of patients with diabetes comparable to amputation. PDN had a greater impact than other serious conditions including dialysis and stroke.⁹

Because of the worsening of symptoms at night, patients may have problems falling asleep resulting in a state of sleep deprivation.^{10,11} Patients are more likely to have employment issues.¹² In addition, patients with severe PDN have a marked reduction in exercise tolerance limiting a key form of therapy for patients with type 2 diabetes.¹³ PDN interferes with patients' self-management of their diabetes through decreased activity and loss of motivation.¹⁴ Finally, patients with PDN have greater anxiety and depression.¹¹

PATHOPHYSIOLOGY

Melzack and Wall in 1965 proposed a pain "gate" where impulses from small unmyelinated C fibers carrying pain signals and myelinated A β fibers carrying light touch and pressure signals enter the dorsal horn of the spinal cord.¹⁵ If the electrical impulses from C fibers outnumber those from the A β fibers then the gate opens allowing transmission of the pain signals. If, on the other hand, the signal from A β fibers predominates, then the gate is closed and pain is inhibited. One example of this gating effect is rubbing an area after trauma resulting in closing of the gate and a lessening of pain. Various changes

affecting central neurons and peripheral nerves have been described which may help explain neuropathic pain. Some of these changes are listed below:

- Peripheral nerve damage has been shown to cause neurons in the dorsal horn to be aberrantly innervated by A β fibers rather than being innervated by C fibers.^{16,17} This input could lead to inappropriate responses to innocuous peripheral stimuli.^{17,18}
- Changes to peripheral nerves leads to activation of N-methyl-D-aspartate (NMDA) receptors located in the dorsal horn of the spinal cord.^{17,19} This activation leads to an increase in depolarization of spinal cord neurons with larger post-synaptic potentials and increased excitability of central neurons.¹⁹
- Sodium channels are increased at the site of axonal damage as well as along the length of the axon. The increased number of channels increases the likelihood of ectopic electrical impulses in pain fibers.²⁰
- Rat models have demonstrated increased C fiber activity arising spontaneously in dorsal root ganglion²¹ and studies by Burcheil showed that spontaneous discharges in afferent axons were more common in hyperglycemic animals.²² This increased stimulation leads to increased nociceptive signals transmitted through the gating system described earlier.

TREATMENT

Glycemic control plays a role in the development and progression of DPN. Hallmark studies such as the DCCT have shown that tight glycemic control can prevent the development of DPN or limit its progression.²³ Evidence proving that good glycemic control will actually improve neuropathy is more limited. A few small studies have shown improvement in DPN including pain symptoms with intensive glycemic control.²⁴ Perkins demonstrated an improvement in DPN in patients with improved glycemic control or triglyceride levels.²⁵ Regardless, controlling blood glucose is part of the standard of care for patients

with DPN. In addition to glycemic control, a number of cardiovascular risk factors have been shown to predict the development and progression of DPN.²⁶ Again, there is limited data that improvement in these risk factors will actually improve DPN or symptoms.

Symptom control with the reduction of pain is the usual focus in treating patients with PDN. Many pharmacological agents are available. The European Federation of Neurological Societies published guidelines for the treatment of PDN in 2010.²⁷ In addition, the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation jointly published guidelines outlining therapies for the treatment of PDN.²⁸ These guidelines incorporate an extensive literature review identifying those therapies that have been used in the treatment of PDN and whether or not there is data to support their efficacy. Only two of

All pharmacologic therapies for PDN are associated with potential side effects. Intolerance can lead to discontinuation of therapy or is dose limiting. In one population based study, of patients with PDN, 12.5% never reported their symptoms to their treating physician and 39.3% had never received treatment for their painful symptoms.

these therapies, pregabalin and duloxetine, are FDA approved specifically for the treatment of PDN. Complete resolution of pain is rare regardless of therapy. A more typical response is a reduction in pain of 30-50% or less with comparable results for either of these agents as well as for gabapentin.²⁸⁻³¹ This degree of response means

incomplete pain relief for many patients. Patients may have episodes of breakthrough pain requiring opioid or other analgesics. Also, since the pain is frequently worse at night, adequate control of pain during the day may be matched with inadequate control in the evening interfering with sleep. Patients may then need additional pain therapy with the possible need for multiple medications and a higher risk for side effects.

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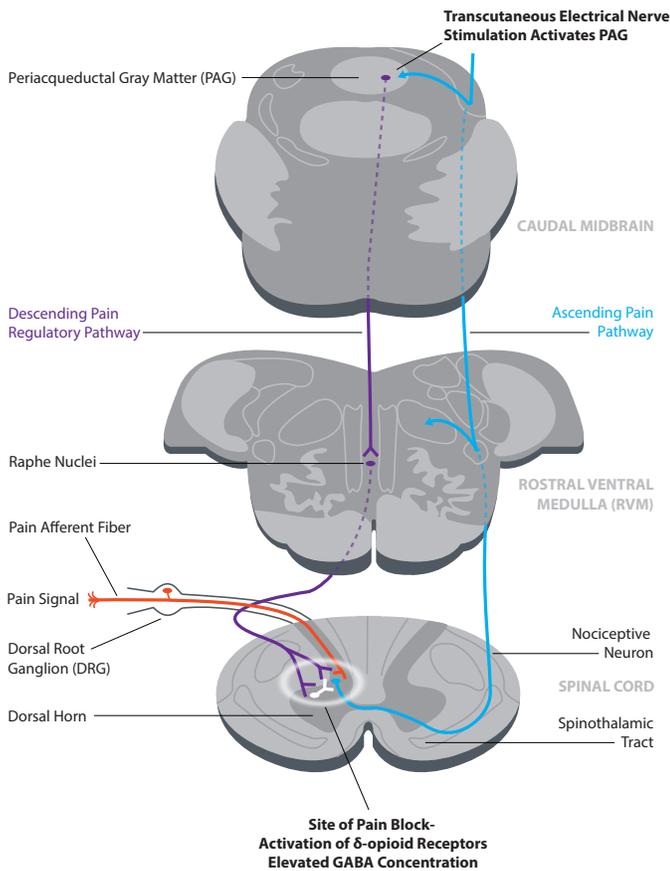
Use of Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation is the delivery of electricity across the intact surface of the skin to activate underlying nerves with the objective of providing symptomatic relief from various forms of pain, such as chronic pain due to DPN.³³ A number of recent systematic literature reviews and meta-analyses concluded that transcutaneous electrical nerve stimulation may be an effective and safe treatment for painful diabetic neuropathy.³⁴⁻³⁷ However, there is a need for additional well designed, larger, randomized clinical trials to solidify these conclusions.

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The physiological principle underlying transcutaneous electrical nerve stimulation is that excitation of Aβ sensory nerve fibers, primarily the deep tissue afferents, blocks transmission of pain signals to the brain. The most commonly cited mechanism of action is the “gate theory of pain” originally proposed by Melzack and Wall in 1965 and discussed above.¹⁵ In recent years, the anatomic pathways and molecular mechanisms underlying transcutaneous electrical nerve stimulation analgesia have been investigated (see Figure 1). Pain signals are blocked by inhibition of nociceptive neurons in the spinal cord dorsal horn.³⁸ This process is facilitated by descending signals

Figure 1. Sites of action of Transcutaneous Electrical Nerve Stimulation



from the periaqueductal gray (PAG) and the rostroventral medial medulla (RVM).³⁸ There is also evidence that pain signals are interrupted in the peripheral nervous system.³⁸ Sensory afferent stimulation causes release of endogenous opioids that inhibit pain through activation of δ -opioid receptors.³⁹ These receptors are located throughout the nervous system, including the dorsal horn of the spinal cord.³⁸ Opioid receptors are G-protein coupled receptors whose activation decreases neuronal activity, such as through ion channel regulation.⁴⁰ Like the morphine sensitive μ -opioid receptor, the δ -opioid receptor induces analgesia, however the two receptor subtypes have a different neuroanatomical distribution and abuse potential.⁴⁰ Transcutaneous electrical nerve stimulation also increases the extracellular concentration of the inhibitory neurotransmitter GABA and decreases the

concentration of the excitatory neurotransmitters glutamate and aspartate in the spinal cord dorsal horn.³⁸

There are many commercial transcutaneous electrical nerve stimulation and related devices⁴⁶ with different characteristics and features. Unlike the relatively straightforward dosing of oral analgesic drugs, nerve stimulation devices are intended to be used by patients with neuropathic pain on an ongoing basis. There is some evidence that a barrier to effective use of these devices is the disproportionate amount of effort needed to regularly apply them for the amount of pain relief achieved.⁴⁷ As currently designed, most commercial devices offer various stimulation modes and capabilities, but they fail to optimize dosing to therapeutic levels. The reasons for this failure include technical limitations in the stimulators, awkward electrode and user interfaces, and lack of automation. Recent advances in commercial transcutaneous electrical nerve stimulation technology, such as the SENSUS™ Pain Management System (NeuroMetrix, Waltham, MA, USA) utilize wearable designs, automation, and stimulation algorithms that adapt to patient physiology to optimize stimulation intensity (See Figure 2).

Figure 2. SENSUS Pain Management System



Review of the Medical Literature

Kumar and Marshall evaluated the use of transcutaneous electrical nerve stimulation in 31 patients with PDN.⁴⁸ Patients were treated for 30 minutes daily for four weeks. A 52% reduction in pain as measured along a visual analogue scale was seen that was statistically significant compared to pain reduction seen with use of a sham

device. Despite the small size of the study (18 patients in the treatment group and 13 in the sham group) and short duration, a statistically significant reduction in pain was seen compared to placebo. The study was performed in a randomized, prospective fashion providing scientific merit to further investigate this form of therapy.

This group further investigated the use of transcutaneous electrical nerve stimulation in a population of 23 patients.⁴⁹ In this study, patients were treated with amitriptyline followed by nerve stimulation or sham for a total of 12 weeks. While not FDA approved for the treatment of PDN, amitriptyline has been shown to provide pain relief.²⁸ Patients experienced a 66% reduction in pain that was statistically significant compared to those treated with amitriptyline plus sham or amitriptyline alone.

Forst and colleagues studied 19 patients in a double-blind randomized prospective study comparing transcutaneous electrical nerve stimulation to placebo. A reduction in pain in the treatment group of 32% was seen that was statistically significant compared to placebo.⁵⁰

Szopinski and colleagues studied 100 patients with both Type 1 and Type 2 diabetes with painful diabetic neuropathy.⁵¹ The treatment group consisted of 80 patients and the control group contained 20 patients. Patients in the treatment group wore a device that provided transcutaneous electrical nerve stimulation for 20 to 40 minutes 2 to 3 times each day for a duration of 1 to 6 months. Control patients wore the same device but it provided no electrical output. Pain was assessed on a visual analog scale ranging from 0% for no pain to 100% for maximum imaginable pain. In the treatment group the level of pain decreased from a score of 75% down to 22%. The control group had no significant decrease in pain. There was no difference in response between patients with type 1 diabetes versus type 2 diabetes in either the treatment group or the control group. At the time of enrollment in the study, all patients reported analgesic use with 38% reporting extensive use, 62% reporting moderate use and no patients reporting occasional use. At the conclusion of the study no patients in the treatment group reported extensive analgesic use, 33% reported moderate use and

67% reported only occasional use. There was no change in the use of analgesic therapy in the placebo group. Further, patients in the treatment group reported improvement in walking which was not seen in the placebo group.

The strengths of these studies are that they were placebo controlled and showed benefit that was both statistically significant and clinically meaningful. Two other studies, neither placebo controlled, have been performed. The first, by Julka and colleagues, was a retrospective analysis of efficacy utilizing a survey.⁵² Again, clinically meaningful statistically significant reduction in pain was seen. But there were a number of limitations

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to the methodology of this study including its retrospective nature, a lack of a control group and the fact that out of a total of 172 patients, data was collected on only 82.

Moharic and colleagues evaluated 65 patients treated with either transcutaneous electrical nerve stimulation, pregabalin or both.⁵³ Statistically significant pain reduction was seen in all 3 treatment groups with the decrease in pain intensity in the transcutaneous electrical stimulation group comparable to that seen in the pregabalin group. The lack of a placebo group and the fact that the study was not blinded limit the strength of the study. Patients treated with transcutaneous electrical nerve stimulation only were also evaluated for temperature thresholds, cold and heat pain thresholds, vibration perception thresholds and touch perception thresholds. No changes were found in any of these thresholds consistent with a central mechanism of action.⁵⁴

Hamza studied 50 patients with type 2 diabetes and peripheral neuropathic pain for greater than six months in a randomized, placebo-controlled crossover study.⁵⁵ One difference in this study was the use of acupuncture needles to deliver the electrical stimulation rather than using surface electrodes. Subjects were treated for 30

minutes three times per week for a total of three weeks. The placebo group received the placement of the acupuncture needles but received no electrical stimulation during the treatment periods. At the end of three weeks all patients underwent a one-week washout period and then were crossed over into the other group. Pain was assessed on a visual analogue scale 10 cm in length. Thus, the degree of pain ranged from no pain at 0 cm to a maximum of 10 cm. Subjects in the treatment group reported a statistically significant reduction in pain from 6.2 cm to 2.5 cm while patients in the placebo group reported no change. In addition, the treatment group reported a significant improvement in both activity and sleep scores. The placebo group reported no change in either score. Finally, subjects in the treatment group reported a 49% decrease in the use of non-opioid analgesic medications compared to 14% in the placebo group.

Reichstein studied 41 patients in a randomized controlled study comparing high frequency external muscle stimulation with transcutaneous electrical nerve stimulation.⁵⁶ While the external muscle stimulation group had a better response rate than the transcutaneous electrical stimulation group (80% vs. 33%), both groups did show a statistically significant reduction in symptoms. Among responders, the degree of pain reduction was similar in both groups. One significant limitation of this study is the limited amount of time patients were actually treated with transcutaneous electrical nerve stimulation. Patients received only 3 days of therapy with one 30 minute session each day. This limited exposure is not considered adequate to assess the affect of transcutaneous electrical stimulation therapy and may account for the relatively low response.⁵⁷ This study is also limited by the lack of a placebo control.

Two systematic analyses have been performed. The first, by Alvaro, reviewed data from 3 studies.^{48,49,52} As previously discussed, 2 of these studies were blinded with a placebo control and one was a non-blinded retrospective analysis. Based on the data, the authors concluded that the studies suggested that transcutaneous electrical nerve stimulation therapy was a “useful and beneficial, noninvasive, and non-pharmacological treatment modality for the management of neuropathic pain.”⁵⁸

The second analysis by Jin³⁴ involved a meta-analysis of data from 3 studies. Two of these studies overlapped with the Alvaro analysis^{48,49} as well as a more recent study.⁵⁰ All three of these studies were blinded, randomized, prospective and placebo controlled. In total, 78 patients were involved. The authors concluded that transcutaneous electrical nerve stimulation therapy “may be an effective and safe strategy in the treatment of symptomatic DPN.”³⁴

Overall, studies that have investigated the use of transcutaneous electrical stimulation for the treatment of PDN have generally shown clinical improvement with this therapy. Prospective placebo controlled trials have been limited by small numbers of patients although the results were statistically significant. Larger studies, have confirmed the results seen in these smaller studies. However, these larger studies were not as methodologically rigorous. In 2007, a task force of the European Federation of Neurological Societies reviewed the available data and concluded that transcutaneous electrical nerve stimulation therapy

In 2010, a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology assessing the efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders stated that it “should be considered in the treatment of painful diabetic neuropathy.”

was probably better than placebo (Level C) for the treatment of neuropathic pain. This review did not separate out diabetic neuropathy from other causes of neuropathic pain including post-herpetic neuralgia and peripheral mononeuropathies.³⁵ In 2010, a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology assessing the efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders stated that it “should be considered in the treatment of painful diabetic neuropathy.”³⁷

Table 3. Summary of Studies demonstrating efficacy of transcutaneous electrical nerve stimulation in the treatment of PDN.

Study	Design	Size	Duration of Treatment	Assessment	Findings
Kumar 1997 ⁴⁸	Blinded Randomized Prospective Placebo controlled	31 patients 18 treatment and 13 controls	30 minutes per treatment 1 x per day 4 weeks	1. Pain on a scale of 0–5 2. Visual Analog Scale	Reduction from 3.17 to 1.44 on pain scale.* 52% reduction vs. 27% in pain on Visual analog Scale.* *Statistically significant compared to placebo.
Kumar 1998 ⁴⁹	Blinded Randomized Prospective Placebo controlled In combination with amitriptyline	23 patients 14 treatment and 9 controls	30 minutes per treatment 1 x per day 12 weeks	1. Pain on a scale of 0–5 2. Visual analog Scale	Reduction from 3.2 to 1.4 on pain scale.* 66% reduction in pain with amitriptyline + transcutaneous electrical nerve stimulation vs. 55% with amitriptyline + sham vs. 26% with amitriptyline alone on Visual Analog Scale.* *Statistically significant compared to placebo.
Julka 1998 ⁵²	Non-blinded Non-randomized Retrospective No placebo	82 patients	35 minutes per treatment Average of 1.9 times per day Average 1.7 yrs	Pain on a scale of 0–10	Reduction of 2 points on pain scale. 34% reduction in pain.
Hamza 2000 ⁵⁵	Double-blind Randomized Prospective Placebo controlled Crossover	50 patients	30 minutes per treatment 3 x per week 3 weeks	Visual Analog Scale	Reduction from 6.2cm to 2.5cm on pain scale.* Improvement in activity score and sleep scores.* Reduction in nonopioid use of 49% in treatment group vs. 14% in placebo group. *Statistically significant compared to placebo.
Szopinski 2002 ⁵¹	Blinded Randomized Prospective Placebo controlled	100 patients 80 treatment and 20 controls	20–40 minutes per treatment 2–3 x per day 1–6 months	Visual Analog Scale	Reduction from 75 to 22 on 100 point scale.* Reduction in analgesic use.* Improvement in mobility.* *Statistically significant compared to placebo.
Forst 2004 ⁵⁰	Double-blind Randomized Prospective Placebo controlled	19 patients	12 weeks	Neuropathy Total Symptom Score (NTSS)	Reduction of 32% on NTSS vs. placebo. *Statistically significant compared to placebo.

Table 3. Summary of Studies demonstrating efficacy of transcutaneous electrical nerve stimulation in the treatment of PDN CONT.

Study	Design	Size	Duration of Treatment	Assessment	Findings
Reichstein 2005 ⁵⁶	Non-blinded Randomized Prospective Compared transcutaneous electrical nerve stimulation to High frequency muscle stimulation therapy No placebo	41 patients	30 minutes per treatment 1 x per day 3 days	Pain on a scale of 1–10	80% of muscle stimulation group and 33% of the transcutaneous electrical nerve stimulation group had reduction in pain. Pain reduction was similar in both groups among responders.
Moharic 2009 ⁵³	Non-blinded Randomized Prospective Compared transcutaneous electrical nerve stimulation to pregabalin therapy No placebo	65 patients 46 treated with transcutaneous electrical stimulation 5 received only pregabalin 14 received both	3 hours per treatment 1 x per day 3 weeks	Visual Analog Scale	51% decrease in intensity, 41% decrease in unpleasantness and 38% decrease in interference with sleep in the transcutaneous electrical nerve stimulation group vs. 53%, 54% and 80% in the pregabalin group.* *All improvements statistically significant compared to baseline.
Moharic 2010 ⁵⁴	Non-blinded Non-randomized Retrospective No placebo	46 patients	3 hours per treatment 1 x per day 3 weeks	Temperature, cold and heat pain thresholds, vibration perception thresholds and touch perception thresholds	No improvement in temperature, cold and heat pain thresholds, vibration perception thresholds and touch perception thresholds.

SUMMARY

PDN, the clinical scenario of neuropathic pain arising as a direct consequence of DPN, is a common complication of diabetes. This pain can be debilitating and have a significant negative impact on a patient's quality of life. A number of mechanisms have been proposed to account for this pain including gating theory, changes in spinal nervation, changes in spinal and central nervous system sensitization as well as ectopic electrical impulses and increased spontaneous C fiber activity. Treatment involves optimization of metabolic parameters to prevent progression and to provide symptomatic relief. Metabolic parameters include glycemic control as well as cardiovascular risk factors. A number of pharmacologic agents have been used to provide symptomatic relief however all have

limitations in terms of their efficacy as well as side effects profile. In addition to pharmacologic therapies, a non-pharmacologic approach with the use of transcutaneous electrical nerve stimulation has also been shown to be of benefit. The physiological principle underlying transcutaneous electrical nerve stimulation is that excitation of A β sensory nerve fibers, primarily the deep tissue afferents, blocks transmission of pain signals to the brain. A number of studies have been performed demonstrating the efficacy of transcutaneous electrical nerve stimulation for the treatment of PDN. These include blinded, randomized, prospective, placebo controlled studies demonstrating benefit. Based on this data the American Academy of Neurology has stated that transcutaneous electrical nerve stimulation should be considered in the treatment of PDN.³⁷



Dr. Snow has extensive experience in diabetes, including patient care, strategic initiatives, and clinical research. Dr. Snow is the Chief Medical Officer at NeuroMetrix and has spent 17 years at the Joslin Diabetes Center, Boston, MA. Dr. Snow served as the Director Medical Programs at the Joslin Center

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