Static Magnetic Field Therapy for Symptomatic Diabetic Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: To determine if constant wearing of multipolar, static magnetic (450G) shoe insoles can reduce neuropathic pain and quality of life (QOL) scores in symptomatic diabetic peripheral neuropathy (DPN).

Design: Randomized, placebo-control, parallel study.

Setting: Forty-eight centers in 27 states.

Participants: Three hundred seventy-five subjects with DPN stage II or III were randomly assigned to wear constantly magnetized insoles for 4 months; the placebo group wore similar, unmagnetized device.

Intervention: Nerve conduction and/or quantified sensory testing were performed serially.

Main Outcome Measures: Daily visual analog scale scores for numbness or tingling and burning and QOL issues were tabulated over 4 months. Secondary measures included nerve conduction changes, role of placebo, and safety issues. Analysis of variance (ANOVA), analysis of covariance (ANCOVA), and chi-square analysis were performed.

Results: There were statistically significant reductions during the third and fourth months in burning (mean change for magnet treatment, −12%; for sham, −3%; P < .05, ANCOVA), numbness and tingling (magnet, −10%; sham, +1%; P < .05, ANCOVA), and exercise-induced foot pain (magnet, −12%; sham, −4%; P < .05, ANCOVA). For a subset of patients with baseline severe pain, statistically significant reductions occurred from baseline through the fourth month in numbness and tingling (magnet, −32%; sham, −14%; P < .01, ANOVA) and foot pain (magnet, −41%; sham, −21%; P < .01, ANOVA).

Conclusions: Static magnetic fields can penetrate up to 20 mm and appear to target the ectopic firing nociceptors in the epidermis and dermis. Analgesic benefits were achieved over time.

Key Words: Diabetic neuropathies; Magnetics; Rehabilitation.

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DIABETIC PERIPHERAL NEUROPATHY (DPN) is a common and often disabling complication of diabetes mellitus (DM). Depending on criteria, DPN is estimated to occur in 50% to 90% of individuals with diabetes for more than 10 years.1-4 As many as half of the 16 million diabetics in the United States will experience neuropathic pain at some point in their lives.5-9 DPN begins insidiously, presenting as a symmetrical sensory polyneuropathy that follows a stocking-glove pattern. Selective involvement of unmyelinated C fibers and small myelinated A delta fibers produces pain of the burning dysesthetic type and is often accompanied by hyperalgesia and allodynia in the feet.7,10-12 Neuropathic pain symptoms fluctuate and can be described as superficial, deep, aching, lancinating, constant, or episodic. Complaints are often worse at night. Although initial symptoms and the course of DPN vary, once neuropathic pain is established, it is almost always progressive, leading to increased discomfort and disability.5,13-15 Furthermore, individuals with DPN are at augmented risk for foot trauma and infections that may necessitate amputative procedures.2,16

From a pathophysiological standpoint, these symptoms are believed to be secondary to ectopic firing of nociceptive afferent axons that are undergoing degeneration.7-9,12 This ectopic depolarization appears to be related to dysregulated expression of sodium and calcium channels17-19 and a deficit in the potassium-internal rectifying channel.20-22 Neurons at the level of the dorsal root ganglion (DRG) also become hyperexcitable after peripheral nerve injury, presumably because of loss of peripheral inhibitory influences.23 Currently, there are no treatments that reverse or arrest progressive diabetic polyneuropathy.24 A variety of standard oral therapies used for symptomatic neuropathic pain include tricyclic antidepressants,25 antiepileptic medications,26 and narcotic analgesics.27,28 Additionally, topical products such as capsaicin29,30 have been applied and have produced incomplete pain relief and significant side effects. Overall, the results have been disappointing and associated with significant side effects.15,31,32 The search for reliable, safe, and effective mainstream treatments for the neuropathic pain of DPN remains a major challenge.13,15,25,27,31,34 and, not surprisingly, patients have explored a variety of alternative approaches, including homeopathy, acupuncture, and magnetic...
therapies. Spurred on by anecdotal reports, the use of permanent magnets for relief of pain has become extremely popular in recent years, with consumer spending exceeding $500 million in the United States and Canada and $5 billion worldwide.\textsuperscript{35,36} The idea that magnetic energy from commercially available, weak magnets applied locally to the feet could influence chronic neuropathic pain may seem absurd, and yet this approach is not new.\textsuperscript{37-41} In the absence of randomized, placebo-controlled trials, the medical community has been understandably skeptical, which has limited the acceptance of magnets as a valid option for pain relief.\textsuperscript{42,43} However, 2 prior pilot studies successfully showed reduced neuropathic pain in 75\% and 90\% of patients with refractory DPN over a 4-month period, with constant application of commercial multipolar foot magnets (450G).\textsuperscript{55,56} These surprising and unexpected favorable results prompted the present study—a nationwide, randomized placebo-controlled investigation into the legitimacy of static magnetic fields in the relief of pain from DPN.

\textbf{METHODS}

\textbf{Enrollment Criteria}

From August 1999 through January 2001, 375 subjects with symptomatic symmetrical sensory and motor diabetic peripheral neuropathy (DPN stages II or III), as defined by Dyck et al.\textsuperscript{44,45} were recruited from 48 sites in 27 states. Consecutive patients from neurologic, pediatric, and diabetic clinics or private practice were enrolled. A few centers advertised their participation in this nationwide study to attract eligible volunteers. The primary providers were skilled clinicians who had previously participated in pharmacologic studies of diabetes and/or pain management. Enrollment criteria required that all subjects have at least 2 abnormalities on neurologic examination (sensory, motor, reflex), moderate (II) to severe (III) neuropathic pain, abnormal nerve conduction or quantitative sensory testing, and/or symptoms of autonomic dysfunction. Symptoms had to be constant and present over 6 months and refractory to various medications. Subjects included persons with insulin-dependent diabetes mellitus (IDDM) and those who were not insulin dependent (NIDDM). Subjects were excluded if other systemic diseases could potentially explain their symptoms. As a safety precaution, pregnant women and subjects who had mechanical insulin pumps or cardiac pacemakers were also excluded. Subjects tabulated validated\textsuperscript{46-50} daily pain scores and similar, but unvalidated, quality of life (QOL) scores for 4 months and agreed that they would not attempt to break blinding of the foot devices. They also agreed to wear the devices constantly, 24 hours per day. Moderate pain was defined as scores of 5.0 to 6.99 and severe pain was defined as 7 and higher. No new analgesic drugs were allowed during the study, but individuals could remain on (or reduce) their current regimen of neuropathic pain medication. The randomized, placebo-controlled, parallel design study was fully explained to all subjects and voluntary withdrawal was allowed without prejudice.

\textbf{Randomization}

Demographic data (age, height, weight, gender, race, glycated hemoglobin [Hb A\textsubscript{1c}], family history, duration of DM, complications of DM, treatment of DM) were collected at each site. Subjects completed a 2-week baseline Likert visual analog scale (VAS) quantification of their pain symptoms 3 times daily to establish a reliable mean pain score. QOL scores were recorded once daily to measure (1) sleep disturbance secondary to foot pain and (2) exercise-induced foot pain after a 10-minute exertion such as walking or other physical activity. After eligibility was confirmed and written informed consent accepted, subjects were randomized consecutively (1:1 via computer assignment) to receive an active magnetic shoe insole or a sham insole of similar appearance. Randomization was stratified by center and gender. Neither the subject nor the research staff was aware of the treatment allocation. If corrective trimming of the device was necessary to provide a comfortable fit in the shoe, a noninvolved secretary or nurse would trim them along identifiable lines around the margins. The subjects and site investigators were not present if trimming was necessary. All data were submitted to a central data bank under the supervision of the statistician who was aware of the assignments.

\textbf{Magnetic Devices}

The devices used in the present study are comprised of a reinforced and flexible magnetic rubber compound pressed into a sheet and cut into the shape of a shoe insole for men and women. Strontium ferrite powder is mixed into this rubber binder and magnetized with a patented pattern of alternating magnetic poles. Each pole is adjacent to and contiguous with another triangular-shaped magnetic pole of opposite polarity on each of the 3 sides of the triangle. This pattern produces a continuous array of alternating magnetic poles in every direction across the insole (fig 1). The strength of the magnetic field is 450G, as measured with a conventional gauss meter on the surface of the insoles at the center of the triangle (10,000G = 1T). The field depth of penetration is 20mm and is reduced inversely with the square of the distance. By far, the simple, most direct method of determining field strength at various distances from the insole surface is by instrument measurement. For example, using a Lakeshore 420 gauss meter with a flat transverse probe has an accuracy of ±25\%. The effective field of the magnet from the insole surface is 20mm. Beyond 20mm, the magnetic field measures in the range of the ambient magnetic field of the earth at about 0.5G. The maximum surface field strength of the magnetic insole is 450G. At a 1-mm distance from the surface, the field strength drops to 249G. At 2mm, the field strength is measured at 150G. At 3mm (approximately \(\frac{1}{8}\)in), the field strength is 90G. Flux density at the target area may be more clinically relevant than the magnetic reading at the surface of the magnet. The specific flux density, however, at the target area is unknown. At 13mm above the surface of the magnetized insole, the reading is only 1.5G. The sham insole’s gauss meter readings did not exceed the 0.5G of the earth’s magnetic field. Both sham and active magnetic shoe insoles could not be distinguished in terms of appearance, consistency, or weight. The magnetic insoles used in the present study were manufactured by Nu-Magnetics Inc,\textsuperscript{19} and are commercially sold under the brand name of Magsteps\textsuperscript{\tiny®} by Nikken Inc.\textsuperscript{19}

\textbf{Outcome Measures}

Pain was measured on an 11-point numeric pain rating scale (VAS; scale range: 0, no pain; 10, worse possible pain). The primary efficacy measure was the reduction in neuropathic pain scores at week 16 compared with baseline scores. We also compared month-to-month changes. We looked specifically at 2 of the most common pain symptom scores of numbness or tingling and burning. Each symptom was recorded 3 times daily so to reduce any new variables (VAS range, 0–10). Similarly, QOL issues were considered primary efficacy measures with reduction of exercise-induced foot pain and sleep interruption secondary to pain (VAS range, 0–10). These were recorded once daily. Secondary outcomes compared baseline
and 16-week values of neurologic examinations, nerve conduction velocity (NCV), quantitative sensory testing (QST) thresholds (Neurometer or Case IV), and other electrophysiologic tests. Safety measures with tabulation of adverse events were monitored as was cause for dropouts. Additionally, an interim study performed before the end of this study at selected sites assessed masking and bias by asking patients and investigators whether they believed that a placebo or active device was used or whether they had no opinion.

Sites
There were 48 investigative sites in 27 states. They included 11 university-based centers and 37 private practices. A neurologic examination was performed before entry to identify the presence of a sensory peripheral polyneuropathy in the feet that met the Dyck criteria of moderate (II) to severe (III) DPN. NCVs of the peroneal and/or posterior tibial (motor) and sural nerves (sensory) were performed in a standardized manner to confirm the presence of neuropathy. Selected sites performed forced-choice QST by using Neurometer (CPT) or Case IV equipment and other neurophysiologic tests, such as biothesiometry and sympathetic skin response (SSR). Because no standard, validated device exists and controversy about their merits surrounds the various devices, we let each site use their standard analysis technique.

Investigational Review Board
Phelps Memorial Hospital Investigational Review Board (IRB) reviewed and approved the protocol, as did IRBs at individual university centers. Phelps Memorial served as a central IRB for many investigative sites and appropriate safety and progress data were submitted to this IRB in a timely fashion. All patients provided written informed consent to participate in this study.

Statistical Analyses
For each of the 4 outcome measures (burning, numbness and tingling, foot pain, sleep scores), a 2 (treatment, sham) × 5 (baseline, 1mo, 2mo, 3mo, 4mo) repeated-measures analysis of variance (ANOVA) was used to assess possible differences between treatment and sham groups over the course of the study. These analyses were followed by a 2 (treatment, sham) × 2 (2mo, 4mo) analysis of covariance (ANCOVA) with baseline score as the covariate to explore treatment effects during the last 2 months of the study. Furthermore, for each outcome measure, we grouped patients into 3 categories of severity based on baseline scores. Ratings of 1 to 4 corresponded to mild pain; 5.0 to 6.99, to moderate pain; and 7 to 10, to severe pain. ANOVAs were used to compare the mean changes separately for each severity group. For each of the outcome measures, chi-square tests for independence were used to assess magnet versus sham group differences in the percentage of patients who had at least a 30% reduction in severe pain. Finally, ANOVAs and ANCOVAs were used to assess treatment effects for subgroups defined by measures known to previously affect outcomes in this population. For all tests, a P value of .05 or less was considered to indicate statistical significance. Subjects with any missing data for an endpoint were excluded for that analysis.

On the basis of published results of clinical trial placebo responses for painful diabetic neuropathy, at an α level of .05 and a power of .80, with 150 subjects per group, it was estimated that a difference between treatment and sham group responses of 17% or more would be statistically significant. Analyses were conducted with SPSS.
Adverse Events

Potential injury to the sole producing ulcer or abrasion or infection was monitored. Mechanical allodynia because of sensitive feet was also tabulated.

Role of Funding Source

This study was initially funded by Nu-Magnetics and supplemented by Nikken Inc. The grant recipients had complete independence regarding study design, data analysis, and manuscript preparation. The study’s protocol was approved by the National Institutes of Health, but not funded.

RESULTS

The flow of patients through the clinical trial is depicted in figure 2. Three hundred seventy-five subjects were randomly assigned to treatment and sham groups, and 259 subjects (69%) successfully completed this 4-month trial. Of the 90 dropouts, 74% in the treatment group and 71% in the sham cohort dropped out before the second month. Of the total group, 45% were lost to follow-up, 24% dropped because of alldynia, and 9% dropped for nonstudy complications. Twenty-six subjects were dropped by the statistician for missing or questionable data. The baseline characteristics for the remaining 259 subjects were similar for treatment and sham groups (table 1). The t tests for independent samples revealed no baseline differences between the treatment and sham groups for the primary end points (table 2). Racial-ethnic proportions at enrollment were a representative cross-section of the US population. In addition, a series of ANOVAs revealed no baseline differences or differences over the study period between patients at university centers and in private practice settings.

Primary Outcomes

Burning. Burning scores decreased 30% for the treatment group from baseline (mean ± standard deviation, 5.13 ± 2.29) to month 4 (3.61 ± 2.44) and decreased 24% for the sham group from baseline (5.27 ± 2.40) to month 4 (4.01 ± 2.81) (P = .000, ANOVA; fig 3). There was a larger decrease in mean scores for the treatment group (−12%) from month 2 (4.09 ± 2.38) to month 4 (3.61 ± 2.44) than for the sham group (−3%) from month 2 (4.12 ± 2.65) to month 4 (4.01 ± 2.81) (P < .05, ANCOVA).

Numbness and tingling. Numbness and tingling scores decreased 29% for the treatment group from baseline
(5.63±2.08) to month 4 (4.02±2.46) and decreased 22% for the sham group from baseline (5.89±2.02) to month 4 (4.57±2.58) (P=.000, ANOVA; fig 4). There was a decrease in mean scores for the treatment group (−10%) from month 2 (4.46±2.23) to month 4 (4.02±2.46) and a small increase for the sham group (+1%) from month 2 (4.54±2.58) to month 4 (4.57±2.58) (P<.05, ANCOVA). For patients with severe pain at baseline, numbness and tingling decreased 32% for the treatment group from baseline (5.58±2.43) and decreased 14% for the sham group from baseline (8.12±.95) to month 4 (6.97±2.38) (P<.01, ANOVA; fig 5). Of the 38 treatment patients with severe pain at baseline, 27 (71%) had mild or moderate pain at month 4. In contrast, of the 40 sham patients with severe pain at baseline, 16 (40%) had mild or moderate pain at month 4 (P<.01, χ²).

Foot pain. Foot pain scores decreased 31% for the treatment group from baseline (5.84±2.33) to month 4 (4.05±2.66) and decreased 25% for the sham group from baseline (5.76±2.29) to month 4 (4.31±2.80) (P=.000, ANOVA; fig 6). A larger decrease in mean scores existed for the treatment group (−12%) from month 2 (4.62±2.53) to month 4 (4.05±2.66) than for the sham group (−4%) from month 2 (4.47±2.68) to month 4 (4.31±2.80) (P<.05, ANCOVA). For patients with severe pain at baseline, foot pain decreased 41% for the treatment group from baseline (8.49±1.07) to month 4 (4.97±3.10) and decreased 21% for the sham group from baseline (8.35±.95) to month 4 (6.56±2.50) (P<.01, ANOVA; fig 7). Of the 40 treatment patients with severe pain at baseline, 29 (69%) had mild or moderate pain at month 4. In contrast, of the 35 sham-device patients with severe pain at baseline, 17 (49%) had mild or moderate pain at month 4. This trend in category change did not reach statistical significance (P=.07, χ²).

Sleep. Sleep scores decreased 30% for the treatment group from baseline (4.83±2.66) to month 4 (3.36±2.76) and decreased 30% for the sham group from baseline (5.19±2.79) to month 4 (3.65±3.04) (P=.000, ANOVA; fig 8). There was a nonsignificant trend for a larger decrease in mean scores for the treatment group (−13%) from month 2 (3.83±2.83) to month

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NOTE. Values are mean ± standard deviation (SD) or as otherwise indicated.
Abbreviation: Demy, demyelinating.

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NOTE. Values are mean ± SD.
4 (3.36±2.76) than for the sham group (−3%) from month 2 (3.76±2.83) to month 4 (3.65±3.04) ($P=.08$, ANCOVA).

### Secondary Outcomes

There was no evidence of deterioration of nerve function clinically or electrophysiologically in those patients reporting improvement in pain scores. Thus, there was no evidence of clinical worsening. Of the 259 subjects, 61 (24%) had Neumar, Case IV, SSR, or biothesiometry studies. No significant differences existed between subjects in the treatment group (n=32) and those in the sham group (n=29) from baseline to 4 months on these measures.

### Subgroup Analyses

For patients not taking oral antidiabetic agents, a larger decrease occurred in mean burning scores for the treatment group (−14%) from month 2 (3.81±2.38) to month 4 (3.30±2.39) than for the sham group (−1%) from month 2 (3.91±2.87) to month 4 (3.86±2.85) ($P<.01$, ANCOVA). There was a nonsignificant trend for a larger decrease in mean numbness and tingling scores for the treatment group (−10%) from month 2 (4.26±2.21) to month 4 (3.84±2.46) than for the sham group (−1%) from month 2 (4.78±2.68) to month 4 (4.24±2.59) ($P=.08$, ANCOVA). A similar pattern was reported for patients with severe foot pain scores, with reductions of 41% and 21% for treatment and sham groups, respectively, and for numbness and tingling, with reductions of 32% and 23% for the 2 groups, respectively. Results remained significant with a Bonferroni correction. By using the 30% pain reduction criterion as suggested by a Farrar stratification analysis, we noted that 50% of patients with magnets had at least a 30% reduction in severe numbness and tingling, compared with 25% of patients with sham devices ($P<.05$, $\chi^2$). Although the percentages for foot pain (32% vs 19%) and burning (42% vs 29%) were impressive, they were not statistically significant. No differences between treatment and sham groups were found based on family history of diabetes, baseline nerve conduction, or Hb A1c scores.

### Blinding

An interim analysis for bias and breaking the blind was performed at those active sites 6 months before study terminated (university and private practice). This analysis was to determine whether the present study was adequately blinded.
Subjects and examining investigators were asked at the end of the study to identify the treatment provided. Sixty-three percent of the subjects responded. Of the 83 treatment group subjects responding, 40 (48%) believed they had active magnets, 31 (37%) believed they had sham magnets, and 12 (15%) did not know. Of the 80 sham-device subjects responding, 29 (36%) believed they had active magnets, 30 (38%) believed they had sham magnets, and 21 (26%) did not know. Of 46 investigators of sham-device subjects, 23 (50%) believed the subjects had active magnets, 22 (40%) believed they had sham magnets, and 8 (17%) did not know. Of 50 investigators of sham-device subjects, 22 (40%) believed the subjects had active magnets, 15 (30%) believed they had sham magnets, and 12 (24%) did not know. There was no significant association between the actual treatment received and the belief about the treatment received for subjects or investigators.

Dropouts

The dropouts were evenly represented and did not impact on the primary analysis for efficacy. We did not use the intention-to-treat (ITT) model for estimates of missing data, because 75% of the dropouts from the treatment group and 71% from the sham group dropped out before month 2. As shown in our figures, the magnetic effects became apparent after month 2; therefore, using the ITT model with most estimates based on data before month 2 would severely bias the analysis. Dropouts secondary to allodynia were equally common in both groups. Foot sensitivity is a well-known phenomenon in symptomatic patients with DPN. Thus, it is not surprising that the application of an insole (magnetized or unmagnetized) would be unpleasant to a small but significant group of patients. There were 90 dropouts (lost to follow-up, allodynia, complications) equally represented out of a sample size of 349 (25.8%). There were no mean differences between the 46 treatment and 44 sham-device patients for age, years since onset of diabetes, and baseline Hb A1c, burning, numbness and tingling, foot pain, and sleep scores (P > .05, ANOVA). The statistician dropped 26 patients (equal representation) because of site difficulties obtaining data and unreliable data.

Safety

Measures of safety included constant reporting of adverse events and the cause for dropouts. There were no significant complications.

Figures

Fig. 8. Sleep mean scores for treatment and sham subjects.

DISCUSSION

This is the first multicenter, double-blind, placebo-controlled study to examine the role of static magnetic fields in a homogeneous cohort of DPN with neuropathic pain. The antinociceptive effect was significantly pronounced during the third and fourth month, indicating that a tonic and chronic exposure must be present to inhibit and influence sensitized afferent fibers. The magnitude of the reduction of burning, numbness and tingling, and exercise-induced foot pain, especially in severe and extreme cases, was comparable or superior to that observed in the gabapentin, tramadol, and lamotrigine studies, but without side effects. Additionally, a change of 1.5 in the 0 to 10 pain scale represents a clinically meaningful difference. This also reaffirms the data from 2 prior pilot studies. Subset analyses identified that subjects with severe pain and those not taking oral hypoglycemic agents responded more favorably than other symptomatic patients. Although our results show a statistically significant reduction in predetermined primary outcome measures, it is difficult to determine the mechanism of action responsible for these benefits. It is of interest that in the pharmacologic trials of tramadol and gabapentin, the subjects with severe and extreme pain responded better than other subjects. Segal et al also noted in testing bipolar magnetic devices in knee pain secondary to rheumatoid arthritis that patients with mild symptoms did not respond as well. DPN pain appears to arise from an increase inafferent signals from degenerating nociceptive afferent fibers. It has been shown that early in the course of painful neuropathies, free nerve endings of nociceptive axons can disappear from the skin but are still present in the sural nerve. One possibility may be that the magnetic field of these insoles somehow directly or indirectly interrupts and suppresses the afferent signal traffic of the C-fiber firing pattern of the distal part of the surviving axon thereby producing an antinociceptive effect. A number of studies have shown that DPN pain could result from depolarization because of dysregulation of normal sodium, calcium, and potassium channel activities. It is well known that sodium channels accumulate in areas of axonal damage and static magnetic fields have been shown to block or reduce action potential via effects on sodium flux. A number of studies using weak pulsed, time-varying electromagnetic fields have shown biologic changes. Adey and Chopart considered the cell membrane as the most likely transducer modifying ion transport of protein and adenosine triphosphatase activity. Membrane lipids with organized arrays of polar molecules, diamagnetic, have been shown to realign anisotropic molecules as well as to summate and interfere with ionic transport. Translational movement or changes in orientation in a magnetic field can influence amplitude of evoked responses. Because phospholipids in cell membranes have both diamagnetic and paramagnetic properties, it is clear that mechanisms exist that can produce conformational changes in various channels and structures. However, it is not known if any of this is pertinent to putative biologic effects of static magnetic fields. Based on our data, we speculate that the kinetic activity of channelized membrane ions and blood flow in a static magnetic field is sufficiently strong to stimulate living tissues and to induce a biologic reaction. Signal transduction pathways appeared to be functionally modulated, and this is a restatement of Faraday’s law of time variation. There is also knowledge that weak magnetic fields can increase the partial pressure of tissue oxygen, thereby improving oxygen delivery to tissues. This property may be important because of a reported reduction in endogenous oxygen tension in DPN. Thus, it is biologically plausible...
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for pain control (ie, rostral anterior cingulate cortex, brainstem) were somehow activated. 29

CONCLUSION

Although many questions remain about a precise mechanism of action, the present study provides convincing data confirming that the constant wearing of static, permanent, magnetic insoles produces statistically significant reduction of neuropathic pain. Considering their safety and minimal cost (<$100), our data suggest that the insoles may be used as adjunctive or monotherapy. Future studies are needed to identify the optimal time to achieve maximum antinoceptive effect and to confirm and extend these results. Additional search for biologic markers (ie, epidermal nerve fiber biopsy, microneuropography) will be necessary in future protocols to determine if permanent structural changes can be produced.

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