Treatment of Fibromyalgia Syndrome Using Low-Intensity Neurofeedback with the Flexyx Neurotherapy System: A Randomized Controlled Clinical Trial

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SUMMARY. *Background.* Treatment of fibromyalgia syndrome (FMS) remains a clinical challenge. Pain, somatic and cognitive symptoms may be due to neurosensitization involving CNS-activated autonomic and musculoskeletal reactions, associated with EEG abnormalities that may respond to brainwave-based stimulation biofeedback. This study's objective was to examine the efficacy and safety of a novel EEG neurobiofeedback treatment, the Flexyx Neurotherapy System® (FNS), and electrophysiological responses in persons with fibromyalgia.

Methods. A randomized, double-blind, placebo-controlled clinical trial was conducted in two private practices: a free-standing neurobiofeedback center and a rheumatologist's office at an academic medical center. Sixty-four participants with FMS (American College of Rheumatology criteria; Wolfe et al., 1990) for at least three years and symptoms for at least 48 months with no recent remission were randomized to treatment. A total of 22 treatment sessions were administered over at least 11 weeks of active (n = 33) or sham (n = 31) FNS therapy. Primary efficacy measures were the Clinical Global Impressions improvement scores, Clinician (CGI-I) and Participant (PGI-I) versions. Secondary outcomes included dolorimetry and tender point count, questionnaires (fibromyalgia symptom scales, CNS Dysfunction Questionnaire, Fibromyalgia Impact Questionnaire, Symptom Checklist-90-R), and EEG activity (delta, alpha, total amplitude).

Results. More participants treated with active FNS than with sham improved partially or fully on the CGI-I at session 22 (p = .01) and follow-up (p = .04). The active FNS group had a higher

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CGI-I full response rate at session 22 ($p < .05$) but not at one-week post-treatment ($p = .07$). Significant active versus sham PGI-I responses were not detected ($p > .10$). There was no significant treatment effect on any secondary outcome measure and no specific symptom improved preferentially with active compared with sham FNS. The most commonly reported side effect was fatigue/tiredness. Pre-treatment delta/alpha EEG amplitude ratio > 1 was associated with PGI-I (but not CGI-I) response independent of treatment group assignment.

Conclusion. FNS monotherapy is insufficient for treating chronic, nonremitting FMS. doi:10.1300/J184v10n02_03

KEYWORDS. Fibromyalgia, Flexyx Neurotherapy System, neurofeedback, controlled clinical trial, treatment

INTRODUCTION

Fibromyalgia is a syndrome of unknown etiology and uncertain pathophysiology (Simms, 1994). Fibromyalgia syndrome (FMS) is characterized primarily by widespread pain, decreased pain threshold, diffuse tenderness, sleep disturbance, fatigue, and often psychological distress (Forseth, Gran, Husby & Forre, 1999; Lawrence et al., 1998; Makela, 1999; McBeth, Macfarlane, Hunt, & Silman, 2001). Diagnosed using the American College of Rheumatology's (ACR) criteria (Wolfe et al., 1990), this condition is more prevalent in women than in men across the entire adult age spectrum (Wolfe, Ross, Anderson & Russell, 1995; Wolfe, Ross, Anderson, Russell & Hebert, 1995). Disability due to FMS is a major public health concern due to impaired functioning in occupational, social and family roles, reduced quality of life, and increased health services utilization (Burckhardt, Clark, & Bennett, 1993; Calahan & Blalock, 1997; White & Harth, 1999; White, Speechley, Harth, & Ostbye, 1999; Wolfe & Vancouver Fibromyalgia Consensus Group, 1996).

A clinical diagnosis of FMS requires widespread pain for at least three month's duration. Decreased pain threshold is elicited by direct digital palpation of specific sites called tender points (Wolfe & Cathey, 1985) and with a pressure algometer (dolorimeter) (Simms, Goldenberg, Felson, & Mason, 1988; Tunks, Crook, Norman, & Kalaher, 1988). ACR criteria define "widespread" as pain on palpation of at least 11 of 18 designated tender point sites (Wolfe et al., 1990).

Treatment of FMS remains a clinical challenge. In a meta-analysis of 49 short-term clinical trials (one week to six months) involving 2,066 participants, Rossy et al. (1999) found that many pharmacological and non-pharmacological treatments benefited persons with FMS. In controlled studies, non-pharmacological treatment was more efficacious than pharmacological treatment alone in improving self-report of FMS symptoms (e.g., pain, fatigue, morning stiffness) and a similar trend for improvement was found on daily functioning measures. However, improvement in daily functioning consistently showed the lowest effect size in both pharmacological and non-pharmacological studies. Moderately large effect sizes were found for improved physical and psychological status but comparisons with pharmacological treatments showed no differential effect. There were significant benefits for non-pharmacological treatment with and without concurrent medication use.

Biofeedback is one non-pharmacological modality. Biofeedback treatment, particularly electromyography biofeedback using surface electromyography (sEMG) procedures, show mixed results (Rossy et al., 1999; Schwartz, 1995; Simms, 1994). Donaldson, Nelson and Schulz (1998), Mueller, Donaldson, Nelson and Lyman (2001), and Flor, Birbaumer, and Turk (1990) suggested that the characteristic FMS neurosomatic symptoms (e.g., cognitive, mood, sleep) may be due to a neurosensitization process that becomes self-perpetuating through CNS-activated autonomic and musculoskeletal reactions, resulting in muscle ischemia and hypoxia and the release of pain-producing sub-

stances in the periphery that feedback to the CNS. Thus, tender point abnormalities may represent secondary hyperalgesia, which depends on central nervous system pain mechanisms (Staud, 2002). The outcome of this process may be a chronic generalized pain syndrome that is associated with EEG abnormalities and that may respond (i.e., by "CNS desensitization") to a brainwave-based biofeedback known as EEG biofeedback or neurofeedback (Budzynski, 1999; Mueller et al., 2001).

Mueller et al. (2001) treated a preliminary series of thirty patients primarily (n = 26) or exclusively (n = 4) with EEG-driven stimulation (EDS), a specific form of neurofeedback, and reported that a variety of FMS symptoms improved substantially. Treatment endpoint in this case series was self-reported "noticeable improvements in mental clarity, mood, and sleep" and change from diffuse to localized pain (Mueller et al., 2001, p. 933). Thus it is not surprising that they found "significant reductions in a broad array of symptomatology" (p. 947). Patients were treated until they responded, at a cost of approximately $3,500 to $4,500 for assessment and treatment. EDS treatment ranged from 16 to 80 hours (mean = 37 hours) spread over 5 to 36 weeks (mean = 15 weeks). Most patients received additional therapies including sEMG biofeedback, physical therapy, massage therapy, and medication.

In this study we investigated the use of the Flexyx Neurotherapy System® device (FNS; Flexyx, LLC, Walnut Creek, CA). Similar to EDS, which is described as an "interactive EEG entrainment device" that uses a combination of EEG biofeedback and frequency-modulated light stimulation that is fed back to the patient to entrain the EEG (Mueller et al., 2001), FNS combines conventional EEG biofeedback and subthreshold photic stimulation (see Ochs commentary in this volume) in an effort to change EEG patterns (Schoenberger, Shiflett, Esty, Ochs, & Matheis, 2001). Initially, FNS was developed for altering EEG patterns associated with cognitive dysfunction and ultimately to improve functioning in persons with traumatic brain injury (Schoenberger et al., 2001). FNS does not require the subject's attention, focus, or orienting toward the feedback because the stimulus is not perceptible. Instead, the feedback signal is thought to affect tissues of the brain and related structures in some as yet mechanistically undefined way without the subject's conscious participation (Len Ochs, personal communication, July 17, 1999). FNS's potential benefit in fibromyalgia has been shown only in the described uncontrolled case series. The most common side effects have been fatigue, anxiety, hyperactivity, and a temporary intensification of symptoms that previously had been problematic (Len Ochs, personal communication, July 17, 1999; Schoenberger et al., 2001). These reactions usually resolved within hours or days following temporary withdrawal from and/or decreased exposure to the feedback, and may have been due to over-treatment.

We conducted what is, to our knowledge, the first randomized, double-blind, placebo-controlled study to assess the efficacy and safety of FNS neurofeedback for short-term (22 sessions; 2 sessions/week for 11 weeks) treatment of patients with FMS.

METHODS

Participants

Outpatients were recruited to the study at two private practice sites, a free-standing neurobiofeedback center in Chevy Chase, MD and a rheumatologist's office located at an academic medical center in Chicago, IL. The Chevy Chase site also recruited via newspaper advertisements and at a public meeting of the local Fibromyalgia Association. Initially, a third site was involved but due to alleged protocol violations and concerns regarding data integrity this site was dropped about midway through its enrollment; data for these participants were not available for analysis. Dr. Len Ochs, developer of the FNS equipment, coordinated research activity at all sites. The Chicago site handled administrative activities and data management. Each study site obtained local institutional review board approval of the protocol. Participants gave written informed consent at screening and were not paid for participating.

Enrollment occurred between September 1999 and June 2001. Selection criteria included: (a) age 18-62 years old; (b) diagnosed

with fibromyalgia by ACR criteria (Wolfe et al., 1990) at least three years before study entry, by a rheumatologist or appropriate specialist; (c) experienced symptoms for at least 48 months with no recent remission of symptoms to any degree; (d) free of chronic viral infection; (e) no history of any significant medical conditions such as hepatitis, herpes, lupus, multiple sclerosis, rheumatoid arthritis, polio, epilepsy, rheumatic fever, or cancer, whether a current condition or in remission; (f) free of any condition contributing to medical instability, such as any history of seizures, asthma, diabetes, hypotension; (g) no history of neck or back surgeries; (h) no multiple chemical sensitivities; (i) no history of debilitating chronic fatigue; (j) free of developmental disabilities, or significant psychological disorder for which treatment has become necessary, or history of electroconvulsive therapy; (k) not currently taking morphine or its derivatives (e.g., oxycontin), benzodiazepines, or fluoxetine; (l) not presently engaged in litigation regarding their physical condition; (m) no prior exposure to the study treatment; (n) attained a minimum educational level of grade 8; and (o) able to read and comprehend English. Those meeting these criteria were invited to a screening evaluation that included dolorimetry and EEG mapping (described below) to determine eligibility. Screening laboratory tests (blood and urine) were done to rule out any significant medical problems that could contribute to symptoms of fibromyalgia or widespread pain.

Procedures

Study Treatment

Based on previous clinical experience, treatment sessions were scheduled twice weekly for eleven weeks. The necessary equipment for EEG neurofeedback consists of (a) a 486 DX2-66 MHz personal computer with 8 megabytes of RAM, 1 gigabyte hard drive, tape backup, 2 serial-I parallel input/output ports, 16550 UART, S-VGA capability, a monitor and mouse, and capable of running Windows 3.1 or Windows 95; (b) J&J Enterprises 1-330 Compact 2-channel EEG with an on-board feedback generator powering; (c) J&J Enterprises goggles, which include diodes embedded in a set of plastic glasses; (d) a set of J&J goggles modified to be incapable of providing any feedback; and (e) Flexyx USE-2 Software and Microsoft Word 6/Excel 5 or MS Office 4.2. The Flexyx USE2 software was written specifically for this system and is not available commercially. The equipment has been described elsewhere (Mueller et al., 2001; Ochs, 1993, 1997; Schoenberger et al., 2001). MLE and LO trained the FNS therapists.

Prior to randomization, participants were required to demonstrate an average delta EEG amplitude of at least 3.0 microvolts with a standard deviation of at least 0.70 on the EEG map. These criteria are based upon clinical traumatic brain injury data (Schoenberger et al., 2001). Brain stem damage is reflected in suppressed amplitudes and this baseline was established to assess the presence of dysfunction while still allowing for the effect of medications.

Data from the FNS screening/mapping session provided the treatment guide for the active/sham FNS treatment sessions. This screening session of topographic EEG assessment was conducted without any feedback component. FNS maps were done under medication conditions requiring that all pain and antidepressant medications that can be safely stopped not be taken for 48 hours prior to mapping. The importance of this mapping procedure is that it generates a critical path specifying the sequence in which one 10-20 site is to be designated as the "active" site from which to measure the EEG during treatment and determines the sequence in which sites are treated. The EEG is monitored for four seconds at each of 21 electrode sites. The electrical activity at this so-designated site controls the pulsation frequency of the feedback.

Eligible participants were randomly assigned to one of the two treatment conditions, either active EEG neurofeedback (active FNS) or a placebo condition (sham FNS), in which all aspects of treatment were identical except that no feedback was given. All participants wore identical-appearing goggles/glasses during the treatment. Although very small electromagnetic pulses may have been delivered through the electrode wires, the sham FNS goggles/glasses should not have provided sufficient electrical input to provide feedback. A dipole switch was added to prevent any stimulation

from reaching the electrode wires before treating the final 29 participants (13 of whom received sham FNS). Separate analyses of this subgroup showed no significant increases in active versus sham FNS treatment response differences so all participants were combined in the analyses. Goggles/glasses were coded by the manufacturer and were assigned to each research site by a third party. We considered the sham (placebo) condition credible because the intensity of feedback in the treatment condition is too low to be perceived visually. Strobing of the diodes could not be perceived by participants in either condition. Double-blinding of both therapists and participants was maintained until after the first follow-up assessment evaluation, one week post-treatment.

During FNS treatment sessions, active and sham, the participants sat comfortably with their eyes closed, engaged in no specific activity, with the glasses held by the therapist so that the ear pieces did not block the diodes, and their ends two inches from the participant's cheeks. The feedback intensity was .001 during all phases of the treatment. Feedback sessions provided for a minimum of one second and a maximum of three seconds per session. A maximum number of three sites were treated during a session. If a participant could not tolerate three seconds per session (i.e., reporting treatment-related discomfort during the session or within the subsequent 24 hours) further reduction in intensity was achieved by holding the glasses up to twenty inches from the participant's face.

Participants were permitted to continue stable doses of medications during the study. Without permitting this, we could not have enrolled subjects in this study; few participants were willing (or thought they would be able) to stop pain or sleep medications, including psychotropics, despite their apparent ineffectiveness (Scharf, 2003). However, pain medications, psychotropics, and anti-inflammatory medications had to be stopped for at least 48 hours before FNS maps (as described above). During treatment, medication doses could be reduced if indicated but not raised, and new medications except for those unrelated to fibromyalgia treatment (e.g., antibiotics, antisinus medication) could not be started.

Randomization

The randomization schedule was obtained from a website (http://www.randomizer.org; June 12, 2006) and was distributed in separate blocks of eight to each site. The randomization ratio varied within each block (i.e., not necessarily 4:4) but an overall 1:1 study ratio of active FNS to sham treatment was planned. Blocks of eight were allocated so that treatment could be unblinded after participants completed the one-week follow-up evaluation and sham FNS nonresponders could be offered an opportunity to repeat the 22-session treatment protocol with open-label active FNS soon after completing the blinded trial. Non-varying and equal (4:4) ratios would allow therapists to determine the treatment allocation sequence because they also administered the open-label treatment.

Measurements

Selecting a single primary outcome measurement that adequately characterizes the FMS treatment response is challenging because there are a number of different aspects. Persons may respond to treatment in diverse ways and FNS could have a variety of effects. Therefore several outcome measurement instruments, each examining a different main domain of symptom(s) and/or function, were used.

Clinical Global Impression

The Clinical Global Impressions Scale (Guy, 1976) global improvement scales, clinician- (CGI-I) and participant- (PGI-I) rated versions, were the primary outcome measures. Although there is no generally accepted and reliable measurement for gauging severity or change in FMS symptoms this instrument is used extensively in clinical trials. White and Harth (1996) reviewed outcome measures used in clinical trials for FMS and found that the most sensitive indicator of change was the physician's global assessment. Physician global assessment score as measured by visual analog scale also was a component of Simms, Felson and Goldenberg's (1991) three-item response criteria set.

A rating of 1 (very much improved) or 2 (much improved) on the CGI-I and PGI-I 7-point scales is considered a full response ("remission"). The clinician-rated severity of illness (CGI-S) subscale ranges from 1 (normal, not at all symptomatic) to 7 (among the most extremely symptomatic patients) and was rated prior to the first treatment session.

Dolorimetry and Tender Point Counts

Dolorimetry is a procedure for quantitatively assessing pain tolerance/threshold over hypersensitive areas. The dolorimeter used was a hand-held spring-loaded gauge with a range of 0-10 kg and capped with a 1.54 cm^2 stopper (pressure threshold meter; Pain Diagnostics and Treatment, Inc., Great Neck, NY). Dolorimetry was performed at the 18 sites delineated in the ACR criteria for fibromyalgia (Wolfe et al., 1990). Those performing this procedure, masters-level trained rheumatology nurse-practitioners in Chicago and trained non-medical research assistants in Chevy Chase, were taught to increase the dolorimeter pressure at a consistent rate of (approximately) 1 kg/second and to record the pressure at which participants reported pain, not tenderness. A mean dolorimetry score was calculated at each assessment by summing measurements from each of the 18 anatomic sites. To reduce the skew of the data, the maximum score recorded at each dolorimetry site was 4 kg/1.54 cm^2. Dolorimetry was repeated at sessions 9, 16, 22 and post-treatment follow-up. Inter-rater reliability data between sites were not obtained.

Tender point counts were based on dolorimetry data. Instead of conducting independent tender point examinations, each dolorimetry-elicited positive site was counted as a tender point. Thus, a "positive" tender point was defined as pain elicited by pressure less than 4 kg/1.54 cm^2 at a dolorimetry site. At study entry, this criterion level of pain had to be present in at least 11 of the 18 ACR criteria-defined sites.

Fibromyalgia Symptom Scales

Participants completed seven Likert-type scales measuring pain (generalized and specific), "fibro-fog" (memory, concentration, multitasking; Donaldson, Sella & Mueller, 1998), depression, and fatigue, before starting treatment and at sessions 5, 9, 13, 16, 19, 22 and at follow-up. For each symptom, participants were instructed to rate its severity over the preceding seven days (including the session day) on a horizontal scale ranging from 1 ("none") to 10 ("extremely severe").

Symptom Checklist-90-R (SCl-90-R)

Psychological factors were measured with the SCL-90-R (Derogatis, 1994), a multidimensional, self-report symptom inventory. The two treatment groups were compared on the three global indices of the overall extent of psychological distress. The Global Severity Index is a mean of all items. The Positive Symptom Total and Positive Symptom Distress Index scores are based on all items endorsed as "not at all" responses. Higher scores indicate more severe symptoms. The SCL-90-R was administered at screening and one-week post-treatment.

Fibromyalgia Impact Questionnaire (FIQ)

The FIQ (Burckhardt, Clark & Bennett, 1991) is a brief, self-rated multidimensional instrument for assessing symptoms, functioning and health status. The time frame is the last seven days. The modified version that we used included a question regarding number of days slept well and a checklist of symptoms experienced in the previous three months. Also, we used horizontal Likert-type scales, similar to the specific fibromyalgia symptom scales and ranging from 0 (no problem/symptom absent) to 9 (symptom very severe), instead of the visual analog scales. The FIQ was administered at screening and one-week post-treatment.

CNS Dysfunction Questionnaire (Flexyx, LLC, 1996)

This instrument consists of eight subscales–sensory, emotions, clarity, energy, memory, movement, pain, and "other problems." It was completed pre-treatment and was repeated at sessions 9, 16, and 22. The principal focus was to assess cognitive concerns ("fibro-fog") which are reported commonly by patients with fibromyalgia. Subscales have 2 to 13 items

each, which are rated on frequency of occurrence from 0 (not at all) to 10 (all the time); the total score is obtained by summing the subscale scores.

Side Effects

Side effects were monitored at each session by asking participants if they had experienced any problems or symptoms. These were graded as 0, none; 1, does not significantly interfere with functioning; 2, significantly interferes with functioning; 3, nullifies therapeutic effect.

Data Analysis

Baseline characteristics were summarized for the whole sample and by treatment group assignment. Categorical variables were compared using chi-square or Fisher's exact test for count data and continuous variables were compared using independent t-tests for means.

Outcome assessments were conducted prior to that session's treatment. Thus, session 1 baseline assessments were conducted after randomization but before the first treatment, and the final on-treatment assessment, which was conducted at session 22, was completed prior to the final treatment. The one-week post-treatment outcomes were conducted after a week of no treatment to assess continued efficacy. Because the purpose of this report is to present acute treatment effects, we are interested mainly in the session 22 response, but for comparison we also report the one-week post-treatment outcomes. Symptom worsening at this follow-up could be due to treatment discontinuation effects and/or loss of supportive contact with staff.

The primary efficacy measure was the proportion achieving full response on the CGI-I and PGI-I scales. Dropping the third study site reduced the expected total enrollment to 64 participants for the two remaining sites. With 32 per treatment group, the power to detect a true active versus sham treatment difference in response rates is .73, based on a predicted 30% difference in percentages of CGI-I responders.

Active versus sham treatment response based on dichotomized end-of-treatment global improvement scores was analyzed using multivariate logistic regression (Hosmer & Lemeshow, 2000) for the last available assessment point (last observation carried forward). Baseline covariates in these models included pre-treatment CGI-S in the CGI-I analysis, and PGI-I since the initial screening score for the PGI-I analysis.

Secondary outcomes included two pain measures (dolorimetry, tender point counts), and four self-report clinical scales (symptom scales, CNS Dysfunction Questionnaire, SCL-90-R distress scales, FIQ). Repeated measures analyses for data collected at more than two time points (including pre-treatment) were conducted using the generalized estimating equation approach (GEE; Diggle, Heagerty, Liang, & Zeger, 2002). GEE models the mean response as a function of time within each treatment group and adjusts for within-site correlations of outcome measures (since subjects within a single site are more likely to be similar). This approach also permits inclusion of subjects with missing data so that subjects may contribute different numbers of observations. Pre-treatment baseline score for the outcome measure was a covariate. Outcomes measured only twice, pre-treatment and end of treatment (either session 22 or one-week post-treatment), were analyzed using repeated measures analysis of covariance. Differential improvement in the active FNS group versus the sham group was assessed by the treatment group-by-session (time) interaction, the statistical test of primary interest. Clinical site (Chevy Chase, Chicago) and its interactions with treatment and time were included in the models. If any site interaction term was statistically significant, treatment effect was re-estimated using only the Chevy Chase sample since most participants were treated there. If all site interaction terms were statistically non-significant they were omitted and the site was retained as a covariate. Safety data are presented according to randomization assignment.

Evoked EEG amplitudes (mean, standard deviation), in microvolts of delta, alpha, and total activity, were obtained before treatment was administered and at sessions 9, 16 and 22. We determined whether the baseline minus endpoint (session 22) amplitude differed between the two treatment groups. CGI-I and PGI-I responses at session 22 were examined as a function of pre-treatment minus session 22 change

in EEG amplitude means and standard deviations to see if treatment outcome was related to EEG change. Finally, we explored whether the global impressions outcomes were related to relative EEG amplitudes (i.e., ratios; Laibow, 1999). We expected better responses if the pre-treatment delta mean amplitude was greater than the alpha mean amplitude (i.e., delta/alpha ratio > 1).

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS for Windows Release 6.1.3, SPSS Inc., Chicago, IL, 1995) and Stata (Stata Release 7.0, Stata Corp., College Station, TX, 2001). Data are presented as frequency counts, percentages, and mean ± 1 sd, unless otherwise specified. Alpha level was set to 0.05 for statistical significance and results are reported as two-tailed tests of hypotheses unless otherwise specified. As described above, multiple symptom-related outcomes were analyzed because of uncertainty regarding the specific outcome measure(s) that FNS might affect. P values from secondary outcome measures were interpreted as descriptive in nature. To avoid possible Type II errors we did not adjust for multiple comparisons (Rothman, 1990).

RESULTS

Recruitment and Retention

Of 159 screened for eligibility (24 in Chicago, 135 in Chevy Chase), 64 (40%) participants met entry criteria and were randomized to treatment (8 [33%] in Chicago, 56 [41%] in Chevy Chase), 33 to active FNS and 31 to sham FNS treatment, and 58 (90.6%) completed all 22 treatment sessions (30 active, 28 sham). Five participants (3 sham, 2 active), all from the Chevy Chase site, did not complete at least one post-randomization efficacy evaluation and were excluded from the treatment outcome analyses. Reasons for discontinuance included an extended trip abroad, preferred taking medication, long commute to treatment sessions, family emergency, and job change that interfered with scheduling treatment sessions. No participant dropped out due to treatment-related side effects. One Chevy Chase participant dropped out after treatment session 14 due to intercurrent illness unrelated to FNS treatment. Last available data for this participant, who was randomized to active treatment, were carried forward in the endpoint CGI-I and PGI-I analyses. GEE analyses were based on the treated sample of 59. Treatment outcome data collected only at session 22 and/or one-week post-treatment could be analyzed only for the 58 study completers.

Pre-Treatment Baseline

Sample Characteristics

Table 1 shows the baseline comparisons for the two treatment groups. Participants ranged in age from 21-62 years old, and were mainly well-educated, middle-aged married women. Most (43; 67.2%) were employed. On average, participants reported that their symptoms began over a decade before study entry and that they were first treated for these symptoms approximately one to three years after symptom onset. However, they were not diagnosed with fibromyalgia until two to five and one-half years later. Most commonly, the onset of fibromyalgia symptoms was attributed to physical trauma (e.g., accident or injury) or some other or unknown cause. Thirteen percent reported a family history of fibromyalgia. The two treatment groups were comparable on all of these characteristics.

Medication Use

Participants randomized to active FNS reported using at least one more type of medication at study entry than those randomized to sham treatment. However, Table 1 shows that the two treatment groups differed only in use of allergy medication/decongestants. Vitamins (79.7%), pain medications (71.9%; persons using opioids were excluded), and psychotropics (64.1%; particularly antidepressants and hypnotics) were the most frequently used medications. Reproductive hormone therapies were used by 34.4% (hormone replacement or oral contraceptive), herbals or dietary supplements or homeopathic remedies by 25%, and muscle relaxants by 18.8%. No other type of medication was used by at least 10% of the sample.

TABLE 1. Baseline Characteristics of Whole Sample and Each Treatment Group

	All Participants	FNS Treatment	Sham Treatment	P value[b]
Number of participants	64	33[a]	31[a]	
Site, number (%)				.71
Chevy Chase, MD	56 (88)	28 (85)	28 (90)	
Chicago, IL	8 (13)	5 (15)	3 (10)	
Age in years, mean (sd)	46.9 (9.2)	45.9 (9.5)	48.1 (8.9)	.35
Gender, number (%) female	59 (92)	30 (91)	29 (94)	1.00
Race/Ethnicity, number (%)				.67[c]
White	59 (92)	31 (94)	28 (90)	
Marital status, number (%)				.43[d]
Married	39 (61)	18 (55)	21 (68)	
Single	18 (28)	10 (30)	8 (26)	
Divorced	7 (11)	5 (15)	2 (6)	
Education in years, mean (sd)	16.3 (2.4)	16.5 (2.5)	16.2 (2.2)	.62
Years since symptom onset, Mean (sd)	11.3 (8.1) (n = 63)	11.4 (8.2) (n = 32)	11.2 (8.1)	.89
Years since diagnosed, Mean (sd)	5.6 (3.2) (n = 63)	5.1 (2.6) (n = 32)	6.2 (3.6)	.15
Years since first treatment, Mean (sd)	9.5 (6.7) (n = 62)	10.6 (7.6) (n = 32)	8.3 (5.4) (n = 30)	.17
Precipitant, number (%)				.95
Post-infection	6 (9)	3 (9)	3 (10)	
Physical trauma	25 (39)	14 (42)	11 (36)	
Infection & trauma	8 (13)	4 (12)	4 (13)	
Other/Unknown	25 (39)	12 (36)	13 (42)	
Family history FMS, number (%)	8 (13)	4 (12)	4 (13)	1.00
Medication groups, mean (sd, Range) [Total = 27]	4.0 (1.9) (1-9)	4.6 (1.9)	3.4 (1.7)	.01
Allergy/Decongestant Medication, number (%)	9 (14)	8 (24)	1 (3)	.03
CGI[e] severity, mean (sd, range)	4.7 (1.1, 3-7)	4.7 (1.1)	4.7 (1.1)	.27
PGI,[f] visit 1, mean (sd, range)	4.2 (0.9, 2-7)	4.3 (1.1)	4.1 (0.7)	.30
Tender points, mean (sd, range)	16.8 (2.0, 11-18)	16.8 (2.3)	16.8 (1.8)	.51
Dolorimetry, mean (sd, range)	1.6 (0.9, 0-3.5)	1.5 (1.0)	1.7 (0.9)	.23

[a] Two participants in the Flexyx Neurotherapy System (FNS) treatment group and 3 subjects in the sham treatment group, all from the Chevy Chase site, dropped out of the study before completing at least one post-treatment assessment and were not included in the outcome analyses. Columns may not sum to 100% due to rounding.
[b] Based on chi-square or Fisher's exact test for count data and on t-test for comparing means.
[c] Comparison of white versus minorities (1 African-American and 1 Hispanic in FNS group, and 2 Hispanics and 1 "Other" in sham group).
[d] Comparison of married versus unpartnered (single, divorced), chi-square test p = .41.
[e] Clinician's Global Impressions, severity of fibromyalgia (FMS) illness at screening.
[f] Patient's Global Impressions, how felt since initial screen.

During the treatment trial, 11 participants (8 sham, 3 active FNS) decreased their pain and/or psychotropic medication ($\chi^2 = 2.33$, df = 1, p = .13).

Clinical Severity

The two treatment groups were comparably symptomatic on the screening CGI-S scale (mean = 4.7; moderately to markedly symptomatic). The two treatment groups also had similar mean dolorimetry (1.5-1.7 kg/1.54 cm^2 and positive tender point (mean = 16.8) scores, indicating marked tenderness. At the first session (before treatment), the active FNS group was slightly but significantly more severely symptomatic on CGI-S change score (active = 4.9, sham = 4.5; t = 2.47, df = 62, p = .016), and the mean PGI (active = 4.3, sham = 4.1) indicated "no change" since screening.

Site Differences

Pre-treatment global impressions and dolorimetry scores differed significantly at the two sites. The Chicago sample was less severely

symptomatic than the Chevy Chase sample on the CGI-S (screen, 3.6±0.5 versus 4.9±1.0, p = .001; session 1, 3.9 ± 1.0 versus 4.9 ± 1.1, p < .02) but not on the PGI. Screening dolorimetry was 2.8±0.5 in Chicago and 1.4±0.8 in Chevy Chase, and tender point scores were 14.0 ± 3.0 in Chicago and 17.2±1.5 in Chevy Chase (both p < .0005).

Treatment Outcomes

Primary Outcomes–Global Measures (CGI and PGI)

As shown in Table 2, there were notable differences in the active FNS group response rates measured with these two scales. In multivariate logistic regression analyses, controlling for baseline severity and treatment site, active treatment was associated with a higher improvement rate according to the CGI-I at session 22 (Wald test = 3.91, df = 1, p < .05). At one-week post-treatment, there was only a non-significant trend for a treatment group difference (Wald test = 3.18, df = 1, p = .07). There were no significant treatment group differences in PGI-I scores at either session 22 or at one-week post-treatment.

TABLE 2. Summary of Treatment Outcomes–Global Impressions Improvement at Final Session and One-Week Post-Treatment[a]

	Session 22		One Week Post-Treatment		P Value[b]	
	FNS	Sham	FNS	Sham	Pre-22	Pre-1-Week Post
	(n = 31)	(n = 28)	(n = 31)	(n = 28)		
CGI-I, n (%)[c]	15 (48)	7 (25)	15 (48)	8 (29)	.05	.07
PGI-I, n (%)[c]	7 (23)	8 (29)	8 (26)	6 (21)	.75	.56

[a] FNS, Flexyx Neurotherapy System®; CGI-I, clinician's global impressions improvement score; PGI-I, participant's global impressions improvement score. CGI-I and PGI-I rated in reference to change since began treatment.

[b] P value for each global impressions improvement score (CGI-I, PGI-I) is based on logistic regression model estimates using the Wald test statistic with one degree of freedom for the treatment effect, adjusted for site and baseline score (CGI-I analysis is adjusted for baseline CGI severity score because CGI-I is not measured at baseline; PGI-I analysis is adjusted for baseline self-reported improvement since screening visit). In all analyses the treatment-by-site interaction term was dropped because it was statistically non-significant. Last observation was carried forward for one FNS-treated subject who dropped out after session 13.

[c] Number (%) rated 'very much' or 'much' improved.

Participants also were categorized according to therapists' ratings of therapeutic effect taking into account partial responses (moderate/marked versus minimal/no change/worse). At session 22, active FNS was rated as having a moderate to marked effect for 56.7% and sham FNS was rated as having a moderate to marked effect for 25%; one-week post-treatment, active and sham FNS were rated as effective for 50% and 25%, respectively. Controlling for baseline symptom severity, active FNS was rated as having a greater therapeutic effect than the sham therapy at session 22 (Wald test = 6.14, df = 1, p = .01) and one-week post-treatment (Wald test = 4.09, df = 1, p = .04).

Secondary Outcomes–Pain and Other Symptom Measurements

Dolorimetry. Table 3 shows that the pain threshold in the FNS treatment group improved minimally through session 22 and at one-week post-treatment follow-up. Differential improvement was not observed between the active and sham FNS groups. Separate analyses with the Chevy Chase sample alone also showed no significant improvement for active versus sham FNS treatment (p > .22).

Tender Points. According to the criteria of Simms et al. (1988) a tender point score reduction of at least 25% or a tender point score of 14 or less (1991) is a clinically meaningful treatment response. As Table 3 shows, no more than 25% of those in either treatment group met either of the Simms et al. response criteria at session 22 or one-week post-treatment. The percentages did not differ significantly between treatment groups.

Symptom Scales. Table 4 shows the baseline and endpoint symptom scale scores. GEE analyses showed no significant treatment-by-time interactions, indicating that symptom reports did not differ between the FNS and sham groups over the course of treatment on any of the seven scales. Analyses were repeated using data from sessions 5, 13, and 19 only, when participants remained on their concomitant medications, to eliminate the "cold-turkey withdrawal effect" associated with their discontinuance for 48 hours preceding EEG mapping (sessions 9, 16, and 22). These results were not substantively different.

TABLE 3. Summary of Treatment Outcomes by Time Point and Treatment Group–Primary Pain Measures Baseline and End Point Scores[a]

	Pretreatment		Session 22		Post-Treatment		P Value[b]	
	FNS (n = 31)	Sham (n = 28)	FNS (n = 31)	Sham (n = 28)	FNS (n = 31)	Sham (n = 28)	Session 22	Post-Treatment
Dolorimetry, mean kg/1.54 cm^2 (sd)	1.47 (0.96)	1.72 (0.81)	1.67 (1.09)[c]	1.56 (0.97)	1.47 (0.96)[c]	1.45 (1.01)	.11	.22
Tender points responders, n (%)			7 (22.6)[d]	7 (25.0)	4 (12.9)[d]	5 (17.9)	1.0	.72

[a] Mean (sd) scores for FNS group at session 22 and 1-week post-treatment include last observation carried forward score for one subject.

[b] FNS, Flexyx Neurotherapy System®; P values for dolorimetry are for the treatment-by-session interaction in the general estimating equation (GEE) models. Dolorimetry score statistics are based on modeling the measures at sessions 9, 16, 22 and 1-week post-treatment follow-up as a linear function of baseline score, treatment, site, session, treatment by session, and site by session (site-by-treatment and treatment-by-site-by-session terms were non-significant and dropped from the models). P values for tender point responders are based on Fisher's exact test.

[c] Mean (sd) includes last observation score for one subject who dropped out before session 22 and post-treatment evaluations but was included in GEE analysis.

[d] Includes session 9 score carried forward for one subject who dropped out before session 22 and post-treatment evaluations.

TABLE 4. Summary of Treatment Outcomes by Time Point and Treatment Group–Specific Symptom Severity Scales Baseline and End Point Scores

	Pretreatment		Session 22		Post-Treatment		P Value[b]	
	FNS (n = 31)	Sham (n = 28)	FNS (n = 31)	Sham (n = 28)	FNS (n = 31)	Sham (n = 28)	Session 22	Post-Treatment
Generalized pain, mean (sd)	6.68 (1.45)	5.96 (2.01)	5.03 (2.30)	5.07 (2.36)	5.33 (2.58)	5.29 (2.26)	.30	.33
Specific pain, mean (sd)	7.35 (1.50)	7.18 (1.61)	6.23 (2.28)	6.00 (2.24)	6.17 (2.38)	6.04 (2.12)	.60	.61
Short-term memory mean (sd)	5.19 (1.76)	5.21 (2.22)	4.40 (2.04)	4.64 (2.09)	4.40 (2.13)	4.54 (2.08)	.53	.38[b]
Concentration, mean (sd)	5.39 (1.56)	5.25 (2.27)	4.47 (2.05)	4.61 (2.20)	4.70 (2.48)	4.61 (2.28)	.88	.92
Multitasking, mean (sd)	4.71 (2.37)	5.39 (2.18)	3.87 (2.27)	4.46 (2.24)	4.20 (2.75)	4.29 (2.11)	.67	.82
Depression, mean (sd)	4.29 (2.21)	4.14 (2.32)	3.43 (2.61)	3.11 (2.02)	3.83 (3.07)	3.71 (2.39)	.88	.76
Fatigue, mean (sd)	7.19 (2.10)	6.11 (2.30)	5.83 (2.36)	5.57 (2.32)	6.23 (2.60)	5.61 (2.27)	.40	.49

[a] FNS, Flexyx Neurotherapy System®; P values are for the treatment-by-session interaction in the general estimating equation (GEE) models. Statistics are based on modeling the scores at sessions 5, 9, 13, 16, 19, and 22 and at 1-week post-treatment follow-up as a linear function of pretreatment baseline (session 1) scores, and treatment, site, session, and treatment-by-session (site by session, site-by-treatment, and treatment-by-site-by-session terms were non-significant and dropped from the models, except as noted in footnote b). For each symptom, severity range = 1 (none) to 10 (extremely severe). One subject in FNS group dropped out after session 13 but was included in the GEE analysis for both session 22 and 1-week post-treatment outcomes.

[b] Separate analysis was conducted with the Chevy Chase sample because the site-by-treatment interaction was significant ($p < .05$) at 1-week post-treatment; the treatment-by-session interaction was not significant in this site-specific analysis.

CNS Dysfunction Questionnaire. We were particularly interested in change in cognitive complaints, especially "fibro-fog," characterized by "foggy" thinking, reduced ability to focus attention and maintain concentration, and forgetfulness (Mueller et al., 2001). On this self-report symptom measure, there was no statistically significant treatment-by-time interaction for the total score or on any of the instrument's eight subscales. Treatment-by-site differences were found on the sensory ($p < .01$) and movement ($p < .04$) subscales but separate analyses with the Chevy Chase sample revealed no significant difference in outcomes between active and sham FNS.

Symptom Checklist-90-R. This instrument

was administered at pre-treatment screening and post-treatment follow-up. As shown in Table 5, there were no significant differential treatment effects on any of the three global distress change scores. On all global scores and the nine symptom scales (data not shown), Chicago participants had higher mean scores both pre- and post-treatment. Moreover, except for the paranoid ideation scale, mean scores were higher in the active treatment group compared with the sham treatment group. Re-analysis limited to the Chevy Chase sample (N = 49) showed no significant pre-post treatment difference between active and sham FNS groups.

Fibromyalgia Impact Questionnaire. Table 6 shows that there were no significant treatment effects for any FIQ item. For the "depressed" and "number of symptoms" items, data were reanalyzed with the Chevy Chase sample alone because there was a significant site-by-treatment group interaction. The treatment-by-time interaction was not significant for either item, indicating no significant difference between the two treatment groups.

EEG Maps and Treatment Response. As shown in Table 7, the active and sham FNS groups did not differ significantly in EEG amplitude change (means and standard deviations) from pre-treatment to the final treatment session. The only EEG correlate of global improvement scales outcome was alpha mean amplitude, which decreased significantly in sham-treated PGI-I responders compared with the sham-treated nonresponders (b = 1.19; Wald test = 3.83, df = 1, p = .05). There was a trend for the alpha standard deviation to be related to PGI-I response in the active FNS group (b = −3.51; Wald test = 3.24, df = 1, p = .07). Delta mean and standard deviation and total EEG amplitude mean and standard deviation were not related to CGI-I or PGI-I response in treatment group- and site-adjusted logistic regression analyses.

A pre-treatment delta/alpha EEG amplitude ratio > 1 was related to PGI-I but not CGI-I response ratings. This relationship was significant at one-week post-treatment; participants with delta/alpha > 1, compared with those who had a ratio < 1, had more than a six-fold higher odds (odds ratio = 6.44, 95% confidence interval = 1.65-25.17; p = .007) of PGI-I-rated "remission." This relationship did not differ by treatment group; the ratio-by-treatment interaction was not significant. At session 22, there was only a trend for the delta/alpha ratio to be related to response (b = 1.12; Wald test = 3.27, df = 1, p = .07).

TABLE 5. Symptom Checklist (SCL)-90-R Global Indices of Psychological Distress Scores[a]

	Pretreatment		Post-Treatment		
	FNS (n = 30)	Sham (n = 27)	FNS (n = 30)	Sham (n = 27)	P Value[b]
GSI, mean (sd)	0.75 (0.48)	0.61 (0.34)	0.65 (0.54)	0.54 (0.44)	.87
PST, mean (sd)	37.4 (18.3)	30.7 (12.0)	32.7 (16.4)	29.7 (16.1)	.67
PSDI, mean (sd)	1.73 (0.37)	1.72 (0.37)	1.63 (0.44)	1.59 (0.41)	.25

[a] FNS, Flexyx Neurotherapy System®; GSI, Global Severity Index; PST, Positive Symptom Total; PSDI, Positive Symptom Distress Index. N = 57, pretreatment SCL-90-R not completed by one sham-treated subject and one-week post-treatment SCL-90-R not completed by one FNS-treated subject who terminated before the final session.

[b] P value for treatment-by-session interaction, representing differential improvement for active versus sham FNS treatment. Repeated measures analysis of covariance model includes treatment group, site, and all interactions.

Adequacy of the Blinding–Participants' Guess of Treatment Group Assignment

Before unblinding at the one-week post-treatment assessment, participants were asked what treatment they thought they had received. Those in both treatment groups were equally accurate in "guessing" their treatment. Twenty (67%; n = 30) in the active FNS group and 19 (68%; n = 28) in the sham FNS group correctly identified the treatment they had received (Fisher's exact test, p [2-tailed] = 1.0). According to the binomial test, neither proportion was significantly greater than chance (50%) expectation (active FNS, p = .10; sham, p = .09). There was no significant site difference in guessing correctly (Chicago, 60%; Chevy Chase, 68%; Fisher's exact test, p [2-tailed] = 1.0).

Safety and Side Effects

Of the 59 participants who completed at least one post-randomization assessment, 31 (52.5%) reported at least one side effect at any time during treatment. Two additional participants, one

TABLE 6. Fibromyalgia Impact Questionnaire Indices[a]

	Pretreatment		Post-Treatment		
	FNS (n = 30)	Sham (n = 28)	FNS (n = 30)	Sham (n = 28)	P Value[b]
Physical functioning, mean, (sd)	1.41 (0.77)	1.32 (0.85)	1.28 (0.82)	1.15 (0.87)	.34
# days feeling good,[c] mean (sd)	1.43 (2.10)	1.61 (1.85)	2.57 (2.60)	2.50 (2.27)	.92
# days slept well,[c] mean (sd)	1.77 (2.14)	1.82 (1.93)	2.43 (2.28)	2.57 (2.39)	.61
# days missed work,[c,d] mean, (sd)	0.55 (1.39)	0.22 (0.73)	0.55 (1.54)	0.08 (0.35)	.46
Pain/symptoms interfere with work,[d] mean, (sd)	4.30 (2.98)	4.39 (2.73)	3.00 (2.79)	3.39 (3.11)	.16
Pain severity, mean (sd)	6.27 (2.41)	6.43 (1.79)	5.23 (2.34)	5.57 (2.23)	.33
Tiredness, mean (sd)	7.63 (1.50)	6.75 (1.58)	6.40 (2.30)	5.61 (2.13)	.81
Waking tired, mean (sd)	8.00 (1.44)	6.75 (1.80)	6.43 (2.18)	5.57 (2.57)	.12
Stiffness, mean (sd)	6.97 (2.17)	6.43 (2.08)	5.47 (2.83)	5.43 (2.17)	.24
Tense/anxious, mean (sd)	5.30 (2.88)	5.04 (2.55)	4.77 (2.79)	3.82 (2.63)	.95
Depressed, mean (sd)	3.23 (1.94)	3.82 (2.42)	3.63 (3.03)	3.39 (2.77)	.17
# symptoms,[e] mean (sd)	17.53 (4.55)	15.68 (4.18)	14.87 (5.76)	13.79 (5.26)	.70

[a] N = 58, one-week post-treatment questionnaire not completed by one FNS-treated subject who terminated before the final session. FNS, Flexyx Neurotherapy System®.

[b] P value for treatment-by-session interaction, representing differential improvement for active versus sham FNS treatment. Repeated measures analysis of covariance model includes treatment group, site, and all interactions.

[c] Number (#) of days in past week (0-7).

[d] Based on 38 subjects employed at study intake, 20 in the active FNS group and 18 in the sham FNS group. Sites combined because only 3 Chicago subjects were employed.

[e] Number (#) of symptoms (0-29).

TABLE 7. FNS EEG Maps[a]

	Pretreatment		Session 22		
	FNS (n = 30)	Sham (n = 28)	FNS (n = 30)	Sham (n = 28)	P Value[b]
Alpha[c] mean (sd)	4.07 (1.27)	4.47 (1.96)	4.20 (1.78)	4.62 (2.25)	.86
Alpha[c] SD, mean (sd)	1.03 (0.38)	1.05 (0.49)	1.03 (0.45)	1.15 (0.63)	.75
Delta[d] mean (sd)	3.69 (0.55)	3.86 (0.77)	3.76 (0.84)	4.04 (1.14)	.76
Delta[d] SD, mean (sd)	1.20 (0.22)	1.41 (0.55)	1.18 (0.33)	1.33 (0.38)	.90
Total, mean (sd)	7.80 (1.34)	8.52 (1.93)	7.94 (1.99)	8.63 (2.42)	.87
Total SD, mean (sd)	1.42 (0.34)	1.61 (0.58)	1.35 (0.42)	1.54 (0.42)	.62

[a] FNS, Flexyx Neurotherapy System®. Pretreatment versus session 22 recordings of EEG amplitude averaged across 21 scalp sites, means (microvolts) and standard deviations (SD). N = 58, post-treatment recording not available for one FNS-treated subject who terminated before the final session.

[b] P value for treatment group-by-session interaction, representing differential improvement for active versus sham FNS treatment. Model includes treatment group, site, and all interactions.

[c] Alpha = 8-12 Hz.

[d] Delta = 1-4 Hz.

in the active FNS group and one in the sham FNS group, reported a side effect only at the one-week follow-up. The percentages reporting side effects differed significantly ($\chi^2 = 7.35$, df = 1, $p < .007$) between active (74.2%) and sham (35.7%) treatment groups. The symptom reported most commonly, fatigue/tiredness, was reported by 13 participants (10 in the active FNS group). Pain, including headache, was reported by 10 participants (6 in the active FNS

group). Three participants in the active FNS group reported pain/fatigue associated with stopping their medications at the FNS mapping sessions (sessions 9, 16, and 22). Four participants in the active FNS group reported sleep, drowsiness, or change in sleep patterns. Three participants in the active FNS group reported stiffness or muscle spasms. No other symptom was reported by more than two participants. Most side effects occurred early in the course of treatment; 21 participants (15 with FNS, 6 with sham) reported at least one at session 5, diminishing to only 10 (6 with FNS, 2 with sham) by the last two sessions and 8 at follow-up. Earlier in treatment, most side effects did not affect functioning. During later sessions, 50%-64% of side effects were rated as severe enough to interfere with functioning. For two participants receiving active FNS, side effects were rated as "nullifies therapeutic effect"; one participant did not report this level of severity until the one-week post-treatment assessment. None dropped out due to side effects, but in a few cases treatment sessions were suspended temporarily before resuming.

DISCUSSION

The major finding in this first randomized controlled clinical trial of FNS for treating FMS was that only the clinician-rated global impressions scores detected a treatment-related response, which persisted through one-week post-treatment follow-up only for the combined partial and full responders. Significantly more participants treated with active compared with sham FNS were rated as partially or fully remitted. This result is tempered by the finding that CGI-I and PGI-I outcomes were discrepant, with clinicians' ratings more optimistic than those of participants. Moreover, a pre-treatment delta/alpha EEG amplitude ratio > 1 was associated with PGI-I (but not CGI-I) response independent of treatment group assignment.

Improvement in global symptoms has been used to measure outcome in clinical trials involving other somatic conditions, such as irritable bowel syndrome (Brandt et al., 2002). As in irritable bowel syndrome, the clinician's treatment strategy for managing FNS is symptom-driven, so we also examined symptom outcomes. Dolorimetry ratings and tender point counts did not improve significantly more in the active than in the sham FNS group, and other symptom, psychological, and functioning measures showed no benefit for active FNS compared with sham.

Three studies on the efficacy of FNS have been published and two, both by the same group, involved patients with fibromyalgia. The first was a retrospective study of 252 patients referred with fibromyalgia, but only 157 met ACR criteria plus had sleep and mental processing problems (Donaldson, Sella & Mueller, 1998). Only 44 completed treatment and 40 reported symptomatic improvement (6 had no symptoms). EEG neurofeedback was combined with sEMG biofeedback and other myofascial treatment, and continued until symptoms reached a plateau, usually after three to six months of the integrated regimen.

The second study, described earlier (Mueller et al., 2001), involved 30 consecutive outpatients with ACR-diagnosed fibromyalgia (5 also had chronic fatigue syndrome). There was no control group, treatment was non-blinded clinical practice, and patients paid for treatment. All but four had at least one additional non-pharmacological therapeutic modality (sEMG, physical and/or massage therapy) and continued treatment until they experienced sufficient symptomatic relief, or ran out of time or money for further therapy. Their patients averaged 51.9 hours of treatment over 14.7 weeks, compared with 22 sessions over a minimum of 11 weeks in our study.

Did we under-treat? Mueller et al. (2001) reported that pain measures (percent of body involved in pain, pressure algometry, tender points; only 17 of 30 had the latter two reassessments) as well as other fibromyalgia symptoms improved significantly at the conclusion of active treatment. Follow-up assessment indicated that, compared to pre-treatment, patients indicated they were on average 62.2 ± 21.6% improved 3 to 18 months (mean = 8.2 months) post-treatment.

In the third study (Schoenberger et al., 2001), 12 patients with traumatic brain injury were randomized to receive 25 FNS treatment sessions over 5 to 8 weeks immediately or after a

delay of 6 to 8 weeks ("wait-list" control group). The immediate active treatment group was compared at time 2 with the delayed (control) group, which was post-treatment for the former group and pre-treatment for the latter group. The active treatment group improved significantly on a range of symptoms. Particularly relevant for fibromyalgia vis-à-vis the "fibro-fog" symptoms (which we measured with the CNS Dysfunction Questionnaire and the concentration, short-term memory, and multitasking symptom scales), significant improvement was observed on measures of cognitive functioning.

Based on the promising results of these three studies, we conducted this double-blind, placebo-controlled clinical trial. The results raise questions regarding FNS's treatment efficacy as well as study validity. What happened?

Does FNS really work or did the global impressions scale measure some other aspect of improvement, such as the quality of the participants' relationship with the therapist? The CGI-I, not the PGI-I, rating was the a priori primary outcome and the outcome on which the power analysis was based. In fact, CGI-I active vs. sham response differences were 23% and 19% at session 22 and one-week post-treatment, respectively. Including partial responders in the analysis of therapeutic effect, the differences were 31.7% at session 22 and 25% at one-week post-treatment. These latter differences are close to our predicted 30% difference, the basis for our power analysis.

Nevertheless, how can we explain the discrepancy between clinician and participant global impressions ratings? For example, did therapists "break the blind" and were ratings biased according to expectations and awareness of treatment allocation (note, we had no measure of clinicians' "guesses," only participants' guesses)? Was site heterogeneity, either in type of FMS patients seen, the therapists/evaluators, or treatment orientation at these two different geographically distinct locales a source of study invalidity? Was the sham treatment a true placebo (i.e., was it really inactive biologically)? Are 22 sessions an adequate treatment regimen? Was the experimental design inconsistent with actual FNS use in clinical practice in regards to the number of treatment sessions and concomitant interventions?

Did the blind remain intact? Although active- and sham-treated participants were equally accurate in guessing treatment assignment, those in the active group were more likely to rate the study treatment as more effective than previous treatment and those in the sham group were more likely to rate study treatment as no different or worse than previous treatment. Moreover, of those rating themselves as remitted, FNS treatment was rated as more effective than previous treatments by 100% at session 22 and 93% at one-week post-treatment. Of those who did not rate themselves as remitted, only 29% at session 22 and 33% at one-week post-treatment rated the treatment as more effective than previous treatment. Thus, there is some evidence that treatment "guesses," perceived comparative treatment efficacy and, to a lesser extent, self-rated improvement (PGI-I) were associated.

An important methodological issue must be raised here–does the site heterogeneity represent true difference in FMS patients, particularly in regards to symptom severity, or does it indicate a lack of inter-rater reliability? Therapists received the same training in administering treatment and recording EEG activity (FNS maps). However, dolorimetry raters did not undergo inter-rater reliability training. Chicago raters were two masters-level trained rheumatology nurse-practitioners with considerable experience in conducting dolorimetry examinations. In Chevy Chase, four people with diverse clinical backgrounds did the dolorimetry ratings–a registered nurse, two myofascial/nationally certified massage therapists, and a very experienced sEMG therapist. Two of these raters left the study but trained their replacements. Dolorimetry has been considered more objective than tender point examination; nevertheless, discrepancies between dolorimetry and tender point digital exam have been reported (Cott et al., 1992; Wolfe, Ross, Anderson, & Russell, 1995; Wolfe et al., 1990). This is a moot point in our case because tender point counts were derived from dolorimetry as described by Mueller et al. (2001); independent digital examination was not done.

Excepting the therapist CGI, all other outcome instruments are participant-rated. Although no specific inter-rater reliability training on the CGI-I scale was conducted, there also

were no statistically significant site differences on this outcome. Analytically, concerns can be raised regarding the comparatively smaller Chicago sample. To compensate, site was included as a factor and separate site-specific analyses were conducted when significant interactions involving site were found. Another problem was that the study's power was diminished after the third site was dropped midway through the study, which was compounded by an effect size that was smaller than expected.

While the pathogenesis of fibromyalgia is not well understood, the proposed theories share the postulate that these patients do not perceive or respond normally to physical or psychological stresses (Block, 1999). These stresses are likely to be multifactorial, requiring a combined therapeutic approach. Furthermore, not all fibromyalgia may be alike–fibromyalgia attributed to different etiologic factors may respond differently in terms of rate and completeness. For example, FMS acquired post-infection (9% of our sample) may be slower to respond compared with FMS that developed post-physical trauma (39% of our sample); 13% of our sample reported both of these factors and 39% reported "other/unknown" precipitants. Donaldson, Sella, and Mueller (1998) reported that those who responded only slightly gave histories of fibromyalgia triggered by a viral infection whereas those who were greatly improved or symptom-free gave histories of an antecedent trauma.

A possible limitation of our study is that those with debilitating chronic fatigue were not included. Thus, our sample may have been somewhat atypical of FMS patients seeking treatment. In fact, our sample could have included patients with co-existing chronic fatigue symptoms but they were not the more severe cases.

The most important finding may be that for fibromyalgia patients EEG treatment alone is not sufficient for recovery. In this study we examined the therapeutic efficacy of FNS monotherapy. Clinically, fibromyalgia patients treated with FNS receive a multimodal treatment regimen including the sEMG and myofascial treatment as well, because the pain from the body tends to perpetuate the CNS problems, preventing recovery (Donaldson, Nelson & Schulz, 1998; Mueller et al., 2001). It may be necessary to combine the EEG stimulation with sEMG to get rid of muscle imbalances that cause spasms. sEMG is used to teach people to retrain their muscles, thereby reducing muscle spasm. The EMG identifies the problem, and the patient is given specific exercises to do at home. The sEMG treatment is coordinated with myofascial release treatment. The fascial constrictions that build up over years of imbalances have to be removed by myofascial therapy in order for the patient to regain full muscle function. The EEG stimulation may facilitate muscle relaxation as well as softening of trigger points/tender points by some as yet not understood mechanism. Lichtbroun, Raicer, and Smith (2001) noted similarly that cranial electrotherapy stimulation, while more effective than a sham treatment comparator for treating fibromyalgia, has potentiated the effects of biofeedback when the two were given together for migraine (Brotman, 1989). Interactions among these various modalities and the need to individualize treatments complicate the design and conduct of clinical trials involving FNS or other EEG-based stimulation for fibromyalgia.

Finally, Paterson and Dieppe (2005) noted that placebo or sham controlled trial designs used for evaluating complex non-pharmaceutical interventions may generate false negative results. Reduced active–sham treatment effect sizes and inadequately powered studies can result from failure to consider that factors such as empathy and focused attention may be integral, not "non-specific," aspects of the total treatment effect. This certainly is a consideration in FNS therapy.

Continued investigation of non-pharmacological interventions in well-designed controlled clinical trials is essential. Wallace (1997), citing Pioro-Boisset, Esdaile, and Fitzcharles (1996), noted that in Canada 91% of FMS patients, compared with 63% of control rheumatic disease patients, use complementary and alternative medicine measures. Our negative study may have been due at least in part to an experimental design that was inconsistent with how FNS is used in clinical practice, such as in terms of concomitant interventions and number of treatment sessions. Thus, differences between research and clinical practice settings in how and when FNS is administered may account for discrepant treatment outcomes.

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