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Clinically Effective Treatment of Fibromyalgia Pain With High-Definition Transcranial Direct Current Stimulation: Phase II Open-Label Dose Optimization

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Abstract: **Despite promising preliminary results in treating fibromyalgia (FM) pain, no neuromodulation technique has been adopted in clinical practice because of limited efficacy, low response rate, or poor tolerability. This phase II open-label trial aims to define a methodology for a clinically effective treatment of pain in FM by establishing treatment protocols and screening procedures to maximize efficacy and response rate. High-definition transcranial direct current stimulation (HD-tDCS) provides targeted subthreshold brain stimulation, combining tolerability with specificity. We aimed to establish the number of HD-tDCS sessions required to achieve a 50% FM pain reduction, and to characterize the biometrics of the response, including brain network activation pain scores of contact heat-evoked potentials. We report a clinically significant benefit of a 50% pain reduction in half (n = 7) of the patients (N = 14), with responders and nonresponders alike benefiting from a cumulative effect of treatment, reflected in significant pain reduction (*P* = .035) as well as improved quality of life (*P* = .001) over time. We also report an aggregate 6-week response rate of 50% of patients and estimate 15 as the median number of HD-tDCS sessions to reach clinically meaningful outcomes. The methodology for a pivotal FM neuromodulation clinical trial with individualized treatment is thus supported.**

Online Registration: **Registered in Clinicaltrials.gov under registry number NCT01842009.**

Perspective: ***In this article, an optimized protocol for the treatment of fibromyalgia pain with targeted subthreshold brain stimulation using high-definition transcranial direct current stimulation is outlined.***

Key words: *Fibromyalgia, pain, noninvasive brain stimulation, high-definition transcranial direct current stimulation, motor cortex.*

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Fibromyalgia (FM) is a chronic pain syndrome that affects most of the musculoskeletal system; symptoms include diffuse pain, fatigue, and emotional distress.[48] The estimated prevalence of this disorder in the general population ranges between 2 and 5%,[2,46] with a higher incidence among females.[27] The pathophysiologic mechanisms accounting for the diffuse signs and symptoms are not yet fully understood, but current evidence suggests that alterations in nociceptive pathways and modifications in sensory processing seem to play a key role in both the initiation and the maintenance of pain in this condition. These pernicious alterations seem to be caused mainly by maladaptive plasticity in brain areas involved in these processes,[10] which is a common finding in chronic pain syndromes.

Different noninvasive brain stimulation (NIBS) techniques have been tested extensively in chronic pain syndromes given their ability to modify brain activity, targeting mainly the primary motor cortex (M1) as an entryway to modulating the aberrant activity of the circuit in charge of pain processing.[9] Several studies[5,14,24,30,37,42] have shown that stimulation of this brain area can induce significant analgesic effects in FM, mainly through modification in sensory processing of pain by thalamic inhibitory networks. Nonetheless, the results are inconsistent and some studies have achieved only marginal benefits. This variability in clinical efficacy may be associated with differences in trial design and stimulation parameters; therefore, optimization and standardization of the treatment framework used in FM may lead to significant improvements in clinical efficacy. For example, the cost of transcranial direct current stimulation (tDCS) is low, it is well tolerated, and broadly deployable, which has made it one of the most frequently used techniques, but its main drawback is that it produces diffuse brain current flow. On the other hand, high-definition tDCS using the 4 × 1 montage (4 × 1 HD-tDCS) allows noninvasive focal application of low-intensity direct current,[12] which is believed to enhance the clinical effects of this therapeutic tool.[7,29,41] Previous results using just a single session of HD-tDCS with a 4 × 1 electrode configuration over M1[4,44] demonstrated an incremental reduction of experimental and FM pain, and exceptionally long neuroplasticity changes,[22] which together support cumulative analgesic effects with repeated sessions.[42]

Therefore, we set out to evaluate the optimal stimulation parameters and criteria for patient selection and evaluation of clinical response in patients with FM receiving 4 × 1 HD-tDCS for pain management. This effort was driven mainly by the critical relevance of obtaining as much information as possible on clinical responses in early study phases to design protocols with high response rates, high efficacy, and limited side effects; which is a prerequisite for the development of pivotal phase III efforts in the field of NIBS. The primary aim of this phase II open-label trial was to establish the mean number of 4 × 1 HD-tDCS sessions needed to achieve a clinically meaningful response, defined as >50% decrease in pain, quantified by a visual analog scale (VAS). In addition, we assessed biomarkers of response, including an electroencephalography (EEG)/event-related potential (ERP) analysis of brain reorganization, known as brain network activation (BNA).[33,36,39] The exploratory aims were to test screening procedures to predict response and individualize treatment.

Methods

Study Design and Overview

The study was conducted in the Neuromodulation Center at Spaulding Rehabilitation Hospital, Harvard Medical School. It was approved by the local institutional review board and conducted in compliance with the Declaration of Helsinki (1964).

The phase II study consisted of an open-label single arm, in which enrolled patients were asked to remain in treatment until a clinically meaningful reduction in pain was achieved for a maximum of 6 weeks of treatment. A clinically meaningful response was defined as a pain intensity reduction of 50% or more compared with VAS baseline measures obtained 1 week before visit 2 using a daily pain diary.

After potential participants were identified, they underwent a detailed telephone screening and were scheduled for a first study visit to the treatment center, at which written informed consent was obtained. On the participants' first visit, baseline measurements were collected, including the Fibromyalgia Impact Questionnaire (FIQ) and sensory assessments (detailed later); participants underwent further screening using the 2010 American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia[47] and were considered enrolled patients after screening.

All enrolled patients were scheduled to complete 10 HD-tDCS sessions in a period of 2 weeks (visits 2–11), after which they completed their first response assessment (stimulation week 2, assessment 1, visit 11; Fig 1). If patients met the criteria for clinical response, and therefore were deemed responders, after any response assessment, subsequent stimulation sessions were discontinued, and patients were asked to complete 2 follow-up assessment visits. Patients who did not meet the criteria for a clinical response (nonresponders) received 5 additional HD-tDCS sessions during the third week of stimulation (visits 12–16), after which a second response assessment was conducted (stimulation week 3, assessment 2, visit 16; Fig 1). For nonresponders, the same procedure, 5 additional HD-tDCS sessions, was repeated during the fourth week of stimulation with a subsequent response assessment (stimulation week 4, assessment 3, visit 21; Fig 1). If patients continued to be nonresponders after visit 21, they received 3 additional HD-tDCS sessions during the fifth week with a fourth response assessment (stimulation week 5, assessment 4, visit 24; Fig 1). After visit 24, nonresponders were scheduled for 3 additional HD-tDCS sessions during the sixth week, when a final response assessment was made (stimulation week 6, assessment 5, visit 27; Fig 1), and at this point, regardless of response, HD-tDCS stimulation was discontinued and