Original Article

A Randomized Clinical Trial of the Effectiveness of Photon Stimulation on Pain, Sensation, and Quality of Life in Patients With Diabetic Peripheral Neuropathy

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Abstract

Context. Peripheral neuropathy is one of the most common complications of diabetes.

Objectives. The purpose of this study was to evaluate the effects of photon stimulation on pain intensity, pain relief, pain qualities, sensation and quality of life (QOL) in patients with painful diabetic peripheral neuropathy.

Methods. In this randomized, placebo-controlled trial, patients were assigned to receive either four photon stimulations (n = 63) or four placebo (n = 58) treatments. Pain intensity, pain relief, and pain qualities were assessed using self-report questionnaires. Sensation was evaluated using monofilament testing. QOL was measured using the Medical Outcomes Study Short Form-36 (SF-36). Multilevel regression model analyses were used to evaluate between-group differences in study outcomes.

Results. No differences, over time, in any pain intensity scores (i.e., pain intensity immediately post-treatment, average pain, worst pain) or pain relief scores were found between the placebo and treatment groups. However, significant decreases, over time, were found in some pain quality scores, and significant improvements in sensation were found in patients who received the

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photon stimulation compared with placebo. In addition, patients in the treatment group reported significant improvements in SF-36 social functioning and mental health scores. Findings from a responder analysis demonstrated that no differences were found in the percentages of patients in the placebo and treatment groups who received 30% or more or 50% or more reduction in pain scores immediately post-treatment. However, significant differences were found in the distribution of the changes in pain relief scores, with most of the patients in the photon stimulation group reporting a slight (28.6%) to moderate (34.9%) improvement in pain relief from the beginning to the end of the study compared with no change in pain relief (43.1%) in the placebo group.

Conclusion. Four treatments with photon stimulation resulted in significant improvements in some pain qualities, sensation, and QOL outcomes in a sample of patients with a significant amount of pain and disability from their diabetes. A longer duration study is needed to further refine the photon stimulation treatment protocol in these chronically ill patients and to evaluate the sustainability of its effects. J Pain Symptom Manage 2010;39:88–99. © *2010 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Neuropathic pain, diabetes, photon stimulation, quality of life, pain, sensation

Introduction

Peripheral neuropathy is one of the most common complications of diabetes. The concomitant loss of protective sensation increases the patients' risk for foot ulcers and contributes to the increased incidence of lower-extremity amputations.[1–3]

The prevalence of painful diabetic peripheral neuropathy (PDPN) ranges between 16% and 26%,[4–6] and a significant percentage of patients experience moderate to severe pain.[5] In addition, PDPN is known to have a profound impact on patients' sleep, mood, daily activities, and quality of life (QOL).[7–12]

A wide variety of analgesic medications (e.g., antidepressants, anticonvulsants, topical agents, opioids) have been evaluated in patients with PDPN.[13–15] The results of a recent systematic review that defined clinical success as a 50% reduction in pain[16] found that tricyclic antidepressants were the most effective analgesics, followed by traditional anticonvulsants and then newer-generation anticonvulsants. However, the review concluded that the efficacy of most of these pharmacological treatments is limited, because for any particular drug, only 30% of patients treated will experience analgesia. In addition, adverse effects occur frequently with all of these medications and often cause patients to discontinue treatment.

Based on the limited efficacy of current analgesics available for the management of PDPN, new approaches are needed to reduce pain and improve patient outcomes. One such approach, which has been tested in patients with PDPN, is photon stimulation delivered using light-emitting diodes (LEDs). Photon stimulation is sometimes referred to in the literature as pulsed infrared light therapy or photobiomodulation.[17,18] In an excellent review,[17] Desmet et al. summarized the clinical and experimental applications of LED photon stimulation. LED arrays were initially developed by the U.S. National Aeronautics and Space Administration for experimental plant growth in space. Their clinical applications began to be evaluated after observations were made that low-energy stimulation of tissues by lasers increased cellular activity during wound healing.[19,20] LEDs have several advantages over lasers for clinical use. They can be configured to produce multiple wavelengths, can be arranged in large flat arrays to treat a wide three-dimensional surface, and are compact. In addition, because LED light is produced out of phase, it does not emit heat. Therefore, at intensities required to penetrate deeper tissues, there is no risk of heat damage

to treated epithelial tissues. Because of this nonsignificant risk (NSR), the U.S. Food and Drug Administration has given NSR approval for therapeutic trials of LEDs in humans. Light emitted by LED arrays at optimal wavelengths (in the near-infrared wavelengths of between 750 and 1,300 nanometers [nm]) penetrates skin and tissue to a depth of approximately 2–5 cm.[18,20]

The mechanism(s) by which near-infrared light produces its biological effects remain to be elucidated. However, a growing body of evidence suggests that one of the primary effects of near-infrared light is the stimulation of mitochondrial cytochromes, which in turn initiates secondary cell signaling pathways that results in increased cellular activity and healing.

Within mammalian tissues, the three major photoacceptor molecules are hemoglobin, myoglobin, and cytochrome c oxidase.[21] Of these three, cytochrome c oxidase is the only one that is involved in energy metabolism and production, because it comprises Complex IV of the electron transport chain that is located within mitochondria. Therefore, cytochrome c oxidase is postulated to be the photoacceptor molecule within mitochondria that, when activated, results in the biological effects associated with photon stimulation.[21–25] In a recent report,[26] pretreatment of rats with near-infrared light prevented the neurotoxic effects of rotenone (a mitochondrial complex inhibitor) on the optic nerve. The authors concluded that near-infrared light therapy might be used to treat neurodegenerative disorders associated with mitochondrial dysfunction.

It is interesting to note that several emerging lines of evidence suggest that one of the mechanisms that underlies the development of PDPN is damage to mitochondria (for review, see Refs. 27–29). Dorsal root ganglia appear to be particularly vulnerable, because they are the origin of reactive oxygen species production in the hyperglycemic neuron. Accumulating evidence suggests that neuronal mitochondria are subject to damage at the level of their DNA and their outer and inner membrane as well as through deregulation of mitochondrial fission and fusion proteins that control mitochondrial shape and number.[27] Although it is not possible at this time to evaluate the underlying mechanism of action of photon stimulation in humans, it is reasonable to hypothesize that the stimulation of mitochondrial cytochromes with near-infrared light may ameliorate or reverse some of the effects of diabetes on mitochondrial DNA within neurons.

Several descriptive studies of patients with PDPN have reported that patients treated with photon stimulation have decreased pain and improved sensation after treatment.[30–32] Recently, four randomized controlled trials evaluated the effectiveness of various forms of photon stimulation delivered using LEDs[33–35] or low-intensity laser therapy[36] for the management of symptoms associated with DPN. Trials by Leonard et al.[34] and Arnall et al.[37] reported significant improvements in peripheral sensation. In contrast, in a four-week[33] and a three-month trial,[35] monochromatic infrared therapy did not improve peripheral sensations compared with placebo.

These conflicting findings may be attributed to relatively small sample sizes, the lack of prespecified risk factor criteria for stratification, the method of delivery and intensity of photon stimulation, the study designs, the methods used to analyze the data, or the choice of outcome measures. Given the paucity of research on photon stimulation, the purpose of this randomized, double-blind, placebo-controlled trial was to evaluate decreases in pain intensity and pain quality scores as well as improvements in pain relief, sensation, and QOL in patients with PDPN who received photon stimulation using the C^3 DPN BiPhase photon stimulator (C3 Medical Technologies, Lafayette, CA).

Methods

Sample and Settings

This randomized, double-blind, placebo-controlled trial recruited most of the patients from the Veterans Affairs Northern California Health Care System (VANCHCS) through physician referrals. Some patients were referred from community programs or patient support groups.

Patients were telephone screened to determine if they met the following inclusion criteria: a diagnosis of diabetes mellitus; average pain in their feet of 3 or more on a 0–10

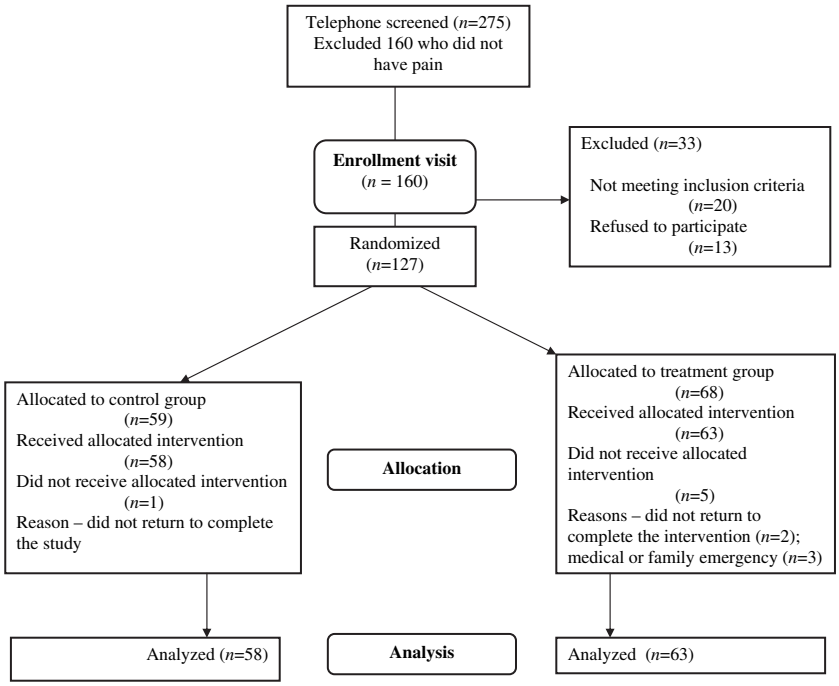

Fig. 1. Study flowchart.

numeric rating scale (NRS); pain in their feet for at least six months; and pain characterized as burning, shooting, or stabbing in nature. Patients were excluded if they reported a history of peripheral vascular disease, vitamin B_{12} deficiency, low back pain with radiculopathy, or another painful condition that was difficult for them to distinguish from their PDPN. The study was approved by the Human Studies Subcommittee at VANCHCS. This protocol is in the National Institutes of Health Clinical Trial Registry (NCT00539175).

Study Procedures

As shown in Fig. 1, 275 patients were telephone screened, and 160 had an enrollment visit. At this visit, the Michigan Neuropathy Screening Instrument[38] was completed to confirm the diagnosis of PDPN. At the end of the enrollment visit, patients signed the consent form; completed the baseline demographic, pain, and QOL questionnaires; and underwent sensory testing. If prescribed an analgesic, patients were instructed not to change the regimen during the study. Of these 160 patients, 20 did not meet the study's inclusion criteria, and 13 refused to continue with the study because of time constraints or transportation difficulties. A total of 127 patients met the second level of screening, and 121 patients completed the study. Three patients who enrolled did not return to complete the study protocol, and three patients were unable to complete the study protocol because of medical or family emergencies. To insure a stratified sample, a block randomization scheme, which accounted for height, pain intensity, and hemoglobin A1c (HbA1c), which are all predictors of DPN,[39,40] was used to randomize patients into the placebo or intervention group.

The C^3 DPN BiPhase photon stimulator was designed to treat both the active and the placebo groups. To maintain the blinding, two operators set key-operated control switches on the back of the photon stimulator based on the patient's group assignment and confirmed the switch locations before each treatment. The research team members who administered the treatments and collected the outcome data were blinded to the patient's group assignment and could not interpret the switch settings.

At the time of the treatment, each patient sat in a standard chair with shoes and socks removed. The 16 pairs of LED treatment modules were placed in the following locations: on the dorsum of the foot, between the 1st and 2nd toes, proximal to the margin of the web; on the dorsum of the foot, between the

2nd and 3rd toes, proximal to the margin of the web; on the dorsum of the foot, between the 4th and 5th toes, proximal to the margin of the web; in the depression anterior and superior to the medial side of the tuberosity of the calcaneum; directly above the tip of the medial malleolus, posterior to the border of the tibia; directly below the depression between the tip of the malleolus and the Achilles tendon; at the midpoint of the transverse popliteal crease, between the tendons of the biceps femoris and semitendinosus; and nine pairs of LED modules on the plantar surfaces of the feet. The plantar surfaces of the feet were optically immersed through the placement of the LED treatment modules. Food-grade plastic wrap was placed between the skin and the LED treatment modules for hygienic purposes. With the exception of the LED modules that were placed on the plantar surfaces of the feet and the two located behind the knees, all other modules contained a multi-axis manipulator that could be aligned/positioned without the use of tools.

Treatments were administered on both feet simultaneously for seven minutes. The first treatment was delivered at half strength to mitigate the slim chance of a pain flare-up on Day 1. Patients received a total of four treatments within a four- to 11-day period depending on their schedule. Most of them received the four treatments within five days. The dose and the treatment schedule were based on one of the investigator's (L. S.) clinical experience using photon stimulation in patients with PDPN. After the completion of each of the treatments, patients rated the intensity of their pain and underwent sensory testing. Before each treatment, patients rated the intensity of average and worst pain, amount of pain relief they experienced, and the severity of various pain qualities in the previous 24 hours.

Description of the C^3 Diabetic Peripheral Neuropathy BiPhase Photon Stimulator and Placebo Device

The C^3 DPN BiPhase photon stimulator used in this study has a main Electronics Control Unit that controls the output power, treatment duration time, and order of treatment sequence of the 32 mosaic LED arrays. These arrays were operated as 16 optical pairs that delivered energy to opposite sides of the body. Each LED treatment module radiates 350 mW of optical energy. The LED diode wavelength chosen for this study was 870 nm. When activated, the active treatment Electronics Control Unit was preset to deliver 1,800 J in a seven-minute treatment period to each lower extremity. The placebo unit's Electronics Control Unit was deactivated (i.e., no energy was delivered) even though the indicator lights illuminated when the power switch was turned to the "on" position. Therefore, neither the patients nor the research team member who administered the treatments were able to determine if the patients were receiving the active treatment or placebo.

Subjective Measures

The demographic questionnaire collected information on the patient's age, gender, ethnicity, living arrangements, marital status, education, employment, history of foot surgery, and low back problems. Medical records were reviewed to confirm the diagnosis of diabetes mellitus and to obtain the patient's most recent HbA1c.

Patients were asked, at the time of enrollment and after each treatment, to rate the intensity of their present pain, using a 0 (no pain) to 10 (worst pain imaginable) NRS.[41,42] In addition, before each treatment, they rated the severity of their average and worst pain, the amount of relief they experienced in their feet or legs, and the quality of their pain in the previous 24 hours. Pain relief was rated on a 0 (pain is worse) to 5 (complete relief) Likert scale.[43] Pain qualities were evaluated using the Pain Qualities Assessment Scale (PQAS), which evaluates the severity of 20 pain qualities using 0–10 NRSs.[44–48]

Patients completed the Acute Recall form of the Medical Outcomes Study Short Form-36 (SF-36) at the beginning and end of the study. The SF-36 is a generic measure of health, functional status, and well-being, which consists of eight subscales. The Acute Recall form asks patients to respond to the items in terms of how they felt in the previous week. The SF-36 has undergone extensive validity and reliability testing.[49–51]

Objective Measures

At baseline and after each treatment, protective sensation was tested at 10 sites on each foot in random order using a 5.07-size Semmes-

Table 1
Demographic and Clinical Characteristics of Patients in the Placebo and Treatment Groups

Characteristics	Placebo Group ($n=58$)	Treatment Group ($n=63$)
Age (years), mean (SD)	64.4 (8.7)	64.1 (10.5)
Education (years), mean (SD)	14.1 (2.7)	14.5 (2.9)
Height (inches), mean (SD)	69.0 (3.7)	68.9 (3.7)
Weight (pounds), mean (SD)	230.7 (56.2)	232.9 (50.6)
HbA1c, mean (SD)	7.6 (1.9)	7.9 (2.1)
Average pain, mean (SD)	5.8 (2.2)	5.2 (2.1)
Worst pain, mean (SD)	6.6 (2.4)	6.0 (2.4)
Total monofilament score—right foot (0–10), mean (SD)	4.8 (3.4)	5.8 (3.4)
Total monofilament score—left foot (0–10), mean (SD)	4.8 (3.2)	5.7 (3.3)
Males, %	84.5	76.2
Lives alone, %	20.7	30.2
Married/partnered, %	67.2	61.9
Ethnicity		
White, %	74.1	74.6
Nonwhite, %	25.9	25.4
Works for pay, %	81.0	79.4
Ulcers on feet/legs, %	17.5	15.9
Surgery on right foot, %	21.8	29.0
Surgery on left foot, %	21.1	29.5
Pain affects work, %	81.0	79.4
Analgesic use, %	60.3	58.6

SD = standard deviation.

Weinstein monofilament. The tester first demonstrated the type of sensation created by the monofilament by touching the patient's hand. Then, patients were asked to take off their shoes and socks, to lie down on the examination table, and to close their eyes. The tester touched each of the sites, in random order, with the monofilament for 1.5 seconds, using only enough pressure to bow the monofilament. The patients were instructed to say "yes" each time they felt the monofilament. The absence of a response was considered an inability to feel the monofilament. In this case, the test was repeated once, and if there continued to be an absence of a response, a "no" was recorded for that site. If calluses or ulcers were present in the testing site, a normal appearing site that was closely adjacent was tested.[52–54] The number of yes responses was totaled separately for each foot to create a sensory score that could range from 0 to 10.

Data Analysis Plan

Data were analyzed using SPSS™ Version 14 (SPSS, Inc., Chicago, IL) and STATA™ Release 9 (Stata Corp., LP, College Station, TX). Descriptive statistics and frequency distributions were generated for the sample characteristics and symptom severity scores. Independent sample *t*-tests and Chi-squared analyses were performed to determine if there were differences in demographic, clinical, and pain characteristics between the two treatment groups. In addition, the groups were compared on all dependent measures obtained before treatment as a validity check of the randomization procedure.

An intent-to-treat analysis was used, and all patients were included in the analyses. The tests for differences between groups from pre- to post-treatment for continuous outcomes were performed with linear mixed models analysis with the SPSS™ MIXED module[55,56] and multilevel negative binomial regression

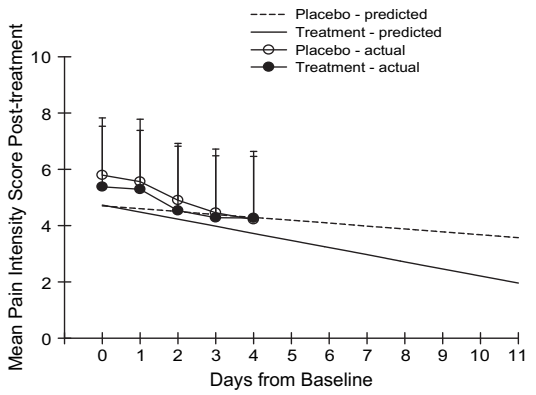

Fig. 2. Predicted and actual changes over time in pain intensity scores immediately post-treatment in the placebo ($n=58$) and treatment ($n=63$) groups.

in STATA™. These more sophisticated statistical methods are superior to analysis of variance, because they take all measurement occasions into account in examining change profiles across all assessments from baseline to the end of the trial. In addition, all observations contribute to the estimated changes for the two groups (i.e., cases with missing values are not dropped from the analyses). An alpha level of 0.05 was considered statistically significant for the tests of the interaction (i.e., group × time effects).

A responder analysis was performed to evaluate the differences in the percentage of patients who achieved a 30% and a 50% change in pain intensity scores immediately post-treatment using the Fisher's exact test.[57,58] In addition, a comparison of the distribution of the changes in pain relief scores, from the beginning to the end of the study, between the placebo and treatment group was performed using the Mann-Whitney *U* test. An alpha level of 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the patients in the placebo ($n = 58$) and treatment ($n = 63$) groups are summarized in Table 1. No between-group differences were found at baseline in any of these characteristics. In addition, as shown in Table 1, no between-group differences were found in any of the baseline pain intensity or monofilament scores.

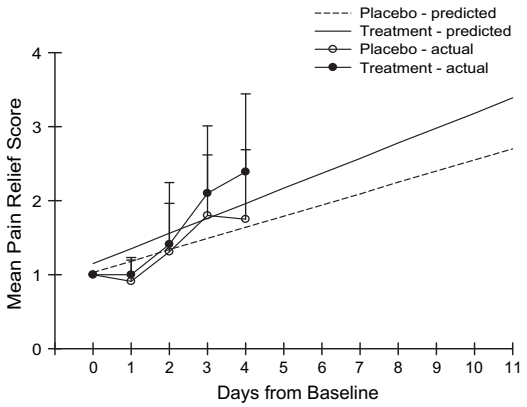

Fig. 3. Predicted and actual changes over time in pain relief scores immediately post-treatment in the placebo ($n = 58$) and treatment ($n = 63$) groups.

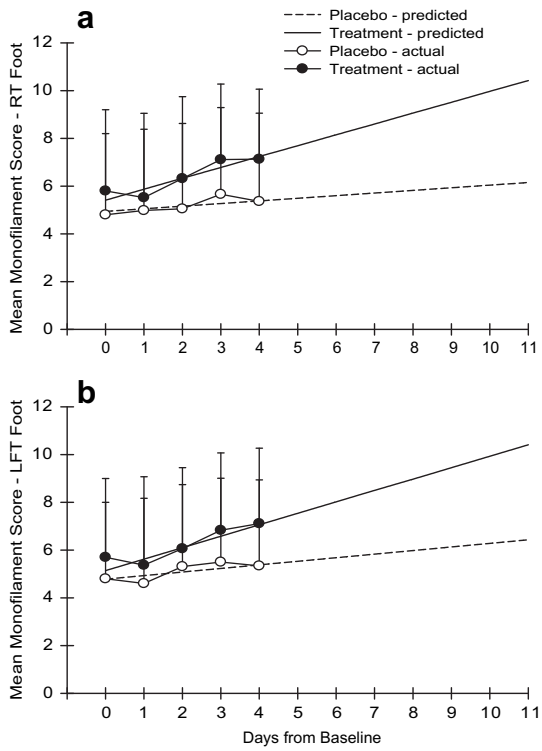

Fig. 4. Predicted and actual changes over time in patients' responses to monofilament testing in the right (RT) (a) and left (LFT) (b) foot in the placebo ($n = 58$) and treatment ($n = 63$) groups.

Differences in Pain Intensity, Pain Relief, Pain Qualities, and Protective Sensations

As shown in Fig. 2, no differences, over time, in pain intensity scores immediately post-treatment were found between the placebo and treatment groups ($P = 0.13$). In addition, no differences, over time, in average ($P = 0.47$) and worst pain ($P = 0.90$) intensity scores were found between the placebo and treatment groups (data not shown).

As shown in Fig. 3, no differences, over time, in pain relief scores were found between the placebo and treatment groups ($P = 0.07$). However, significant group × time interactions were found for three of the 20 pain quality scores. Patients who received the photon stimulation reported significant decreases, over time, in the following pain qualities: tingling ($P = 0.005$), cramping ($P = 0.004$), and itchy ($P = 0.04$).

Table 2
Results of the Responder Analyses

	≥30% Change		≥50% Change	
Variables	Placebo Group ($n=58$)	Treatment Group ($n=63$)	Placebo Group ($n=58$)	Treatment Group ($n=63$)
Pain scores immediately posttreatment	50.9%	50.0%	28.6%	38.7%
Fisher's exact test, P		1.00		0.33
Distribution of Changes in Pain Relief Scores From the Beginning to the End of the Study				
Pain Relief Score	Placebo Group ($n=58$)%		Treatment Group ($n=63$)%	
Worse	3.4		1.6	
No change	43.1		22.2	
Slight improvement	37.9		28.6	
Moderate improvement	8.6		34.9	
A lot of improvement	6.9		11.1	
Complete relief	0.0		1.6	
Mann-Whitney U test	$Z=3.49$, $P<0.0005$			

Figure 4a and b illustrates the changes over time in patients' responses to monofilament testing of 10 sites on their right and left foot respectively. Based on the significant group × time interactions for the right foot ($P=0.003$) and left foot ($P=0.008$), patients who received the photon stimulation reported a significant increase in sensation in both feet over the course of the study compared with those in the placebo group.

Results of the Responder Analysis

As shown in Table 2, no differences were found in the percentages of patients in the placebo and treatment groups who received a 30% or more or 50% or more reduction in pain scores immediately post-treatment ($P=$ 1.00 and 0.33, respectively).

As shown in Table 2, significant differences were found in the distribution of the changes in pain relief scores, from the beginning to the end of the study, between patients in the placebo and treatment groups ($Z=3.49$, $P<0.0005$). Although most of the patients in the placebo group were categorized as having no change in pain relief scores (43.1%), most of the patients in the photon stimulation group reported slight improvement (28.6%) or moderate improvement (34.9%) in pain relief from the beginning to the end of the study.

Table 3
Pretreatment and Post-treatment Medical Outcomes Study Short Form (SF-36, Acute Recall) Scores of Patients in the Placebo and Treatment Groups

	Pretreatment Scores[a]		Post-treatment Scores[b]	
SF-36 Scores	Placebo Group ($n=58$) Mean (SD)	Treatment Group ($n=63$) Mean (SD)	Placebo Group ($n=58$) Mean (SD)	Treatment Group ($n=63$) Mean (SD)
Physical functioning	40.3 (25.0)	46.1 (26.9)	42.1 (26.1)	48.1 (27.6)
Role physical	37.8 (27.4)	42.2 (27.1)	41.1 (30.2)	47.2 (27.1)
Bodily pain	36.0 (17.9)	42.2 (19.4)	39.7 (17.9)	47.5 (19.3)
General health	39.3 (19.9)	45.8 (21.2)	42.3 (20.4)	48.9 (22.3)
Vitality	36.8 (20.4)	42.3 (24.3)	40.2 (20.4)	46.7 (24.3)
Social functioning	56.4 (29.9)	59.6 (30.1)	59.3 (30.8)	**67.4 (27.4)**
Role emotional	64.7 (28.9)	60.3 (32.4)	68.6 (26.9)	63.9 (31.0)
Mental health	61.5 (23.9)	64.0 (22.0)	64.6 (24.2)	**68.5 (20.5)**
Physical component subscale	31.4 (9.7)	34.9 (8.3)	32.3 (10.2)	36.2 (8.6)
Mental health component subscale	43.8 (13.6)	43.7 (13.3)	45.7 (13.2)	46.2 (12.3)

SD = standard deviation.
[a]No differences were found between the placebo and treatment groups in any of the SF-36 pretreatment scores.
[b]Significant group × time interactions were found for social functioning ($P=0.004$) and mental health ($P=0.051$) subscale scores (see bolded values).

Differences in Quality of Life

As shown in Table 3, no between-group differences were found in most of the SF-36 subscale scores. However, significant group × time interactions were found for both the social functioning ($P = 0.004$) and mental health ($P = 0.05$) subscale scores. Patients who received the photon stimulation reported significant improvements in these two SF-36 subscale scores over the course of the study when compared with patients in the placebo group.

Discussion

Findings from this randomized, double-blind, placebo-controlled trial suggest that the administration of photon stimulation, in the manner specified in the study protocol, resulted in significant improvements over time in sensation, social functioning, and mental health. In addition, patients who received the photon stimulation reported significant decreases in three pain quality scores.

Decreases in sensation associated with DPN can result in significant morbidity, including foot ulcers[59] and falls.[60] The improvements in sensation in patients who received the photon stimulation were significant. In fact, patients in the treatment group went from perceiving sensations in only five of 10 sites on average to almost all 10 sites at the end of treatment, compared with only six sites in the placebo group. An equally important finding from this study is the significant between-group differences in pain quality scores. Specifically, patients who received the photon stimulation reported decreases in tingling, cramping, and itchy sensations. These findings are somewhat consistent with previous reports that used an earlier version of the PQAS to assess the effects of pharmacological treatments on neuropathic pain.[46,48]

A somewhat surprising but important finding in this study is the significant improvements in the mental health and social function scores on the SF-36 in patients who received the photon stimulation. At baseline, the SF-36 scores of both groups were significantly lower than those of the general population but comparable to previous reports of chronically ill diabetic patients with neuropathy[61] or painful foot ulcers.[62] Despite the relatively short treatment, patients who received the photon stimulation reported improvements in social functioning and mental health that were both statistically significant and clinically meaningful. Several reports in the literature suggest that clinically meaningful differences in QOL are in the range of 0.2−0.5 standard deviation units, which is comparable to the results obtained in this study.[63]

Although decreases in pain intensity scores were found in the treatment group, they did not reach statistical significance. This lack of significant differences in the pain scores may be related to the relatively small sample size. Based on post hoc power analyses, sample sizes in the range of 70−160 patients per group would be needed to detect significant between-group differences. In addition, it should be noted that patients in this study had higher pain intensity scores than those reported in previous studies,[34,36] which may reflect more severe PDPN or chronic pain of longer duration. In fact, in this study, most of these patients reported chronic pain in the moderate to severe range, which may require a longer duration of treatment with photon stimulation before significant decreases in pain intensity are reported by these chronically ill patients.

Several limitations of this study should be noted. The relatively small sample of primarily older men who were recruited from Veterans Affairs facilities limits the generalizability of the study findings. However, the significant comorbidity and physical and psychological disability (as evidenced by the baseline SF-36 scores) of these patients, as well as the significant amount of chronic pain they reported, may have blunted some of the effects of the photon stimulation that might be more dramatic in a younger and healthier sample of patients with PDPN. Another limitation is that the dose and duration of treatment were chosen based on the clinical experience of one of the co-investigators (L. S.). It is possible that a higher dose and/or a longer duration of treatment would have resulted in decreases in pain intensity.

Despite these limitations, the findings from this study, in a sample of patients with significant comorbidity and a significant amount of

pain and loss of sensation from their DPN, suggest that this treatment results in significant improvements in some pain qualities, sensation, and QOL. Future research needs to evaluate the effectiveness of photon stimulation in a variety of patient populations with painful and nonpainful peripheral neuropathy, evaluate different doses and durations of treatment, and determine the underlying mechanisms of action of this novel therapy.

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