Electric Current and Local Anesthetic Combination Successfully Treats Pain Associated With Diabetic Neuropathy

In an open-label trial, a unique electric current combined with a local anesthetic reduced pain in patients who have diabetic neuropathy.

Cynthia Cernak, DPM, FACFAS, FACPOPPM, FASPS
Wisconsin Neuropathy Center
Kenosha, Wisconsin

Elizabeth Marriott, MD
Aurora Advanced Healthcare
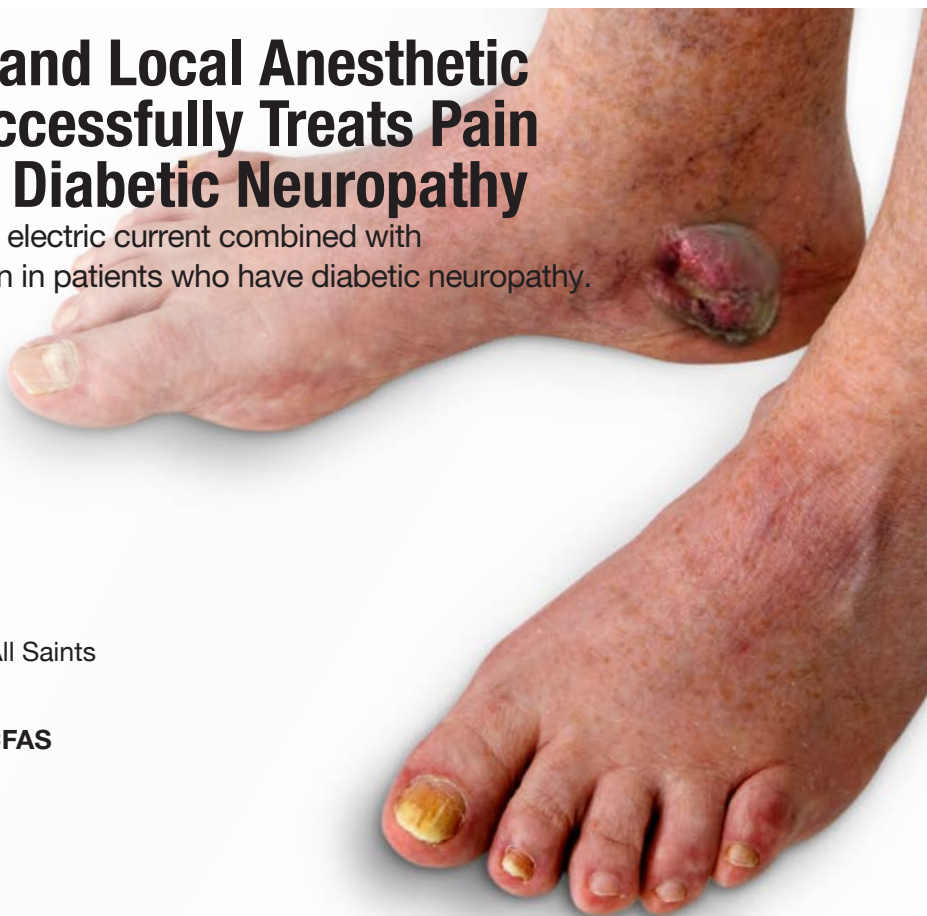Grafton, Wisconsin

John Martini, MD
Wheaton Franciscan Healthcare–All Saints
Racine, Wisconsin

Jeremy Fleischmann, DPM, AACFAS
Briana Silvani, R.NSC.T
Michael T. McDermott
Wisconsin Neuropathy Center
Kenosha, Wisconsin

Editor's Note: This article describes an advance in electromagnetic treatment—the simultaneous use of a local anesthetic with an electric current. The two combined measures produce a block of nerve transmission by different mechanisms, which not only provide immediate pain relief but lasting relief in many patients by a reset mechanism that we, frankly, don't fully understand.

Many studies show that electric currents and electromagnetic energy waves derived from an electric current, including laser, infrared, and radio, provide short-term pain relief by blocking nerve transmission at the spinal cord gates, releasing local endorphins, and reducing edema. Tissue healing, which provides long-term relief, is produced by activation of fibroblasts and angiogenesis. The study described in this paper tackles a difficult patient population: diabetics with neuropathy. Results were outstanding. We should now seriously consider adding a local anesthetic to our electromagnetic treatments to enhance therapeutic outcomes.

More than 24 million Americans have diabetes, and it is estimated that between 40% and 50% of these people will experience some form of nerve damage from their diabetes.[1] Diabetic peripheral neuropathy (DPN) is a major cause of morbidity in patients, which is often manifested in the form of pain.

Considered the most distressing symptom of DPN, pain can be potentially disabling.[2] Pharmacologic treatment of pain in patients with DPN includes tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, and anticonvulsants.[3] The only two drugs approved by the FDA for DPN are the antidepressant duloxetine (Cymbalta) and the anticonvulsant pregabalin (Lyrica). Patients with localized DPN may also
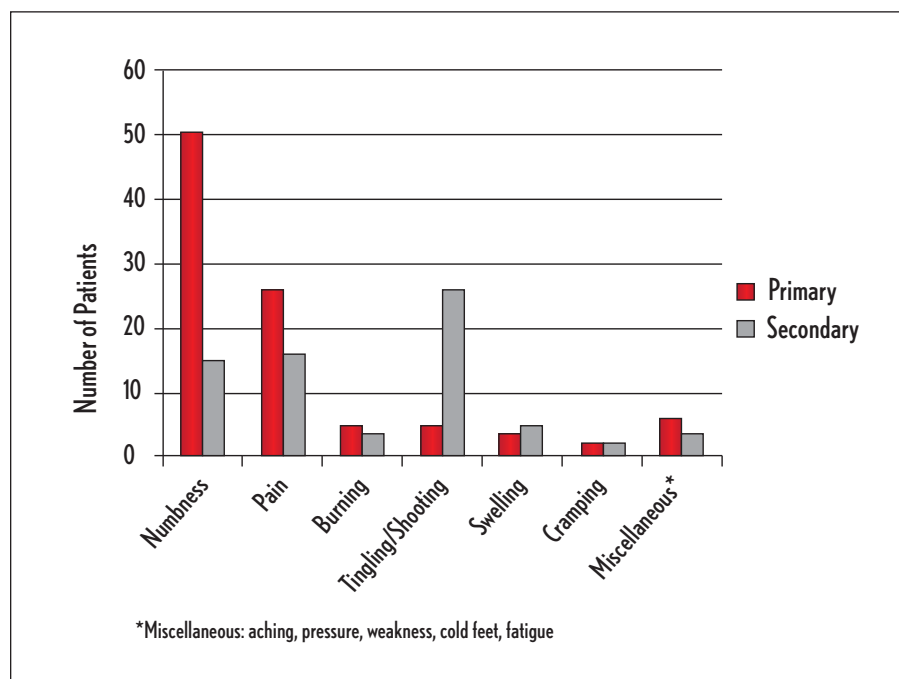
Figure 1. Reported pre-treatment pain symptoms. All patients evaluated (n=101) were asked to describe their pain symptoms (some only had primary symptoms).

try lidocaine patches (Lidoderm) or capsaicin before using a systemic medication.[4]

Despite advances in understanding the metabolic causes of neuropathy, treatments aimed at interrupting the pathological processes have been limited. What is known is that the first pathological change in the microvasculature is vasoconstriction, and as the disease progresses, neuronal dysfunction correlates closely with the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia.

Neuronal ischemia is a well-established characteristic of diabetic neuropathy (DN). Since all organs and systems are innervated, DN affects all peripheral nerves, including pain fibers, motor neurons, and autonomic nerves.

Available treatment options offer limited efficacy and potential side effects.[5] Therefore, our approach was to combine bupivacaine with electrical stimulation. The bupivacaine is used to dilate capillaries and venules in the microcirculatory system, thereby causing increased circulation, which has been shown effective in various clinical studies to decrease pain in diabetic and nondiabetic patients.[6] The electrical stimulation will provide both varied amplitudes and frequencies of electronic signals through computer-controlled, exogenously delivered specific parameter electroanalgesia.

While both bupivacaine and electrical stimulation are well studied, it is appropriate to further describe the difference between the electroanalgesia chosen versus standard electric current devices. Most electric current devices fall into a low frequency class with an amplitude modulation (AM) output of <2,000 Hz and 20 mAmp power. In these types of low-level

machines, pain decrease is noted but there is no prolonged relief of pain.[7] The device used in this study incorporates both AM, frequency modulation (FM), and AM/FM modes of stimulation to prevent accommodation. A frequency range of 2,500 to 23,000 Hz with an energy delivery of up to 100 mAmp is possible. This allows for all of the benefits of medium frequency (2,000 to 100,000 Hz) stimulation, giving the patient the best possible chance for pain relief.

Methods

One hundred fourteen patients who had DPN-related pain were offered entry in this open-label trial. All study participants received a description of the treatment protocol and provided written informed consent to participate in the study. A total of 101 patients chose to complete the combined electric current and local anesthetic therapy protocol. The first patient enrolled in the trial in May 2008 and the last to enroll was in July 2010.

Of the 101 patients evaluated, there were 58 females and 43 males. The mean age of the study participants was 66.5 years old with a range of 31 to 87 years old. Patient ethnicity included 87% Caucasians, 9% Blacks, 4% Hispanics.

The entry criteria for this study were pain symptoms related to DPN. Figure 1 describes the primary and secondary pain characterized by each patient. Of the 101 patients enrolled, 67.6% had confirmed type 1 diabetes mellitus or type 2 diabetes, and 32.4% had prediabetes.

Procedures

Out of the 101 patients, 60 received a baseline nerve conduction study (NCS) before their first treatment. Patients received a total of 12 electroanalgesia treatments, which were

given 3 times per week (Monday, Wednesday, and Friday) for 4 weeks. The treatment duration was 25 minutes applied to either one or both feet, depending on where the neuropathy was present. During the first and third (Monday and Friday) treatment of each week, injections of 0.25% bupivacaine were performed using a 27-gauge needle. The injection sites were determined by the peripheral distribution of neuropathic pain. Up to four nerves were blocked in the same visit, including the sural, superficial peroneal, deep peroneal, saphenous, and posterior tibial.

Pre- and post-treatment pain assessments were given to each patient. The two assessments provided were the numeric rating system (NRS); and a quality of life pain questionnaire, which was administered either before or during treatment. The questionnaire measured and assessed quality of life–related items such as sleep, balance, walking, exercise, and participation in everyday activities creating a post-treatment score for each patient. At the conclusion of the study, if patients reported an incomplete response (defined as any pain score greater than 0 on the numeric rating scale) from the initial protocol, they were offered to complete a second course of therapy.

Of the 101 study participants, a subset of 60 were given a post–NCS to measure the effects of treatment on the function and ability of electrical conductance of the motor and sensory nerve.

Results

The average pre-treated pain score on a scale of 0 to 10 was 5.39, and the average post-treatment score was 0.98, indicating an 81.8% reduction in symptoms. It is important to note that 31 of the 101 patients reported numbness as their primary symptom,

Table 1. Patient Response to Pain Scale and Questionnaire			
% Improvement (Pain Scale)	Number of Patients	% Improvement (Questionnaire)	Number of Patients
100	37	100	0
90-99	2	90-99	38
80-89	13	80-89	27
70-79	3	70-79	16
60-69	6	60-69	7
50-59	4	50-59	2
40-49	2	40-49	0
30-39	1	30-39	2
20-29	2	20-29	4
10-19	0	10-19	3
0-9	31*	0-9	2

*31 patients described numbness as no pain or N/A. Each was recorded as "0."
Table 1 describes the improvement between pre- and post-treatment scores for all study participants. The questionnaire responses help us better understand the 31 patients who described numbness as no pain during our visual analogue assessment.

which they did not define as pain, thereby entering an N/A when questioned by staff members. The above results interpret all N/A answers as a "0." If we evaluate the 70 patients who did not report numbness as their primary symptom, the pre-treatment pain scores were 7.79, and the post-treatment pain score was 1.0, indicating an 87.2% reduction in symptoms.

The results in the first column of Table 1 identify the same 31 patients as those who did not receive an improvement in pain, but the patient response questionnaire captured their improvement in quality of life. Post-treatment quality of life benefits included improved pain-free sleeping, balance, walking, and enhanced ability to exercise—all of which were reported consistently across both genders.

Twenty-three patients who reported an improved pain score had recorded an NRS score indicating that their pain was not entirely resolved. These patients requested a second course of treatment to further improve the pain response. At the conclusion of the second treatment, all study participants reported a pain score of "0," and responses to the pain questionnaire (quality of life) showed that 15 of the 23 patients had a 90% to 99% improvement; 5 patients had an 80% to 89% improvement; 2 patients had a 70% to 79% improvement; and 1 patient had a 0% to 9% improvement.

Objective Results

Pre– and post–NCS assessing both motor and sensory nerves were given to a subset of patients within one

Table 2. Patient Response to Motor and Sensory Nerve Conduction Studies (n=57)[a]					
	Peroneal Motor Nerve		Tibial Motor Nerve		Peroneal Sensory Nerve	Sural Sensory Nerve
	Ankle	Fibula Head	Ankle	Pop Fos	Lower Leg	Lower Leg
Improvement	25	25	29	27	23	18
No Improvement	30	30	21	21	6	3
No Response	2	2	7	9	28	36

[a] Patients were randomly selected into a substudy in which 57 patients received pre- and post-treatment nerve conduction velocity studies to determine motor and sensory treatment response.
Pop Fos, popliteal fossa

month of completion of the combined electric current and local anesthetic therapy protocol. A total of 3 patients out of 60 discontinued the trial prior to getting their post-NCS, leaving 57 patients for evaluation.

The results in Table 2 demonstrated a trend toward increased amplitude and decreased latency of motor nerve function after treatment. These trends in motor nerve function may represent a decline in neurological morbidity of DPN as nerve function improves. In both sensory nerves tested, the plurality of patients did not have a recordable response both pre- and post-treatment. However, more than 40% of patients did show an improvement in peroneal sensory nerve conduction while more than 31% showed an improvement in their sural sensory nerve.*

Substudy patients were further categorized by disease severity. Of the 57 patients evaluated, by definition, 19 patients were placed in each category: mild, moderate, and severe.[8]

The graph in Figure 2 (page 35) analyzes the percent of patients stratified by disease severity that showed improvement after combined electric current and local anesthetic therapy. The results indicate that patients who were diagnosed and treated earlier had improved motor results and significantly better sensory results. Also of importance is the difference between motor and sensory nerve

improvement in patients with severe symptoms. Because motor response typically precludes sensory response, it is possible that patients with severe disease may not have experienced their full results from the treatment protocol at the time the NCS was completed.

Patients who discontinued the trial were a result of personal choice, disinterest, and natural death. No trial discontinuations were related to the combined electric current and local anesthetic therapy protocol or side effects from either the injections or electroanalgesia.

Out of the 101 study participants, 23 are 1 year post-treatment without relapse of pain symptoms. Each is reporting improved quality of life and benefitting from the therapy.

Discussion

The results of this open-label trial show that combined electric current and local anesthetic therapy decreases pain in a significant number of patients who have DPN. These results have been clearly proven subjectively. Our objective findings through nerve conduction velocity tests have also shown improvement in motor nerve function after treatment and some improvement in sensory nerve function. Sensory nerve improvement was experienced more by patients staged with mild disease, which indicates that either early diagnosis and treatment

may be an important factor in projecting outcomes or that the timing of the post-treatment NCS may have been too close to the patient's combined electroanalgesic therapy.

The skepticism entering the trial by all researchers existed on multiple levels. First, there was a belief that all electricity was considered the same, and secondly, we expected that this protocol would yield results similar to Anodyne. Anodyne is an infrared light therapy system that was cleared by the FDA in 1994. It uses an 890 nm wavelength, which provides a combination of topical heat and an increased local release of nitric oxide to relieve pain. While the authors found Anodyne to provide some relief, they learned that their patients would require continued maintenance therapy to feel better. Moreover, when treatment was terminated, most patients became symptomatic.

Our first concern—that all electricity is created equal—was disproved. While we are truly in the early phase of determining what different amplitudes and frequencies in different parts of the body may do for different diseases, we are confident that varied intensities and duration of electronic signals elicit an improved response with less accommodation. The identical protocol was tested with alternative electrical stimulation devices, which were missing one or more of the key differentiating engineered designs of

the tested product. These characteristics are a frequency range of 2,500 to 23,000 Hz, an energy delivery system providing up to 100 mAmp, and the incorporation of both AM/FM modes of stimulation.[9] Results using two alternative products with the protocol were less than successful.

Low–frequency stimulation devices (eg, transcutaneous electrical nerve stimulation) will stimulate the nerve at a frequency that allows the nerve to recover between stimulus deliveries. This produces a decrease in pain, according to the Melzack and Wall theory of gait control of pain at the spinal cord level. The energy delivered is limited, and the therapy has no prolonged effect. The use of AM/FM modulation with a frequency of 4,000 to 23,000 Hz allows pain control similar to electric current devices but has the added benefit of a prolonged effect.[10]

High-frequency electroporation of the skin results in increased power delivered to deep tissue with potential healing of deep tissue and improved blood flow. According to Wedensky, inhibition is sustained depolarization—an inability to recover from depolarization until a current exceeds 2,000 Hz through multiple stimulations within an absolute refractory period of the nerve cell. Most nerve cells have absolute refractory periods of 1/1,000 seconds (or more), so a frequency of more than 2,000 Hz will cause sustained depolarization. Therefore, our stimulation rate of more than 4,000 Hz is fast enough to block the propagation of nerve impulses. The middle frequency (2,000 to 100,000 Hz) delivered energy that allows cAMP (second messenger) to release in the cell starting processes for healing and increased metabolism with a balancing of cell function. cAMP also blocks release of inflammatory
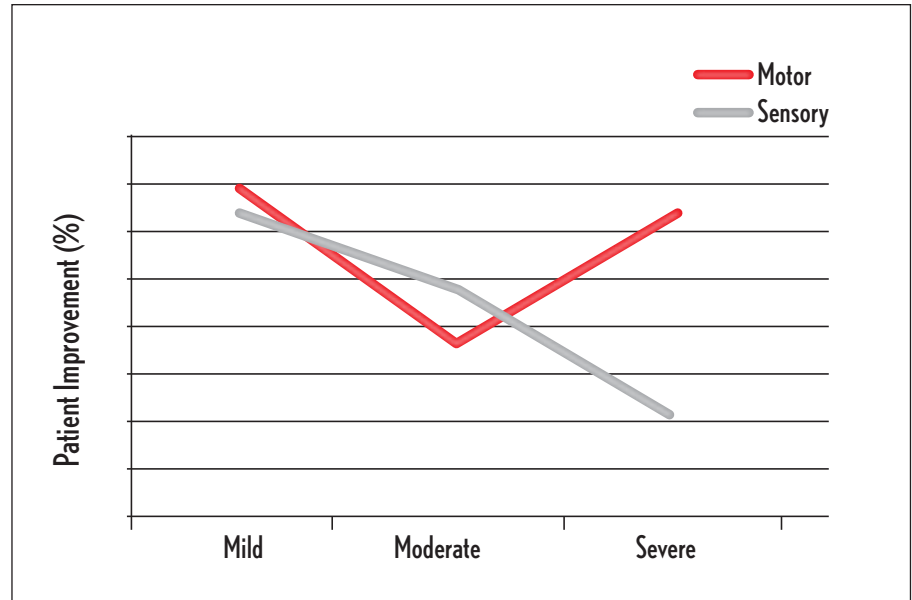

Figure 2. NCS findings: results based on disease severity. The 57 patients who had pre– and post–nerve conduction studies were categorized by disease severity to determine whether early identification and treatment of disease yielded improved response.
NCS, nerve conduction study

mediators from the cell that may be partially responsible for the pain response.[11,12] These responses are only seen with frequency rates of more than 4,000 to 20,000 Hz,[13] which may help explain the results seen in this study.

Nerve blocks interrupt the passage of impulses through a nerve via chemical means. These nerve blocks are technically considered electrical because they occur at voltage-gated channels. We believe that by combining electricity with nerve blocks, patients experienced a synergistic effect, which led to positive and prolonged outcomes.

Our second concern addressed duration of effect and the need for maintenance therapy after the treatment protocol is complete. Currently, 21 of the 101 patients evaluated are 1 year or more post-treatment without relapse of pain symptoms.

The trial results exceeded our expectations and patient feedback was impressive. There are currently

few satisfactory therapies available that manage the numbness and pain associated with DPN. Therefore, there is a clear need for additional treatments—especially those such as combined electric current and local anesthetic therapy—that demonstrate clinical efficacy without the side effect profile of other therapies. While we are comfortable with the clinical results, we have extended our goal to further understand the physiological effects of combined electroanalgesia therapy. The following information is derived from an ongoing substudy that assesses pre– and post–epidermal nerve fiber density (ENFD) biopsies on patients who were treated with combined electroanalgesia therapy. To date, the 5 patients who have completed the ENFD substudy have experienced small nerve fiber regeneration. These results are promising and clearly require deeper analysis.

The results of this open-label study indicate that using combined electric current and local anesthetic therapy

to treat the pain and numbness associated with DPN is effective and is not associated with any side effects. Patient follow-up will be provided to better understand the duration of therapy and its long-term effects on motor and sensory nerve function.

Acknowledgement: The authors gratefully acknowledge the following for their contributions to these studies: William Paul, MD, University of Florida Department of Anesthesiology, and Gary DelloStritto. The authors also thank the patients who participated in these open-label studies.

*Note: Nationally, a 5% margin of error is associated with NCS. To reduce variability, the investigator ensured that all pre- and post-tests were completed by the same nerve technician with the same machine in the same environment. For all NCS, patients who showed a 5% improvement or less were recorded as "no improvement."∎

Authors' Bios: *Cynthia Cernak, DPM, FACFAS, FACPOPPM, FASPS, has been a practicing podiatric surgeon for more than 15 years. She graduated from Scholl College of Podiatric Medicine in Chicago, Illinois, in 1989. Dr. Cernak is board certified in podiatric surgery and orthopedics. She is a fellow of the American College of Podiatric Surgeons, and a fellow of the American College of Podiatric Orthopedics. In 2004, Dr. Cernak completed fellowship training in decompressive nerve surgery at the Dellon Institute in Baltimore, Maryland.*

She is a founding member of the Institute of Peripheral Nerve Surgery. Dr. Cernak is a frequent lecturer on the topics of complications and management of the diabetic foot, and treatment options for peripheral neuropathy. She currently serves on the board of directors for the alumni association of Rosalind Franklin University of Podiatric Medicine. She also recently became a member of the Association of Extremity Nerve Surgeons and the American Society of Podiatric Surgeons.

Elizabeth Marriott, MD, earned her medical degree from Loyola University Chicago Stritch School of Medicine. Her internal medicine internship and residency in neurology were completed at Loyola University Medical Center. She is board certified in neurology and vascular neurology. Her areas of interest include vascular neurology, stroke, and cerebrovascular disease. She also treats a wide range of neurological disease as a general neurologist.

John Martini, MD, is a family practitioner with 25 years' experience as a family doctor in Racine and Kenosha, Wisconsin. He received the Compassionate Doctor Recognition in 2011, in addition to a Patients' Choice Award that same year. Dr. Martini graduated from the Medical College of Wisconsin in Milwaukee. He completed a residency and is board certified in family practice. He is currently Associate Professor of Clinical and Community Medicine with the Medical College of Wisconsin.

Jeremy Fleischmann, DPM, AACFAS, is a podiatry surgeon who completed his residency at Regions Hospital in St. Paul, Minnesota. He worked at Wisconsin Neuropathy Center, LLC, from 2009 to 2011, and helped treat neuropathy patients during his tenure there.

Briana Silvani, R.NSC.T, is a board-certified electroneurodiagnostic technologist specializing in nerve conduction studies. She has been an active member of the American Association of Electrodiagnostic Technologists since 2004.

Michael T. McDermott is a medical technician at Wisconsin Neuropathy Center, LLC, who is involved with the doctors during the treatments. Mr. McDermott helps educate patients about the treatments and ensures they follow the protocol set by physicians. Mr. McDermott is also a member of the US Army National Guard.

Dr. Cernak and her co-authors have no financial information to disclose.

References

1. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2008.

2. Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology.* 1993;43(4):817-824.

3. Mendell JR, Sahenk Z. Clinical practice: painful sensory neuropathy. *N Engl J Med.* 2003;348(13):1243-1255.

4. King SA. Diabetic peripheral neuropathic pain: effective management. http://www.consultantlive.com/pain/article/10162/1337377. Accessed January 23, 2012.

5. Robinson-Papp J, Simpson DM. Safety profile of treatment in diabetic peripheral neuropathic pain. *Pain Med.* 2007;8(suppl 2):S43-S49.

6. Rader AJ, Barry TP. A proposed mechanism for pain relief following MIRE therapy. http://www.diabeticmctoday.com/HtmlPages/DMC1106/DMC1106_neuro_rader.html. Accessed January 23, 2012.

7. Reichstein L, Labrenz S, Ziegler D, Martin S. Effective treatment of symptomatic diabetic polyneuropathy by high-frequency external muscle stimulation. *Diabetologia.* 2005;48(5):824-828.

8. Rosenfalck P, Rosenfalk A. *Electromyography: Sensory and Motor Conduction.* Copenhagen, Denmark: Rigshospitalet Laboratory of Clinical Neurophysiology; 1975.

9. Woessner J. Electric nerve blocks. *Weiner's Pain Management.* Boswell M, Cole E (eds). Informa Healthcare: London, UK; 2006:1233-1242.

10. Pliquett U. Recent advances in skin electroporation: mechanism and efficacy. *Second World Congress for Electricity and Magnetism in Biology and Medicine*; 1997:44.

11. Odell RH Jr, Sorgnard RE. Anti-inflammatory effects of electronic signal treatment. *Pain Physician.* 2008;11(6):891-907.

12. Odell RH Jr, Sorgnard R. New technique combines electrical currents and local anesthetic for pain management. *Pract Pain Manage.* 2011;11(5):52-68.

13. Schwartz RG. Electric sympathetic block. *Osterr Z Phys Med Rehabil.* 2006;16(1):3-10.