

Original Article

Scrambler Therapy May Relieve Chronic Neuropathic Pain More Effectively Than Guideline-Based Drug Management: Results of a Pilot, Randomized, Controlled Trial

Giuseppe Marineo, PhD, Vittorio Iorno, MD, Cristiano Gandini, MD, Vincenzo Moschini, MD, and Thomas J. Smith, MD

Delta Research & Development (G.M.), Centro Ricerche Bioingegneria Medica, University of Rome "Tor Vergata," Rome, Italy; Centro di Medicina del Dolore "Mario Tiengo" (V.I., C.G., V.M.), IRCCS Fondazione Ospedale Maggiore Policlinico, Mangiagalli and Regina Elena, Milan, Italy; and Division of Hematology/Oncology and Palliative Care (T.J.S.), Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia, USA

Abstract

Context. Neuropathic pain is common, disabling, and often difficult to treat.

Objectives. To compare guideline-based drug management with Scrambler therapy, a patient-specific electrocutaneous nerve stimulation device.

Methods. A clinical trial with patients randomized to either guideline-based pharmacological treatment or Scrambler therapy for a cycle of 10 daily sessions was performed. Patients were matched by type of pain including postsurgical neuropathic pain, postherpetic neuralgia, or spinal canal stenosis. Primary outcome was change in visual analogue scale (VAS) pain scores at one month; secondary outcomes included VAS pain scores at two and three months, pain medication use, and allodynia.

Results. Fifty-two patients were randomized. The mean VAS pain score before treatment was 8.1 points (control) and 8.0 points (Scrambler). At one month, the mean VAS score was reduced from 8.1 to 5.8 (−28%) in the control group, and from 8 to 0.7 points (−91%) in the Scrambler group ($P < 0.0001$). At two and three months, the mean pain scores in the control group were 5.7 and 5.9 points, respectively, and 1.4 and 2 points in the Scrambler group, respectively ($P < 0.0001$). More relapses were seen in polyradicular pain than monoradicular pain, but retreatment and maintenance therapy gave relief. No adverse effects were observed.

Conclusion. In this pilot randomized trial, Scrambler therapy appeared to relieve chronic neuropathic pain better than guideline-based drug management. *J Pain Symptom Manage* 2012;43:87–95. © 2012 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Address correspondence to: Giuseppe Marineo, PhD, Delta Research & Development, Via di Mezzocammino, 85 00187 Rome, Italy. E-mail: g.marineo@mcLink.it, or Thomas J. Smith, MD, Duffy Palliative Care Service, Sidney Kimmel Cancer Center, Johns

Hopkins, 600 North Wolfe Street, Blaylock 369, Baltimore, MD 21287-0005. E-mail: tsmit136@jhmi.edu

Accepted for publication: March 15, 2011.

Key Words

Chronic neuropathic pain, analgesics, refractory pain, Scrambler therapy, electroanalgesia

Introduction

Neuropathic pain is common, chronic, disabling, and often difficult to effectively treat.¹ Common types of neuropathic pain include postsurgical pain, postherpetic neuralgia (PHN), spinal cord stenosis (SCS) (also known as narrow canal syndrome), and chemotherapy-induced peripheral neuropathy.² Although conventional treatments such as opioids, neuroleptics, and other drugs help, all have side effects and limited effectiveness.³

Scrambler therapy is a novel approach to pain control that attempts to relieve pain by providing “nonpain” information via cutaneous nerves to block the effect of pain information. Scrambler therapy synthesizes 16 different types of nerve action potentials similar to endogenous ones, assembles them into sequences, and uses algorithms to determine a patient-specific cutaneous electrostimulation to reduce pain. Scrambler therapy has relieved refractory chronic pain in uncontrolled clinical trials. In the pilot trial, 11 cancer patients with abdominal pain received 10 daily one-hour treatment sessions.⁴ Pain was reduced from 8.6 to 2.3, on a numeric rating scale from 0 to 10, after the first treatment and to <0.5 ($P < 0.0001$) at the end of 10 sessions. In the second trial, 226 patients with neuropathic pain, including failed back surgery pain, brachial plexus neuropathy, and others, were treated.⁵ Eighty percent of patients had greater than 50% pain relief. Smith et al.⁶ treated 16 patients with refractory chemotherapy-induced neuropathic pain with 10 daily hour-long sessions to the painful areas. Pain scores were reduced by 58% from the start of treatment to the end. No toxicity has been observed in any trial. However, all these trials were single-arm trials with no control group.

The purpose of this study was to directly compare management of chronic refractory neuropathic pain by Scrambler therapy with management using current guideline-based drug treatment⁷ in a randomized controlled trial.

Methods**Study Population**

Patients were eligible if they had chronic neuropathic pain rated as 6 or more on a visual analogue scale (VAS) on at least four days each week, for the prior three months despite treatments including antidepressants, anticonvulsants, and opioids. Patients were treated at Ospedale Maggiore, Policlinico Mangiagalli and Regina Elena of Milan at the Centre for Pain Medicine “Mario Tiengo.” Most of the recruited patients were already undergoing treatment in this facility and had been given the standard treatment for neuropathic pain by their physicians. The inclusion and exclusion criteria are listed in Table 1.

The monitoring of patients during and after treatments always took place at the same facility, the Centre for Pain Medicine in Milan. Two research assistants performed the Scrambler therapy under the direction of the treating physicians. These two research assistants collected the pain assessments in both arms of the study.

Informed consent was obtained from all patients. The Scrambler therapy device had been granted Ministry of Health approval for hospital and ambulatory use. The hospital’s scientific and health unit, acting as the institutional review board, approved and monitored the study.

Randomization and Stratification

For this trial at one center, the patients who were eligible (pain ≥ 6 for at least three months, despite treatment according to local practice) were classified according to their pain diagnosis (postsurgical, PHN, SCS). They were then assigned to a treatment group: alternative drug therapy according to the European Federation of Neurological Societies (EFNS) guidelines and in standard practice at this center, or Scrambler therapy with no change in the ineffective drug regimen. They were assigned consecutively in the order they were enrolled in the trial, for example, the first PHN patient to drug treatment, the

Table 1
Inclusion and Exclusion Criteria

Inclusion	Exclusion
Presence of mainly neuropathic pain	Cancer-related pain
VAS pain intensity ≥ 6 in the preceding three months	Presence of serious psychiatric disorder (schizophrenia, manic-depressive psychosis, primary major depression)
Failure to respond to currently used pharmacologic treatment of neuropathic pain (antidepressants, anticonvulsants, and opioids)	Presence of dermatologic conditions that preclude application of skin electrodes
Absence of significant responses to TENS or other similar electroanalgesic methods	Uncontrolled seizures
In addition to pain, presence of related sensitivity symptoms: allodynia, hyperpathia, hyperesthesia	Use of antiseizure medications
Presence of pain for at least six months	Any form of medical "metal" device (e.g., pacemakers, defibrillators, vascular clips or stents, cardiac valve or joint replacements)
Frequency of pain more than four days per week	
Age >18 years	
Consent to Scrambler therapy treatment	

second PHN patient to Scrambler therapy, the third PHN patient to drug treatment, and so forth. The assignment was done in order by the research assistants, with no exceptions. Allocation was not concealed (Fig. 1).

Standardized Control Treatment

The control group patients were managed by the same team of pain specialists using the most up-to-date EFNS guidelines. The most common baseline therapy (typically amitriptyline, gabapentin, and tramadol) before randomization, which had resulted in a baseline VAS pain score of 8.1, was switched to

a potentially more effective one (typically amitriptyline, clonazepam, and oxycodone). Low-dose clonazepam is classified as an anticonvulsant, has documented efficacy in case series,^{8–10} and is the standard practice at this center when gabapentin has not been effective.

Standardized Scrambler Treatment

The Scrambler attempts to deliver "non-pain" information to the area in pain by simulating five external artificial neurons. Action potentials that resemble normal nerve impulses are digitally synthesized, assembled into packets of information strings, and delivered using standard silver gel electrodes similar to electrocardiogram electrodes. Each new packet is created with an algorithm that takes into account the previous outputs, dynamically modifying four main variables. These variables include the following: 1) type of action potential to use (16 different possible combinations); 2) packet-associated frequency (from 43 to 52 Hz); 3) packet time duration (0.7–10 seconds); and 4) the amplitude of modulation. The system quickly tries different combinations until pain relief is achieved. (The technology details are described in patent number PCT/IT2007/000647.) The impulses are transmitted by surface electrodes placed on the skin in the dermatome areas of pain above and below the dermatome. The electrical charge used in Scrambler therapy is low, and the U.S. Food and Drug Administration has approved it as safe. At the highest setting, "70" on the dial from 10 to 70, the

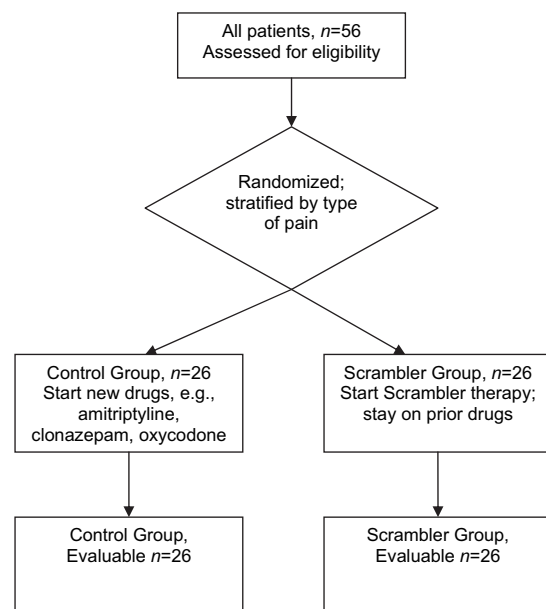


Fig. 1. Assignment of patients to treatment groups.

amperage (A) is 3.50–5.50 mA, and the maximum current density is only 0.0002009 W/cm².

Each Scrambler therapy patient was given a 45-minute daily treatment for 10 consecutive days, Monday through Friday. The stimulus was increased to the maximum intensity individually bearable by the patient that did not cause any additional pain or discomfort. The principal investigator (V. I.) chose the best treatment areas during the first visit, which were then replicated daily. The Scrambler therapy group maintained their starting drug treatment with no changes. Normally the electrodes are never applied directly on the painful area but in the dermatomes above and below the pain affected area. For example, if the pain involves L3, the first electrode is positioned close to but outside of the painful area in dermatome L2 or L3 and the other on the opposite side of the pain area in zone L3 or L4. Once the electrodes are positioned, the operator slowly raises the stimulation level until pain relief is obtained; if not obtained, the operator can add or move channels to increase the coverage. There are a total of five channels, or paired sets of electrodes. If pain is not relieved, the electrode placement or stimulus is changed.

Data and Statistical Considerations

The primary endpoint was the change in pain VAS scores¹¹ from entry to the scores at one, two, and three months. Pain intensity was measured by an unmarked 10-cm long VAS.¹² The patients were classified as having “monoradicular pain” if they had one dominant area of pain, for example, one area of

PHN, and “polyradicular pain” if they had multiple areas of pain.¹³ Allodynia was tested with von Frey elements by the research assistants and recorded as “present” or “not present.” The sample size of 26 in each arm was determined using an anticipated effect size of –1.59, with a starting VAS pain score of 6 and a standard deviation of 2 to give a 5% alpha error margin and 80% power. All statistical calculations were done with StatMate 2 (GraphPad Software, Inc., La Jolla, CA; <http://www.graphpad.com/StatMate/statmate.htm>).

For the primary endpoint of pain, a repeated-measures analysis of variance (ANOVA) was done with the VAS score as the dependent variable and time (baseline, one month, etc.), treatment (treated or control), and treatment by time interaction terms as the independent variables. The repeated-measures model accounts for the correlations that might arise from the same individuals being observed over time. Secondary endpoints included change in pain scores by the type of pain and mono- or polyradicular nature of the pain, change in allodynia, and change in medication use and doses; all were measured at entry, one, two, and three months. Changes in pain intensity over time were analyzed with one-way ANOVA and the Tukey-Kramer Multiple Comparisons Test. The difference in medication type and in dosage, and in allodynia, was evaluated using repeated-measures ANOVA.

Results

The randomized patients were similar in both groups, as shown in Table 2. The study

Table 2
Demographic Comparison of the Groups

Patient Description	Control Group (<i>n</i> = 26), <i>n</i> (%)	Scrambler Therapy Group (<i>n</i> = 26), <i>n</i> (%)
Sex		
Male	10 (38.46)	9 (34.61)
Female	16 (61.53)	17 (65.38)
Age, mean (SD), years	53 (16.14)	56 (16.26)
Diagnoses		
Postsurgical neuropathic pain	14 (53.84)	14 (53.84)
PHN	8 (30.76)	8 (30.76)
SCS	4 (15.38)	4 (15.38)
Pain score at entry, after six months of standard treatment	8.11/10 ± 1.03	8.01 ± 1.12

SD = standard deviation.

sample statistical validity was confirmed with the normality test of Kolmogorov and Smirnov ($P > 0.1$).

The primary endpoint results are shown in Fig. 2. The VAS pain score in the control group fell by 28% at one month. Average VAS pain intensity in the Scrambler therapy group decreased from entry to T1 (one month), T2 (two months), and T3 (three months) (ANOVA $P < 0.0001$). The treatment by time interaction term was significant ($P < 0.0001$) suggesting that the decline in the VAS score over time in the treated group was significantly steeper than the control group (Fig. 2.) The comparison between the two arms of the study at monthly intervals confirmed this significance ($P < 0.001$, Tukey-Kramer Multiple Comparisons Test). Results shown in Table 3 document that pain scores were reduced significantly with Scrambler therapy compared with the control group (all results $P < 0.001$ by ANOVA). Pain was reduced in all groups: postsurgical neuropathic pain ($P < 0.0001$ by ANOVA), PHN ($P < 0.0001$), and SCS ($P = 0.0108$). Fig. 3 shows the effect in the different diagnoses.

Scrambler therapy appeared to be effective in both mono- and polyradicular pain, but more patients relapsed in the polyradicular

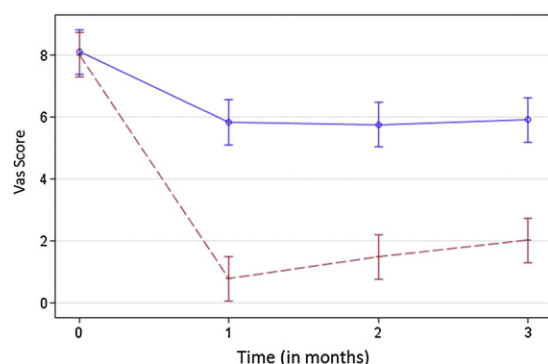


Fig. 2. Effect of treatment on pain scores over time. A repeated-measures ANOVA with the VAS score as the dependent variable and time (baseline, one month, etc.), treatment (treated or control), and treatment by time interaction terms as the independent variables. The repeated-measures model accounts for the correlations that might arise from the same individuals being observed over time. The treatment by time interaction term was significant ($P < 0.0001$), suggesting that the decline in the VAS score over time in the treated group was significantly steeper than that in the control group.

Table 3
Mean Variation in Pain Intensity (by VAS) Over Time

Time of Assessment (months)	Group	
	Control	Scrambler Therapy
T0, entry	8.11/10 ± 1.03	8.01 ± 1.12
T1, one month	5.84/10 ± 1.34	0.78 ± 1.78
T2, two months	5.76/10 ± 1.40	1.49 ± 2.39
T3, three months	5.91/10 ± 1.44	2.03 ± 3.14

All results statistically significant, $P < 0.001$ by ANOVA.

group, as shown in Fig. 4. These pain relapses at three months were statistically significant in the Scrambler therapy group ($P < 0.001$, Tukey-Kramer Multiple Comparisons Test) but not in the control group ($P > 0.05$). This relapse was observed only in patients with polyradicular neuropathy, compared with those with mononeuropathy ($P < 0.001$, ANOVA test by Tukey-Kramer Multiple Comparisons Test). The control group changes had no difference in the relapse rate when comparing the type of pain ($P > 0.05$).

Scrambler therapy appeared to have a positive effect on allodynia. Allodynia was reduced at one and three months in the Scrambler therapy group (Fig. 5). The changes were statistically significant comparing the Scrambler therapy group with the control group at one month ($P = 0.0017$, Fisher's Exact Test), two months ($P = 0.0094$), and three months ($P = 0.0644$). However, given the simple method of assessment ("yes" or "no") done in this pilot trial, further work is needed to confirm this effect.

Scrambler therapy was associated with significant pain medication dose reductions, as shown in Fig. 6. The percentage reduction was calculated compared with the initial dose at entry, then reassessed at times T2 and T3.

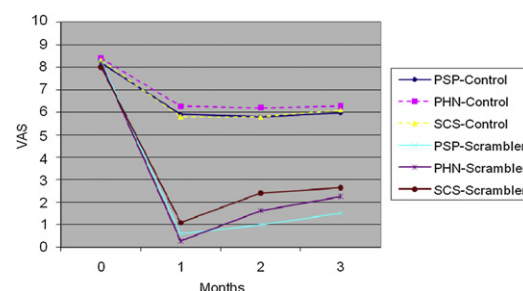


Fig. 3. Effect of treatment by type of pain. PSP = postsurgical pain.

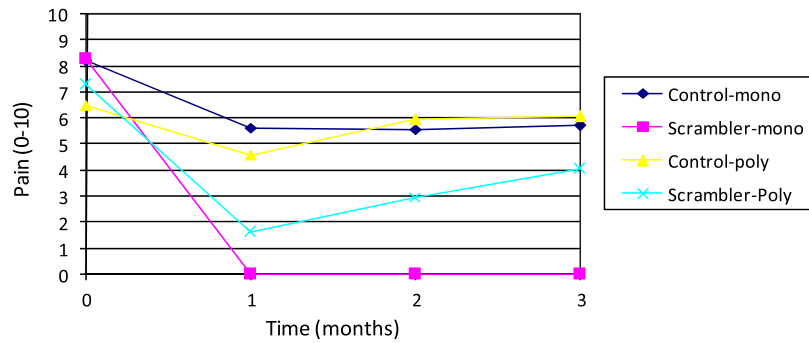


Fig. 4. Effect of therapy by mono- or polyneuropathy.

At T3, opioids were totally eliminated in 11 of 17 cases, halved in one case, and unvaried in five cases. Anticonvulsants were eliminated in 17 of 24 cases, reduced in one case, and unvaried in six cases. Lastly, antidepressants were eliminated in nine of 19 cases, reduced in four cases, and unvaried in six cases. Dosage variation was statistically significant (repeated-measures ANOVA: $P < 0.0001$).

Discussion

In this small, randomized, controlled trial, Scrambler therapy appeared to reduce pain, allodynia, and pain drug use significantly better than guideline-based drug therapy. In 21 of 26 patients, pain could be relieved entirely. Scrambler therapy was associated with a 91% pain reduction compared with a 28% reduction using new medications.

Chronic pain syndromes can be helped by patient-specific (adjusted to the tolerance of the individual patient) direct nerve stimulation.^{14–16} The mechanisms by which direct patient-specific nerve stimulation reduce pain

include raising the “gate” threshold for pain at the spinal cord, reducing “wind up” (central sensitization of the spinal cord and brain that amplifies the abnormal feelings), reducing impulses from the damaged nerve, and reducing psychological maladaptation to pain.¹⁷ Spinal cord stimulation gave a 50% pain reduction in small nonrandomized series for chronic pain from complex regional pain syndrome I (median change in VAS 10 to 0–2, $P < 0.01$, sustained)¹⁸ and PHN (median change in VAS 9 to 1, sustained).¹⁹ Spinal cord stimulation gave over 50% pain reduction in a randomized trial compared with conventional medical management in patients with failed back syndrome (mean scores fell from 7.6 to 3.8 or less, sustained for 24 months, $P < 0.001$).²⁰ This same >50% effect size has been observed in randomized trials of intraspinal drug delivery systems compared with conventional pain management, when opioids and local anesthetics can be infused²¹ to act directly on nerves. However, spinal cord stimulation and intrathecal drug delivery involve invasive expensive technology with the possibility of serious complications.

Scrambler therapy differs from transcutaneous electrical nerve stimulation (TENS) in

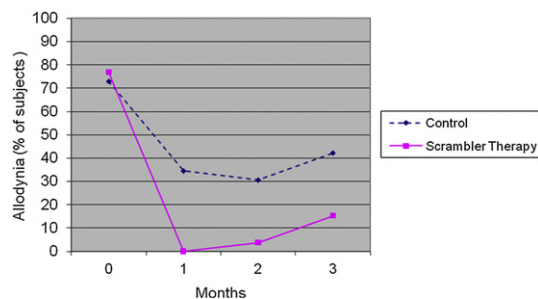


Fig. 5. Effect of treatment on allodynia. Allodynia was assessed as present or absent. The graph shows the percentage of subjects in each arm that had allodynia at each time point.

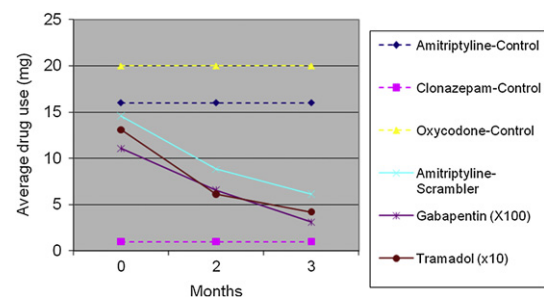


Fig. 6. Effect of treatment on pain medication use.

many aspects, although both provide stimulation via peripheral nerves. Clinically, TENS therapy has been shown effective in postoperative pain and musculoskeletal pain, but the number and quality of randomized controlled trials are often inadequate for particular conditions.²² We were not able to find any randomized trials of TENS for SCS or chronic postsurgical pain. As reviewed by Niv et al.,²³ the TENS effect in PHN has been limited in randomized trials and disappears a few hours after treatment. TENS provides an on-off biphasic current without variation, whereas Scrambler therapy provides continuously changing variable nonlinear waveforms. Recent studies with TENS units have used a continuous pulse pattern, pulse width of 200 microseconds, and a pulse frequency of 80 Hz, increased until the patient feels a strong sensation. The Scrambler therapy average charge per phase is 38.8 microcoulombs, similar to conventional TENS devices. The phase duration is 6.8–10.9 microseconds, and the pulse rate is 43–52 Hz. Because the frequency delivered by the device never exceeds 52 Hz, the mean energy delivered per second is generally less than most standard TENS devices, which deliver a square wave with frequencies greater than 52 Hz.

How Scrambler therapy causes pain relief requires further study, but our observations may inform mechanisms. First, Scrambler therapy gives new “nonpain” information such that patients report new sensations in the pain area (pressure, itching, “bee sting” sensations, and a flow of impulses). Second, it is not simple C-fiber electrical stimulation, which would produce pain. Third, Scrambler therapy is not producing paresthesias because the patient does not feel numbness and can still feel other noxious stimuli. Fourth, Scrambler therapy analgesia occurs quickly, suggesting that the receptors are transmitting the “nonpain” information. Fifth, the sustained pain relief for days or months suggests either resetting of calcium channels (as with ziconotide) or remodulation of the pain system’s response. Finally, the patient feels the sensation throughout the dermatome, not just under the electrode patch, suggesting the spread of “nonpain” information along the lines of nerve transmission. Clearly, more study is needed to define the effect and the mechanisms.

There are limitations to this study. First, this is a well-balanced, randomized, controlled study similar to that done comparing implantable drug delivery systems with guideline-based care,²⁴ but it is not a “sham” trial. Some researchers will insist that the only proof of efficacy is a randomized, double-blind, believable placebo, or sham-controlled trial, but these may be difficult to perform.²⁵ It has been hard to devise appropriate blinded studies because Scrambler therapy requires adjustments of the electrode placement and dose, titrated to pain relief, before the actual daily treatment is begun. Alternative methods to control for placebo effect include two strategies done here: first, to set a pain relief goal that would likely be unobtainable with placebo, and second, to allow an effective comparison control group. Here, the reduction in pain was 91%, much higher than typically seen with placebo. For example, in a randomized trial of electrostimulation for back pain, the sham group had a 9% reduction in back pain,²⁶ and a study involving various nonpharmacological therapies in low back pain showed that the placebo effect was less than two points on a normalized 0–10 scale.²⁷ The second alternative to a placebo-controlled trial allows an effective control comparison group. Here, the control group had a 28% reduction in pain by the end of the first month, consistent with the 14%–20% reduction seen in worst and usual pain in the guideline-managed group of a large randomized trial,²⁸ and the 39% reduction in pain seen in the guideline-managed control group of a cancer pain trial.^{20,25} A second limitation to the study is the type of treatment provided to the control group. Although some clinicians would suggest alternative drug treatments, this was the current practice at this Italian pain center, and the control group had a very reasonable 28% reduction in pain. A third limitation is the small sample size, but the study was powered to detect a relatively large difference in pain control and accomplished this.

There are strengths to this study, in addition to the limitations. The patients were well balanced in the two arms. The patient-reported outcomes are all standard, reproducible, and valid. The magnitude of the pain relief effect is large, persistent, consistent with the reduction in pain medication use, and consistent with the size of the pain relief in the

single-arm uncontrolled Scrambler therapy studies. The comparison group had good relief of pain from standard guideline-based measures applied by the expert group, as noted above. The pain relief was well beyond the 50%²⁹ and 33%³⁰ reductions proposed as being clinically important for chronic pain.

In conclusion, the pain relief obtained in this small, pilot, randomized trial encourages further development of both treatment and of knowledge regarding Scrambler therapy. This knowledge will provide a better understanding of the mechanisms of action and new opportunities for the treatment of all forms of pain. It also provides more knowledge of effect size for further randomized placebo- or sham-controlled trials, which are underway.

Disclosures and Acknowledgments

Dr. Giuseppe Marineo holds property rights to the Scrambler Therapy basic research and international patent to its technology development.

References

1. Botez SA, Herrmann DN. Sensory neuropathies, from symptoms to treatment. *Curr Opin Neurol* 2010;23:502–508.
2. Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer* 2008;44:1507–1515.
3. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150:573–581.
4. Marineo G. Untreatable pain resulting from abdominal cancer: new hope from biophysics? *JOP* 2003;4:1–10.
5. Sabato AF, Marineo G, Gatti A. Calmare therapy. *Minerva Anestesiol* 2005;71:479–482.
6. Smith TJ, Coyne PJ, Parker G, Dodson P, Ramakrishnan V. Pilot trial of a patient-specific cutaneous electro-stimulation device (MC5-A Calmare®) for chemotherapy induced peripheral neuropathy. *J Pain Symptom Manage* 2010;40:883–891.
7. Attal N, Cruccu G, Haanpää M, et al. EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13:1153–1169.
8. Hugel H, Ellershaw JE, Dickman A. Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain. *J Pain Symptom Manage* 2003;26:1073–1074.
9. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Clonazepam open clinical treatment trial for myofascial syndrome associated chronic pain. *Pain Med* 2000;1:332–339.
10. Zakrzewska JM. Medical management of trigeminal neuropathic pains. *Expert Opin Pharmacother* 2010;11:1239–1254.
11. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005;14:798–804.
12. Dixon JS, Bird HA. Reproducibility along a 10 cm vertical visual analogue scale. *Ann Rheum Dis* 1981;40:87–89.
13. Tan JC. Practical manual of physical medicine and rehabilitation, 2nd ed. Philadelphia, PA: Elsevier Mosby, 2006.
14. Folletti A, Durrer A, Buchser E. Neurostimulation technology for the treatment of chronic pain: a focus on spinal cord stimulation. *Expert Rev Med Devices* 2007;4:201–214.
15. de Leon-Casasola OA. Spinal cord and peripheral nerve stimulation techniques for neuropathic pain. *J Pain Symptom Manage* 2009;38(Suppl 2):S28–S38.
16. Mailis-Gagnon A, Furlan AD, Sandoval JA, Taylor R. Spinal cord stimulation for chronic pain. *Cochrane Database Syst Rev* 2004;(3). CD003783.
17. Jensen MP. A neuropsychological model of pain: research and clinical implications. *J Pain* 2010;11:2–12.
18. Harke H, Gretenkort P, Ladleif HU, Rahman S. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study. *Eur J Pain* 2005;9:363–373.
19. Harke H, Gretenkort P, Ladleif HU, Koester P, Rahman S. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. *Anesth Analg* 2002;94:694–700.
20. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;132:179–188.
21. Smith TJ, Staats PJ, Pool G, et al. Intrathecal implantable drug delivery systems give sustained pain control, less side effects, and possibly better survival for six months: results of a randomized clinical trial vs. comprehensive medical management. *Ann Oncol* 2005;16:825–833.
22. DeSantana JM, Walsh DM, Vance C, Rakel BA, Sluka KA. Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Curr Rheumatol Rep* 2008;10:492–499.
23. Niv D, Maltzman-Tseikhin A, Lang E. Postherpetic neuralgia: what do we know and where are we heading? *Pain Physician* 2004;7:239–247.

24. Smith TJ, Staats PJ, Pool G, et al. Randomized clinical trial of comprehensive medical management of refractory cancer pain vs. comprehensive medical management plus intrathecal implantable drug delivery systems. *J Clin Oncol* 2002;20:4040–4049.
25. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain* 2010;149:177–193.
26. Ghoname EA, Craig WF, White PF, et al. Percutaneous electrical nerve stimulation for low back pain: a randomized crossover study. *JAMA* 1999;281:818–823.
27. Chou R, Huffman LH, American Pain Society, American College of Physicians. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007;147:492–504.
28. DuPen S, DuPen A, Polossar N, et al. Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. *J Clin Oncol* 1999;17:361–370.
29. McQuay HJ, Moore RA, Eccleston C, Morley S, Williams AC. Systematic review of outpatient services for chronic pain control. *Health Technol Assess* 1997;1:1–135.
30. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–158.