ARTICLE CLASS OF EVIDENCE

Scrambler therapy improves pain in neuromyelitis optica

A randomized controlled trial

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Abstract

Objective
To determine whether Scrambler therapy is an effective, acceptable, and feasible treatment of persistent central neuropathic pain in patients with neuromyelitis optica spectrum disorder (NMOSD) and to explore the effect of Scrambler therapy on co-occurring symptoms.

Methods
We conducted a randomized single-blind, sham-controlled trial in patients with NMOSD who have central neuropathic pain using Scrambler therapy for 10 consecutive weekdays. Pain severity, pain interference, anxiety, depression, and sleep disturbance were assessed at baseline, at the end of treatment, and at the 30- and 60-day follow-up.

Results
Twenty-two patients (11 per arm) were enrolled in and completed this trial. The median baseline numeric rating scale (NRS) pain score decreased from 5.0 to 1.5 after 10 days of treatment with Scrambler therapy, whereas the median NRS score did not significantly decrease in the sham arm. Depression was also reduced in the treatment arm, and anxiety was decreased in a subset of patients who responded to treatment. These symptoms were not affected in the sham arm. The safety profiles were similar between groups.

Conclusions
Scrambler therapy is an effective, feasible, and safe intervention for central neuropathic pain in patients with NMOSD. Decreasing pain with Scrambler therapy may additionally improve depression and anxiety.

Clinicaltrials.gov identifier
NCT03452176.

Classification of evidence
This study provides Class II evidence that Scrambler therapy significantly reduces pain in patients with NMOSD and persistent central neuropathic pain.

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Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Podcast
Dr. Jeff Ratliff talks with Dr. Maureen Mealy about her paper on the use of scrambler therapy for pain in neuromyelitis optica.
NPub.org/gi1twt

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Glossary

AE = adverse event; **CI** = confidence interval; **FSA** = Food and Drug Administration; **Neuro-Qol** = Quality of Life in Neurological Disorders; **NMOSD** = neuromyelitis optica spectrum disorder; **NRS** = numeric rating scale; **QoL** = quality of life; **SAE** = serious AE; **TENS** = transcutaneous electric nerve stimulation.

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the CNS that causes recurrent inflammatory attacks of the optic nerves and spinal cord, leading to blindness, paralysis, and death.[1] Despite these devastating consequences of the disease, patients have reported that pain is among the most prevalent and debilitating symptoms that affect mood, mobility, and quality of life (QoL).[2–8] In particular, central neuropathic pain is pervasive, severe, and intractable to treatment and affects 62% to 91% of patients with NMOSD.[3,9] Currently, there is no standard of care for central neuropathic pain treatment, and the most frequently used medications for its treatment in NMOSD are antiepileptics, antidepressants, and nonsteroidal anti-inflammatory agents. Descriptive studies in NMOSD acknowledge the inadequate effect of these medications,[2,3] and effective treatment for central neuropathic pain in NMOSD is still lacking.

Scrambler therapy is a novel, noninvasive technology with Food and Drug Administration (FDA) 510(k) approval, "Scrambler ST 5 TENS Device" (K081255), granted in February 2009 for acute, chronic, and postoperative pain.[10] Scrambler is a type of transcutaneous electric nerve stimulation (TENS) that uses peripheral nerve stimulation of ascending C fibers to modify nociceptive responses with the intent of reorganizing maladaptive signaling pathways in the sensory cortex.[11] This neuromodulatory therapy has been investigated for the treatment of persistent peripheral neuropathic pain, largely in open-label observational trials, in several conditions including chemotherapy-induced neuropathy, postherpetic neuralgia, and postsurgical neuropathic pain with promising results.[11–17] Patients report sustained relief after undergoing daily treatment sessions for 10 consecutive weekdays.[11]

Anecdotal evidence supports Scrambler therapy for use in patients with persistent central neuropathic pain,[18,19] but no rigorous studies have systematically tested the benefit or sustainability of Scrambler vs a placebo treatment. The current study investigates the use of Scrambler for the treatment of central neuropathic pain in patients with NMOSD, given the substantial unmet need and lack of investigation into pharmacologic or nonpharmacologic intervention for pain management in this patient population.

Methods

We conducted a randomized, single blind, sham-controlled trial in patients with NMOSD who have central neuropathic pain using Scrambler therapy. The central hypothesis that guided this study was that Scrambler therapy is an acceptable and feasible treatment that significantly reduces pain and improves co-occurring symptoms in patients with NMOSD.

Standard protocol approvals, registrations, and patient consents

We enrolled 22 patients with NMOSD (11 per arm) at the Johns Hopkins Neuromyelitis Optica Clinic. Participants with severe limitations in mobility or sight due to their disease were given the option to have study visits conducted in their homes. The protocol was approved through the Johns Hopkins Institutional Review Board (IRB00115699) and launched on March 2, 2018. Written informed consent was obtained from each participant before study enrollment. The study was registered through ClinicalTrials.gov (NCT03452176). The FDA granted Scrambler therapy 510(k) approval for acute, chronic, and postoperative pain, "Scrambler ST 5 TENS Device" (K081255), in February 2009.[10]

Participants

Participants with self-reported neuropathic pain caused by NMOSD were recruited through the Johns Hopkins Neuromyelitis Optica Clinic. For participation eligibility, patients were ≥18 years of age with an NMOSD diagnosis based on the 2015 international consensus diagnostic criteria,[20] regardless of anti–aquaporin 4 serostatus.[21,22] For inclusion, neuropathic pain needed to be attributable to an inflammatory spinal cord lesion, indicated by MRI from a previous clinical myelitis event. Persistent pain needed to be rated at a level of ≥4 on an 11-point numeric rating scale (NRS), with persistent pain defined by presence for >3 months. Patients needed to be stable in their disease such that they had no spinal cord relapses within 6 months before enrollment. Patients were eligible to use any combination of standard-of-care medications for pain treatment, including antiepileptic, antidepressant, opioid, or nonsteroidal anti-inflammatory medications, with no adjustments to the regimen within 30 days of enrollment. Patients with a known or suspected concomitant diagnosis of peripheral neuropathy were excluded. Patients with an ongoing concomitant central neurologic disorder were excluded, as were those who used an investigational agent for pain control within 30 days of enrollment, were pregnant or breastfeeding, were cognitively or mentally incompetent, or had implantable pain management or arrhythmia devices.

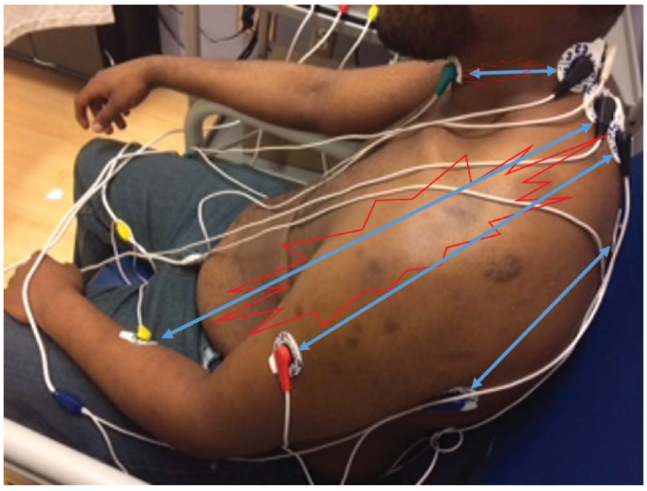
Randomization and masking

After consent and screening, participants were randomly assigned to receive Scrambler treatment vs sham at a 1:1 ratio

for 10 consecutive weekdays. Recruitment was batched with the use of a randomized block design stratifying across medication class (antiepileptic, antidepressant, opioid, or none) and pain level at screening (moderate 4–6, severe 7–10) to promote similar distributions across groups in this small study. The rationale was to increase homogeneity between groups due to limited data that suggest response to Scrambler therapy may differ as a result of interference of medications used for pain.[23] Randomization assignments were assigned by a third-party using randomizer.org.

Scrambler therapy was administered via the GEOMC Pain Scrambler, model MC-5A (Seoul, Korea). Electrodes were placed on participants receiving treatment within the dermatome above and below the level of injury in a sufficiently sensitive area closest to the pain (figure 1). For instance, if the patient had pain in the back from C3 to C8, a set of electrodes would be placed at C2 (above the pain) and T1 (below the pain). Stimulation intensity was increased until a maximum tolerable threshold was reached without being painful, per the established protocol.[24] If the patient felt a constant burn, sting, or feeling of discomfort, electrodes were repositioned. The exact electrode positioning depended on the demarcation of the surface pain area and analgesic response of the patient. Once the channel was regulated to the patient's maximum intensity, pain was assessed by asking the patient how s/he felt in the area of pain covered by the electrodes and adjusted for desired effect of reduced pain or analgesic response. Additional channel pairs were similarly implemented as necessary on the basis of the size of the pain area, up to 5 pairs in total. Electrodes remained in the established position and intensity for 35 minutes from the time that proper placement was instituted. Because central pain is often more pervasive compared with peripheral neuropathy, >1 area was often targeted.

Figure 1 Example of electrode placement for Scrambler therapy recipient



Electrode placement is demonstrated on a participant with neuromyelitis optica spectrum disorder with a cape pattern of pain from C3 to C8 dermatomal involvement. The goal is to surround the area of pain with pairs of electrodes. Each pair is indicated by a double blue arrow. An additional pair (not shown) went from the C2 to T1 region, to the right of the spinal column. Scrambler therapy electric signal travels between each pair of electrodes. The signal is alternating current, maximum 5.5 mA, maximum current density 0.0002009 W/cm^2, and 16 different waveforms.

For the sham group, small motors (<1 cm) that produce a vibratory sensation similar to a wearable activity tracker (i.e., FitBit) were connected to each electrode to simulate Scrambler stimulation but without electric charge. Channel pairs were similarly applied in a sufficiently sensitive dermatome closest to the pain, surrounding the level of spinal cord injury. The sham sensation was applied for 35 minutes.

For both groups, the Scrambler machine was kept behind a curtain to help preserve masking. The machine itself was turned on for all participants, although without emitting any stimulation in those receiving sham, so that the alert indicating termination of treatment would be heard by all participants regardless of treatment assignment. Because treatment effect has been shown to vary across technicians, 1 technician was trained in the proper delivery of Scrambler treatment and performed all interventions.

Study objectives and measures

Our primary objective was to test the hypothesis that Scrambler therapy is an effective, acceptable, feasible, and safe treatment of persistent central neuropathic pain for patients with NMOSD. To test this hypothesis, we performed a randomized, single blind, sham-controlled trial testing Scrambler therapy in patients with NMOSD. The primary outcome was feasibility and acceptability. Secondary endpoints included both safety and effectiveness at the end of the 10-day treatment period. Feasibility of treatment was examined to determine whether the intervention was appropriate for this patient population, toward the effort of informing a larger, phase III study. This was measured by assessing the following: adherence to visit schedule and response to the following question asked directly after completion of the 10-day treatment period: "Do you think you received treatment?" (Yes/No). Acceptability was measured by assessing response to the following question, also asked directly after the treatment course: "Would you want to continue treatment in clinic, if available?" (Yes/No).

Safety of the intervention was evaluated by comparing adverse events (AEs) and serious AEs (SAEs) in the treated vs sham groups. These were monitored and documented before initiation of each treatment daily, at termination of the final treatment, and at the 30- and 60-day follow-up.

Effectiveness was evaluated on the basis of the degree of improvement in pain, comparing the treatment group to the sham group. Before the initiation of Scrambler therapy and at the completion of treatment, patients were asked to rate their pain by the 11-point NRS score. Patients additionally reported NRS pain scores at 30 and 60 days after therapy completion to assess sustainability of treatment effect.

Although not powered appropriately, an exploratory objective was aimed at assessing the relationship between improved pain and other co-occurring symptoms. Before the initiation of Scrambler therapy, patients were asked to complete each of the following measurement tools to determine baseline pain severity and interference, anxiety, depression, and sleep disturbance, respectively: Brief Pain Inventory,[25] Quality of Life in Neurological Disorders (Neuro-QoL)[26] Short Form version 1.0–Anxiety, Neuro-QoL Short Form version 1.0–Depression, and Neuro-QoL Short Form version 1.0–Sleep Disturbance. Measurement tools were accessed by participants via a secure online portal. Participants were provided with an alphanumeric code that enabled their responses to be linked to their demographic and clinical data in a confidential manner. Questionnaires were mailed to participants without internet access with a postage-paid envelope provided for return of questionnaires. Patients again completed all measurement tools at the end of treatment and at 30 and 60 days after the end of treatment.

Statistical analysis

As a measure of feasibility of treatment, adherence to visit schedule was ascertained. We report the number of patients in each group who were able to complete all treatments. The Fisher exact test was performed to assess whether adherence is independent of group assignment. For each of the 2 survey questions used to assess feasibility and acceptability, as described above, a 95% confidence interval (CI) for the proportion of participants answering "yes" was calculated. Given the small number of patients in the study, exact binomial CIs were calculated because normal distribution could not be assumed.

Descriptive statistics were used to report AEs and SAEs. Incidence and severity were compared between groups.

Effectiveness was based on degree of improvement of pain and compared NRS pain scores in the treatment group and sham group using the Friedman one-way repeated-measure analysis of variance by ranks test at baseline, after treatment, and at the 30- and 60-day follow-up. Wilcoxon signed-rank testing was used to determine sustainability over time by comparing scores at baseline to those after treatment, at the 30-day follow-up, and at the 60-day follow-up. A χ^2 analysis comparing the number of treated patients who thought they received treatment with the number of sham patients who thought they received treatment was performed to determine whether masking was effective.

The target sample size of 22 (11 per arm) was based on previous studies that suggested that the average pain value at baseline is at least 4 on the 0 to 10 NRS with an SD of the original pain value expected to fall in the range of 1 to 1.5 in this patient population.[11,14,27–30] A conservative estimate of the SD of the change across patients from day 1 to 10 was up to ≈2. With 11 patients in each arm and under these assumptions, we were able to detect a change of 2.5 points in the Scrambler group at 80% power, with a difference in proportions of 60% between the 2 groups.

To explore the impact on co-occurring symptoms when intervening on pain, scores were tabulated for each of the following from the measurement tool data: anxiety, depression, sleep disturbance, and pain interference. Friedman one-way repeated-measure analysis of variance by ranks was tabulated for each symptom, comparing the change at baseline, after treatment, and at the 30- and 60-day follow-up time points in each arm. A subanalysis was similarly conducted in those patients who responded to Scrambler treatment vs sham. On the basis of a cohort of adult patients with spinal cord injury who reported clinically meaningful change in pain over time,[31] response was defined as a decrease in NRS pain scores of 1.80 points between baseline and end of treatment.

Demographic and clinical characteristics were compared between the Scrambler and sham groups by use of the Mann-Whitney U and χ^2 testing, as appropriate.

Data availability

Public Law 110-85 (also known as the FDA Amendments Act of 2007) mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. We support efforts to promote data sharing toward the advancement of science and registered this clinical trial, providing trial design, eligibility criteria, and outcomes measures.

Classification of evidence

This study provides Class II evidence of Scrambler therapy use in patients diagnosed with NMOSD who have central neuropathic pain.[32]

Results

Twenty-two patients (11 per arm) who were deemed eligible for participation in this clinical trial were enrolled, were treated, and received follow-up between March and December 2018 (figure 2 and table e-1, doi.org/10.5061/dryad.nr82sv2). Participants were treated with Scrambler therapy or sham. Most patients were female (91%) and black (59%). All participants were seropositive for aquaporin 4 immunoglobulin G. The median baseline NRS pain level was 5 points for both the treatment and sham groups (mean 5.6). The median Expanded Disability Status Scale score was 6.0 and 4.5 for the treatment and sham groups, respectively. Patient characteristics were similar between groups (table 1).

Feasibility/acceptability outcomes

There was no difference between groups in the number of participants who completed all treatments (p = 0.22). All participants in the treatment arm completed all treatments, and 2 participants in the sham arm completed only 9 of 10 sessions: 1 patient experienced a family emergency, and the other had a urinary tract infection that interfered with the trial.

A χ^2 analysis revealed that masking of the intervention was adequate; no difference was found between those in the treated group who thought they received Scrambler therapy and those in the sham group who thought they received therapy ($p = 0.20$; 95% CI 0.91–5.04). In addition, χ^2 analysis suggested that those who received the sham intervention were as likely to want to continue treatments as those who received treatment ($p = 0.67$, 95% CI 0.56–3.61).

Safety outcome

All AEs were logged daily before and after each treatment, as well as at the 30- and 60-day follow-up (table e-2, doi.org/10.5061/dryad.nr82sv2). No SAEs were reported during the 10-day treatment period among participants in either study arm. During follow-up, 2 SAEs were reported within the same patient: patient 3 (sham arm) developed a port and bloodstream infection 30 days after completion of the 10-day sham course and required hospitalization for IV antibiotic treatment. Because the infection was unresolved, the patient was rehospitalized 30 days later for IV antibiotics. Given the temporal profile and the fact that the patient did not receive Scrambler treatment, these infections were not thought to be related to the study. Neither Scrambler therapy nor the sham condition resulted in increased pain severity in these trial participants.

Figure 2 Consolidates Standard of Reporting Trials (CONSORT) flow diagram

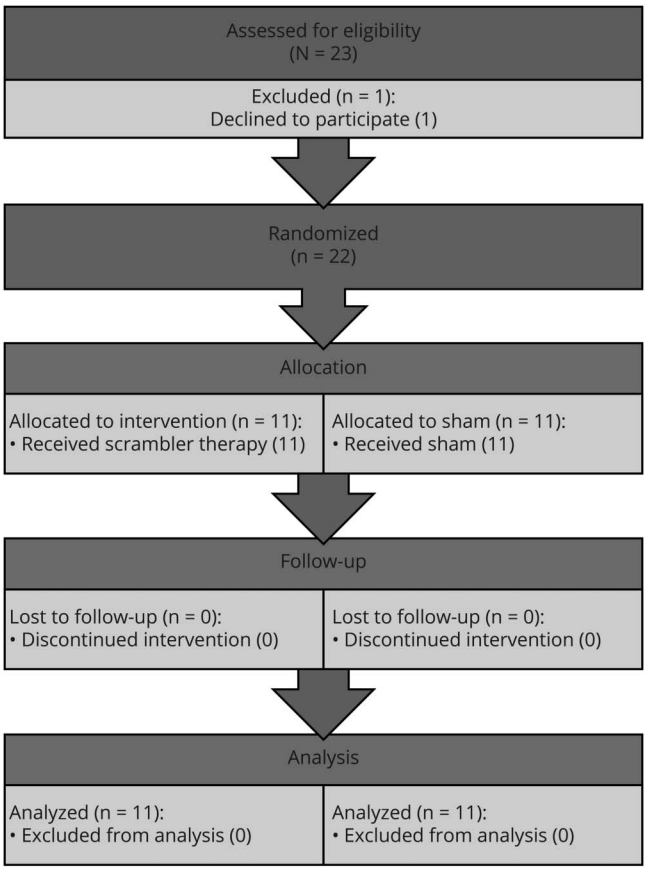


Table 1 Demographic and clinical characteristics of participants

	Treatment	Sham	*p* Value
Participants, n	11	11	1.0
Female sex, n (%)	10 (91)	10 (91)	1.0
Race, n (%)			
Black	6 (55)	7 (64)	0.89
White	3 (27)	4 (36)	
Other	2 (18)	0 (0)	
Age, y			
Median (IQR)	56.2 (7.2)	57.5 (13.8)	0.94
Mean (SD)	55.2 (9.6)	52.8 (14.9)	
Disease duration, y			
Median (IQR)	11.0 (12.8)	6.0 (7.6)	0.34
Mean (SD)	11.7 (8.8)	7.6 (5.6)	
Delay in diagnosis, y			
Median (IQR)	0.5 (8.8)	0.3 (1.0)	0.29
Mean (SD)	4.3 (5.3)	1.0 (1.5)	
AQP4 serostatus, n (%)			
Positive	11 (100)	11 (100)	1.0
EDSS score			
Median (IQR)	6.0 (3.0)	4.5 (3.0)	0.63
Mean (SD)	5.1 (2.3)	4.7 (2.0)	
Baseline NRS pain rating			
Median (IQR)	5.0 (2.8)	5.0 (3.2)	0.76
Mean (SD)	5.6 (1.7)	5.6 (1.8)	
Pain medication regimen, n (%)			
Treated	7 (64)	8 (73)	0.65
AEDs	6	8	
Antidepressants	5	3	
Opioids	3	3	
Untreated	4 (36)	3 (27)	

Abbreviations: AED = antiepileptic drug; AQP4 = aquaporin 4; EDSS = Expanded Disability Status Scale; IQR = interquartile range; NRS = numeric rating scale.

Effectiveness outcomes

The effectiveness of Scrambler therapy was determined by the impact on pain over time in the treatment group compared to the sham group, as measured by the NRS pain score. NRS pain scores were recorded at baseline, immediately after treatment vs sham, and at 30 and 60 days after treatment vs sham. After the 10-day protocol, Scrambler therapy resulted in a reduction in median NRS pain scores from 5.0 to 1.5 ($p <$

0.001), whereas the sham condition resulted in a reduction in median NRS pain scores from 5.0 to 4.0 (p = 0.4239) (figure 3). In the Scrambler therapy arm, 8 of 11 participants had a clinically meaningful improvement in pain, with 4 participants experiencing complete pain eradication immediately after the protocol. NRS pain scores remained significantly decreased at 30 days in the Scrambler-treated group (p = 0.0195). Furthermore, 3 of the 4 complete responders at the end of treatment remained pain-free at 30 days (27%). Overall, the effect was not sustained at 60 days (p = 0.0518), with 1 complete responder remaining pain-free. Because of this, a post hoc power calculation was conducted that was based on current study data to determine the sample size needed to detect a change in this secondary endpoint for use in a larger phase III trial. It was determined that 29 patients per arm would be necessary, given a mean 60-day score of 4.07 in the Scrambler treated arm and 5.32 in the sham arm with an SD of 1.89.

Exploratory outcome

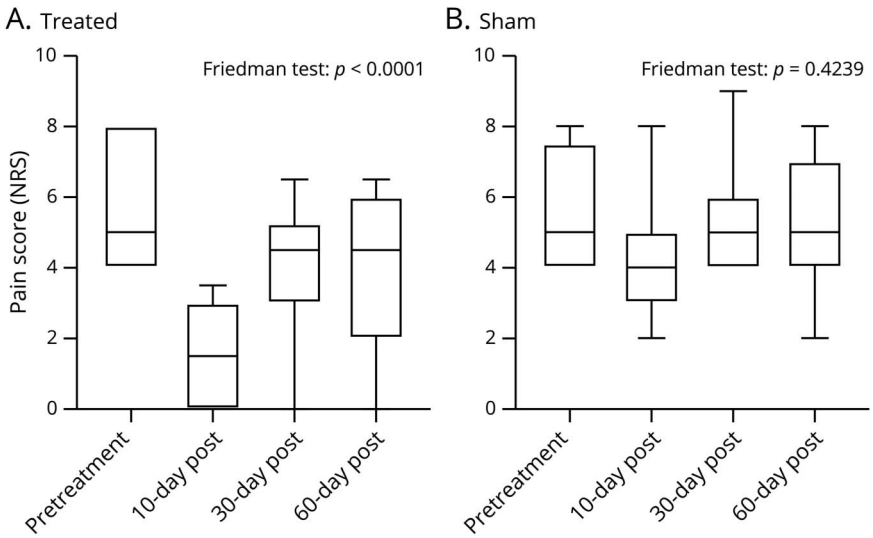
The median depression T score in the treatment arm significantly decreased after treatment with Scrambler therapy (p = 0.03). There were no significant decreases in anxiety (p = 0.10), sleep disturbance (p = 0.26), or pain interference (p = 0.37) after the Scrambler intervention. In the Scrambler therapy arm, 8 participants had a clinically meaningful improvement in pain, indicated by a decrease in NRS pain score of ≥1.80. When we consider only these patients, the change in median anxiety T scores becomes significant (p = 0.02), while sleep disturbance and pain interference remain unchanged (p = 0.64 and p = 0.68, respectively). Among those in the sham arm, the median anxiety, depression, and sleep disturbance T scores did not change over time (p = 0.15, p = 0.60, and p = 0.36, respectively). Four participants had a clinically meaningful improvement in pain in the sham arm. When we consider only these patients, all symptoms remain unchanged over time.

Discussion

The results of this sham-controlled trial in patients with NMOSD demonstrate that Scrambler therapy is an acceptable, feasible, and safe intervention for central neuropathic pain, with evidence that supports efficacy. Participants who received Scrambler therapy had a significant reduction in pain compared to those who received sham treatment. This was sustained at 30 days after the treatment course. Notably, there was no difference in the number of patients who thought they were assigned to the treatment vs sham groups, which suggests that any placebo effect was controlled for through the established sham intervention. To date, most research investigating the effect of Scrambler therapy on pain has involved open-label trials for peripheral neuropathic pain management.[12–15,33,34] Four studies have used a random controlled design, including 2 unblinded prospective randomized trials that tested Scrambler against an active comparator[30,35] and 2 that have applied a blinded randomized sham-controlled design. One involved patients with chemotherapy-induced peripheral neuropathy, which found no difference compared to Scrambler therapy placed on the back near the spine (n = 14).[36] In a second prospective placebo-controlled trial in patients diagnosed with low-back pain (n = 30), the treatment group was found to have a significant reduction in pain compared to the control group.[37] The sham group received Scrambler therapy at what was thought to be subtherapeutic doses.

Results suggest that the trial is feasible and acceptable. Adherence with the full program comprising 10 sequential weekday visits was similar in both groups, and there was no

Figure 3 Box and whisker plots depicting median change in NRS pain scores across time points



(A) Scrambler-treated and (B) sham arms. NRS = numeric rating scale.

difference in the number of participants who completed the trial and follow-up in both groups. Both groups also reported an interest in continuing treatments beyond the trial period, indicating a strong desire for pain relief with nonmedical therapies. Because many of our participants with NMOSD were severely disabled and unable to commute to the clinic on a regular basis, we offered home treatment in both arms. This likely improved feasibility and protocol adherence and suggests that a study that enables home treatments would make NMOSD participant enrollment and retention easier for a larger study.

This prospective interventional trial of a therapy to treat pain in patients with NMOSD investigated Scrambler therapy specifically for central neuropathic pain. The rationale for Scrambler use in patients with NMOSD involves the peripheral sensitization of nonmyelinated ascending C fibers, the slightest stimulation of which is interpreted by the brain as persistent pain.[9] In addition to evidence that Scrambler therapy improves pain from peripheral neuropathy, investigation into Scrambler therapy in patients with central neuropathic pain syndromes has been limited to 2 case studies (hemorrhagic brainstem cavernoma and transverse myelitis) before our study, both of which reported improvement in pain.[18,19]

Opioids are frequently used for breakthrough therapy in patients with NMOSD given the severity and intensity of pain in this population. Doses and numbers of medications are often increased due to opioid tolerance, causing side effects, particularly at higher doses, which are independently associated with fatigue.[2] With growing awareness of the dangers of polypharmacy, Scrambler therapy provides a nonpharmacologic option for central neuropathic pain treatment. Advancing alternative mechanisms for pain treatment, including Scrambler therapy, may allow reduced medication dosing such that other symptoms with which the patient is already struggling are not exacerbated.

Recent research in chronic disease suggests that treating 1 symptom in isolation of other co-occurring symptoms does not affect QoL.[38] However, small studies specific to patients with NMOSD indicate that treating pain may have the greatest impact on improving QoL.[39,40] While the current study did not measure QoL, the findings suggest that among those who responded to Scrambler therapy, intervening on pain decreases depression and anxiety, which may, in turn, affect QoL.

This study was limited by several factors. First, the design of this study was single-blinded due to the fact that the technician knew whether treatment or sham was being delivered by necessity. To mitigate the bias this potentially introduced, measurement tools and survey data were collected by an unrelated study coordinator. Second, although patients were recruited with the use of a randomized block design to mitigate the risk of confounding effects from pain medication class on the basis of previous data that reported that the type of medication may be predictive of response to Scrambler therapy,[23] our study was not powered to sufficiently compare efficacy results across classes of pain medications because patients were often on multiple medications. The effect that modifying pain through Scrambler therapy had on co-occurring symptoms was also limited by the sample size.

Lastly, while it was encouraging that a difference was detected between the Scrambler-treated and sham arms, this study was not powered to effectively examine sustainability of treatment through the 60-day follow-up period. The practicality of using Scrambler increases if the effect is sustained. The trend toward significance at 60 days suggests that a larger study that includes 29 patients per arm may uncover sustained effect. Furthermore, re-emergence of pain in treatment of both central and peripheral pain conditions has been described,[18,19] and pain has been shown to be amenable to subsequent booster treatments, often with fewer Scrambler treatment sessions needed.[12] Anecdotally, 1 complete responder from the current study was subsequently treated when pain began to re-emerge after study completion and remains pain-free months later. Thus, adapting the protocol to include subsequent booster treatments when pain emerges should be considered for future studies. Overall, the effectiveness, feasibility, and safety profiles we report support the need for a larger phase III study to further examine the effect of Scrambler on pain, reduction of analgesic medication use, co-occurring symptoms, and QoL in a larger NMOSD patient cohort.

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Disclosure

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Publication history

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Sharon L. Kozachik, PhD, RN	Johns Hopkins University School of Nursing, Baltimore, MD	Contributed to the conceptualization and design of the study, data analysis, interpretation of data, and revising manuscript content
Lawrence J. Cook, PhD	Department of Pediatrics, University of Utah, Salt Lake City	Contributed to data analysis, interpretation of data, and revising manuscript content
Lauren Totonis, MSN	Johns Hopkins University School of Nursing, Baltimore, MD	Contributed to data collection and revising manuscript content
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Jerilyn K. Allen, ScD, RN	Johns Hopkins University School of Nursing, Baltimore, MD	Contributed to study design and revising manuscript content
Marie T. Nolan, PhD, RN	Johns Hopkins University School of Nursing, Baltimore, MD	Contributed to study design and revising manuscript content
Thomas J. Smith, MD	Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD	Contributed to study design, acquisition of the MC5-A for study purposes, data collection, interpretation of data, and revising manuscript content
Michael Levy, MD, PhD	Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston	Contributed to the conceptualization and design of the study, data collection and analysis, interpretation of data, and drafting/revising manuscript content

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