STUDY PROTOCOL

A RANDOMIZED SHAM-CONTROLLED STUDY OF HOME-DELIVERED NON-INVASIVE NEUROSTIMULATION FOR MIGRAINE

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SUMMARY

Migraine affects 36 million Americans and more than 3 million suffer from chronic migraine. Despite advances in medical treatments, there is a need for better preventive and abortive therapies for this debilitating illness. Previous research has indicated that non-invasive neurostimulation may have prophylactic effects on migraine and improve symptoms and functional outcomes in migraineurs. One such method is a non-invasive transcranial direct current stimulation (tDCS). tDCS is delivered via a battery-powered device that painlessly transfers electrical current of low intensity (1 to 2 milliamperes, mA) to the surface of the head. tDCS is considered by the FDA a non-significant risk method, and several tDCS models are marketed to the public. In previous pilot studies tDCS delivered in multiple sessions had prophylactic effects on migraine and improved migraine-related symptoms such as pain. Limitation of previous studies was that tDCS was not available for at-home use and patients had to travel daily to the research facility to receive the stimulation. This caused excessive burden to patients and resulted in short term stimulation protocols, up to 20 sessions. Recently, tDCS has been developed for self-application by patients at home settings, which enabled daily tDCS applications in longer stimulation protocols. The objective of this single-center double-blind randomized sham-controlled two-parallel-arm study is to examine the prophylactic effects of tDCS on migraine in a longer protocol in home settings.

Specific Aims:

1) To evaluate efficacy and safety of tDCS self-delivered in daily 20-minute applications for 2 months (60 days) by adult migraine patients at home for migraine prevention and migraine symptom management, as compared to sham tDCS application.

2) To evaluate patients' satisfaction with the procedure.

The study will include 60 adults from general population of the New York metropolitan area, of age 18-65 years, who experience 4 migraine days or more per month and fully meet the Inclusion/Exclusion criteria described in detail below in the study protocol. For each participant the study will last about 90 days (30 days of the baseline followed by 60 days of the study intervention), and involve 3 study visits. At Visit 1, patients will provide written informed consent and undergo screening for the eligibility. This will be followed by 30 days of baseline at home during which patients will keep daily records of migraine occurrence and provide answers to a set of symptom-related questionnaires. Patients with 4 or more migraine days per month who fully meet the study eligibility criteria at the end of the baseline period will be randomized in double-blind manner into two groups: Group 1 will be randomized to receive active tDCS in daily 20-minute applications for 60 days; Group 2 will be randomized to receive sham tDCS in daily 20-minute applications for 60 days, self-applied at home. Following randomization, Visit #2 will be held either in the patient's home or in the research facility, based on the patient's preference. tDCS device will be deployed to the patient and instructions on tDCS use will be provided. The first tDCS/sham self-application by the patient will be done at Visit 2. Daily tDCS/sham self-application by the patient at home will continue for the rest of the 60-day period. Study staff will be in regular remote contact with the patient via phone and HIPAA-compliant videoconferencing. Upon conclusion of the intervention, tDCS device will be collected from the patient at Visit 3 held either in the patient's home or in the research facility, based on the patient's preference. Safety monitoring will continue bi-weekly by phone for 30 days after the last tDCS/sham application.
Outcome assessment will be carried out at the end of the baseline, and at the end of month 1 (day 30; secondary end-point) and month 2 (day 60, primary end-point) of the tDCS/sham intervention.

The primary outcome measure will be *Change in mean number of migraine days per month*. Secondary outcomes are: *Percentage of responders*, (having at least 50% reduction of monthly migraine days); *Change in monthly migraine attack frequency*; *Change in monthly acute antimigraine drug use*; *Change in mean headache severity per migraine day; Change in quality of life; Change in depressive symptoms; Tolerability; Satisfaction.*

PURPOSE AND RATIONALE OF THE STUDY

This project addresses a gap in available approaches to migraine prophylaxis and symptom management. Migraine is a condition that affects 36 million Americans and more than 3 million suffer from chronic migraine. Despite advances in medical treatments, there is a clear need for better preventive and abortive therapies for this debilitating illness. Previous research has indicated that non-invasive neurostimulation, such as that using the non-invasive transcranial direct current stimulation (tDCS), may have prophylactic effects on migraine and improve symptoms and functional outcomes in migraineurs if delivered in multiple sessions. Limitation of previous studies was that tDCS was not available for at-home use and patients had to travel daily to the research facility to receive the stimulation. This caused excessive burden to patients and resulted in short term stimulation protocols, up to 20 sessions. Recently, tDCS has been developed for self-application by patients at home settings, which enabled daily tDCS applications in longer stimulation protocols.

OBJECTIVES AND SPECIFIC AIMS

The goal of this study is to examine the effects of tDCS on migraine and related symptoms in a longer stimulation protocol in home settings.

Specific Aims are:

1) To evaluate efficacy and safety of tDCS self-delivered in daily 20-minute applications for 2 months (60 days) by adult migraine patients at home for migraine prevention and migraine symptom management, as compared to sham tDCS application.

2) To evaluate patients' satisfaction with the procedure.

BACKGROUND

The burden of living with migraine: Migraine is a condition that affects 36 million Americans with more than 3 million suffering from chronic migraine. Migraine is one of the top ten causes of years lived with disability worldwide (Disease Incidence, 2017). Episodic and chronic migraine are not biologically distinct conditions and are differentiated by the frequency of attacks. When headaches occur on 15 or more days each month and when additional, also arbitrary conditions are met, the patient is considered to have chronic migraines. Episodic migraine attacks usually last 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

The WHO considers a day lived with severe migraine as disabling as a day lived with dementia, quadriplegia or acute psychosis and more disabling than blindness, paraplegia, angina or rheumatoid arthritis.

Gaps in available treatments: The drugs to treat migraines are divided into abortive and preventive categories. There are eight FDA-approved preventive treatments for migraine headaches. They include two antihypertensive drugs in the beta-blocker family and two epilepsy drugs for episodic migraines, injections of onabotulinumtoxinA for chronic migraines, and three injectable CGRP monoclonal antibodies, for both episodic and chronic migraines. Drugs that are not approved by the FDA, but generally considered effective are several antidepressants.

A recent study (Ford et al., 2017) of 1487 patients (70% female), 91% with episodic migraineurs showed that acute treatment was prescribed for >90% of the patients, and >50% had a current prescription for preventive treatment. Despite taking acute and/or preventive treatment, 29% of episodic migraineurs (including some patients with ≤3 headache days/month) had moderate-to-severe headache-related disability. Preventive treatment was discontinued or switched at least once by 26% of episodic migraineurs. Of those patients who gave collective reasons for discontinuation/switching preventive treatment, over 70% selected lack of efficacy and tolerability/safety. Another study (Ifergane et al, 2006) looked at acute therapy of migraine with triptans. Of the 1498 patients who filled a first triptan prescription, during a 1-year follow-up period, 841 patients (56%) purchased triptans only once. The reasons for such low adherence to treatment include lack of efficacy, side effects, cost, and other.

There is a clear need for better preventive and abortive therapies for this debilitating illness.

Non-invasive neuromodulation using transcranial direct current stimulation (tDCS): tDCS (Figure 1) is a novel non-pharmacological, non-invasive neurostimulation method delivered via a battery-powered device that painlessly transfers electrical current of low intensity (1 to 2 milliamperes, mA) to the surface of the head, typically via two large (20-35cm^2) saline-soaked sponge electrodes (Nitsche and Paulus, 2000; Woods et al., 2016). tDCS is considered by the FDA a non-significant risk method, and several tDCS models are marketed to the public. Within the past 15 years, number of studies using tDCS in humans have been published, and have demonstrated that tDCS has been successfully used in combination with other pharmacological and non-pharmacological treatments for various conditions and can be added to care as usual; the patients may continue their medication regimen and treatment plan.

Previous pilot research has indicated that tDCS delivered in multiple sessions can have prophylactic effects on migraine and improve symptoms and functional outcomes in migraineurs (Auvichayapat et al., 2012; Antal et al., 2011). Overall, tDCS is a highly innovative approach which may result in a substantial improvement of quality of life improvement in patients with chronic migraine.

A major limitation of previous studies was that tDCS was not available for at-home use and patients had to travel daily to the research facility to receive the stimulation. This caused excessive burden to patients and resulted in short term stimulation protocol with limited the number of tDCS applications, for example delivering tDCS only twice or three time per week in total of 10 sessions, resulting in clinically insignificant or substantially delayed effects (DaSilva et al, 2012). Recently, tDCS has been developed for self-application by patients at home settings, and enabled daily tDCS applications in longer stimulation protocols without the burden of excessive travel to the research facility (Knotkova et al., 2017; 2018; Riggs et al., 2017; 2018; Charvet et al., 2015; Chung et al, 2019, under editorial consideration). To date, longer stimulation protocols involving daily tDCS applications for up to 6 months in chronically ill patients reported good acceptability and safety profile of this method (Imm et al., 2019; Bystad et al., 2017). The tDCS device used in this study, *Soterix mini-CT,* was developed by Soterix Medical Inc. based in New York City, specifically for administration by patients at home, and has enhanced safety features for dose control: The device can only deliver one stimulation dose, 20 minutes of real tDCS or sham tDCS, each day. Sessions are regularly monitored by study personnel via phone and HIPAA compliant videoconference.

DESIGN AND OVERVIEW

This study will employ a single-center double-blind randomized sham-controlled two-parallel-arm design and involve 60 adults with migraine. For each participant, the study will involve 3 study visits and last about 90 days (30 days of the baseline followed by 60 days of the tDCS/sham study intervention). A post-study safety monitoring will continue bi-weekly by phone for 30 days after the last tDCS/sham application.

At Visit 1, patients will provide written informed consent and undergo screening for the eligibility. This will be followed by 30 days of baseline at home during which patients will keep daily records (Daily Diaries) of migraine occurrence and provide answers to a set of symptom-related questionnaires. Patients with 4 or more migraine days per month who fully meet the study eligibility criteria at the end of the baseline period will be randomized in double-blind manner into two groups: Group 1 will be randomized to receive active tDCS in daily 20-minute applications for 60 days; Group 2 will be randomized to receive sham tDCS in daily 20-minute applications for 60 days, self-applied at home. Following randomization, patients will continue keeping the Daily Diaries and Visit #2 will be held either in the patient's home or in the research facility, based on the patient's preference. tDCS device will be deployed to the patient and instructions on tDCS use will be provided. The first tDCS/sham self-application by the patient will be done at Visit 2. Daily tDCS/sham self-application by the patient at home and records in the form of Daily Diaries will continue for the rest of the 60-day period. Study staff will be in regular remote contact with the patient via phone and HIPAA-compliant videoconferencing. Upon conclusion of the intervention, Visit 3 held either in the patient's home or in the research facility, based on the patient's preference. tDCS device will be collected from the patient. Safety monitoring will continue bi-weekly by phone for 30 days after the last tDCS/sham application.

Outcome assessment will be carried out at the end of the baseline, and at the end of month 1 (day 30±2; the secondary end-point) and month 2 (day 60±2, the primary end-point) of the tDCS/sham intervention.

STUDY SAMPLE

The study will include 60 adults from general population of the New York metropolitan area, of age 18-65 years, who experience 4 or more migraine days per month and fully meet the following Inclusion/Exclusion criteria.

Inclusion Criteria

- Age 18 - 65 years;
- Has episodic or chronic migraine with or without aura, diagnosed according to the International Classification of Headache Disorders 3rd edition (ICHD-3) criteria, for at least the past 12 months;
- Migraine occurring on 4 or more days per month, as documented through the 30-day baseline;
- No change in prophylactic therapy in 3 months preceding the baseline;

- If on antidepressant, blood pressure or epilepsy medication for reason other than migraine, the medication regimen is stable for at least 3 months preceding the baseline; Able to follow instructions in English;
- Understand the informed consent process and provide consent to participate in the study.

Exclusion Criteria

- History of severe head trauma, brain surgery, implants in the head or neck; history of seizures;
- Skin disorder or skin defects which compromise the integrity or sensitivity of the skin at or near locations where tDCS will be applied;
- Not able to prepare and operate the tDCS device after being instructed in tDCS use;
- Not able to respond to questionnaires and rating scales;
- Concurrent use of another neurostimulation device (such as spinal cord stimulator cardiostimulator, deep brain stimulator, vagus nerve, transcranial magnetic, or supraorbital transcutaneous electric nerve stimulators);
- Concurrent use of Botox or CGRP monoclonal antibodies treatments;
- Unstable acute medical condition;
- Any serious, malignant or non-malignant, acute or chronic medical condition or active psychiatric illness that, in the Investigator's opinion, could compromise patient safety, limit the patient's ability to complete the study, and/or compromise the objectives of the study;
- Used any investigational drug, biologic, or device within 30 days prior to screening, or 5 half-lives, whichever is longer;
- Taking opioid analgesics or barbiturates on more than 2 days a week;
- Taking medications acting as NMDA-antagonist.

OUTCOME MEASURES AND ENDPOINTS

Outcome assessment time-points will be at the end of the 30-day baseline (±2 days), at the end of month 1 (day 30±2 days, the secondary end-point) and month 2 (day 60±2 days, the primary end-point) of the tDCS/sham intervention.

The primary comparison will be the between-group comparison at the end of month 2 of the tDCS/sham intervention.

The primary outcome measure will be *Change in mean number of migraine days per month*.

A note: A migraine day is defined as any calendar day on which the patient had onset, continuation, or recurrence of a migraine as recorded in the diary. A migraine is defined as a migraine (with or without aura) lasting at least 30 minutes. Any calendar day on which acute migraine medication is used is counted as a migraine day.

Secondary outcome measures will be:

1. *Percentage of responders*, determined as a number of patients having at least 50% reduction of monthly migraine days between the one-month baseline and post-intervention, in each of the two study groups;
2. *Change in monthly migraine attack frequency*,
3. *Change in monthly acute antimigraine drug use*,

all determined from the patients' diaries;

4. *Change in mean headache severity per migraine day* determined from Pain NRS ratings on migraine days;
5. *Change in quality of life* determined from ratings on the migraine-specific MSQ questionnaire;
6. *Change in depressive symptoms* determined from the Hamilton Depression Scale (HamD);
7. *Tolerability* determined from occurrence of side effects and adverse events related, probably related or possibly related to tDCS, through the study;
8. *Satisfaction* - percentage of patients stating at the end of the trial that they are very satisfied, moderately satisfied, or not satisfied with the treatment, determined from the 8-item tDCS User Survey at the end of the intervention;

STUDY PROCEDURES AND METHODS

Procedural schema

Event/Time	Procedures
Visit 1	Consenting, Screening, Baseline Daily Diaries dispensed
30-Day Baseline	Baseline Daily Diaries kept Study eligibility affirmed
Randomization	In double-blind manner to active tDCS or sham tDCS
Visit 2 (within 3 days after randomization)	Questionnaires MSQ and HamD administered tDCS familiarization, training, equipment dispensing First tDCS/sham self-application under in-person supervision of study personnel
Daily tDCS/sham at home for 60 days	Daily Diaries kept Interim outcome assessment in remote on Day 30±2 of tDCS/sham: Questionnaires MSQ and HamD, Daily Diaries evaluation
Visit 3 (within 3 days after tDCS/sham completion)	End-of-study outcome assessment: Questionnaires MSQ, HamD, tDCS User Survey, Daily Diaries evaluation, AEs evaluation Equipment collected Monetary compensation for time and effort dispensed
Post-study safety follow-up (for 30 days after last tDCS/sham)	Two bi-weekly phone calls

Recruitment: The study will include general public – adult men and women living at home (not at an institution, such as nursing home etc) in boroughs of New York City and its suburbs. The study plans to randomize 60 patients. In order to account for screen failures and possible drop out during the baseline period prior randomization, it is anticipated that about 75 patients will have to be consented and screened.

The main source of referrals will be from staff of the New York Headache Center (Sub-investigator Dr. Mauskop). Other recruitment outreach will include patients' self-referrals through IRB-approved flyers/advertisement material disseminated in boroughs of New York City and its suburbs.

Upon the initial contact, patients will be asked if they wish to receive information about the study. If yes, study personnel will provide detailed information and answers questions. Patients will be given enough time to consider the study participation. If a patient expresses interest in participating in the study, the study personnel will schedule the initial visit (Visit #1).

Visit #1: The visit will take place at a designated room at the New York Headache Center. At the visit, the study staff will guide the patient through the process of review and signing the Informed Consent and HIPAA authorization to allow study staff to obtain necessary medical information from patient's medical record. The patient will receive a copy of the signed Informed Consent and HIPAA authorization. Study staff will then collect profiling demographic and clinical characteristics and review medical information for the purpose of eligibility screening. Patients who meet the study Inclusion/Exclusion criteria at screening will receive instructions on how to keep Participant's Daily Diaries and will proceed to the baseline.

30-day Baseline (at home): Through the baseline, patients will keep daily diaries to document migraine occurrence, related symptoms and medication intake. The diaries will be sent once a week via encrypted HIPAA-compliant email or by fax to the study personnel. Patients who report 4 or more migraine days per month at the end of the baseline period and fully meet the Inclusion/Exclusion criteria will be eligible to undergo randomization and proceed to the interventional phase of the study.

Randomization. Randomization list will be computer generated by study statistician using the block-of-six method. Both the patient and study personnel, except for statistician will be blinded to the sham vs active tDCS treatment assignment. tDCS devices will be programmed to sham or active tDCS mode in accordance with the randomization list.

tDCS stimulation protocol and device. The active tDCS will involve 20-minutes of direct current at intensity of 1.5 mA. Sham will include 30 seconds of stimulation at 1.5 mA, followed by 0 mA for the remaining time. The stimulation pads (electrodes) will be placed in a simple headband, as depicted in detail in the Patient tDCS Instructional Brochure. The tDCS device for this study will be *Soterix mini-CT* (Soterix Medical Inc., New York, NY). The tDCS mini-CT was developed for at home administration and has enhanced safety features: a unique keypad access system that allows the user to apply only the pre-determined dose each day. The device will be deployed to the patient at Visit #2.

Visit #2 - Familiarization with tDCS and Device Deployment will be held either at the patient's home or at a designated room at the MJHS Institute, whichever is more convenient for the patient. Familiarization will build on tDCS information provided to the patient via flyer and tDCS booklet prior consenting. The study personnel will demonstrate the equipment and function of the device, instruct the patient on the use of the device, and will review the IRB-approved instructional booklet with the patient. The patient will have an opportunity to experience the sensory sensation associated with tDCS procedure by applying 30 seconds of tDCS stimulation on the arm at the intensity 1.5 mA that is planned be used in the study. The study personnel will also instruct the patient how to establish video connection for a remote contact with the tDCS supervising study personnel located at the MJHS Institute via a HIPAA-compliant Zoom application via the patient's phone, tablet or personal computer. (Patients who do not possess any of these electronic devices will be given an electronic Tablet equipped with Zoom capability for the study duration).
At the end of Visit 2, the patient will carry-out the first tDCS/sham application under in-person supervision of study personnel.

tDCS/Sham Applications in Home Settings. After the first 20-minute tDCS/sham self-applied by the patient at Visit #2, the tDCS/sham self-applications will continue daily for the total of 60 days. Reminders will be sent by the study personnel via email and text message daily. In addition, study staff will be in regular remote contact with the patient via phone and/or HIPAA-compliant videoconferencing, at least three times per week during the first week and at least twice a week during the remaining weeks.

During the intervention period of the study, patients will continue keeping daily diaries, to document migraine occurrence, related symptoms and medication intake, as done at the baseline period. Patients will receive reminders about the diaries via email and text messages. The diaries will be in electronic form and patients will be sent the diaries to the study site once a week via encrypted HIPAA-compliant email or by fax.

Upon conclusion of the first and second month of the tDCS intervention, the patient will provide answers to the quality of life questionnaire (MSQ), Hamilton Depression Scale, and to the 8-item tDCS User Survey (at the end of the second month only). as well as his/her impression of having received either active or sham treatment, in order to evaluate the blinding. **Visit #3 – Device Return** will be held either at the patient's home or at a designated room at the MJHS Institute, whichever is more convenient for the patient, upon conclusion of the study intervention. At the visit, patients will answer to the questionnaire package including MSQ, HamD, and tDCS User Survey. tDCS device and remaining study materials and supplies will be collected, and the patient will receive monetary compensation for time and effort associated with the study intervention procedures (see in detail below, section Administrative Issues – Compensation).

Safety Monitoring will be carried out throughout the study in accordance with the Safety Monitoring Plan (described in detail below) and will continue bi-weekly by phone for 30 days after the last tDCS/sham application.

ASSESSMENT TOOLS AND DATA COLLECTION

Profiling/Characteristics of the Sample

Demographic characteristics (age, gender, education level, marital/living status, employment status) will be determined from the patient's self-report. Clinical characteristics (diagnosis, illness duration, medications and other treatments) will be determined from the patient's self-report, review of medical record, and Karnofsky Performance Status.

Outcome Assessment

Outcome assessment will utilize the following tools:

- Patients's Daily Diaries will be used to take notes of days on which a migraine attack occurs, duration of the attack, severity of migraine pain during the migraine attack, acute antimigraine drug use, and occurrence of any other (non-migraine) headache. Time needed to fill-in the diary is about 1-3 minutes per day (filled-in only on days when headache or migraine medication intake occur).

- Pain Numerical Rating Scale (Pain NRS) is an eleven point [0-10] scale for rating of pain intensity, with the anchor points 0=no pain and 10=worst pain imaginable. Administration time is about 1 minute, rated only on migraine days.

- Migraine-Specific Quality of Life Questionnaire (MSQ) is a validated 25-item questionnaire evaluating impact of migraine on physical, emotional and social component of patients' life. Recall period is four weeks. Administered at the baseline, at the end of month 1 and month 2 of tDCS/sham application. Administration time is about 5 minutes (Rendas-Baum et al., 2013).

- Hamilton Depression Scale (HamD) is a validated 17-item instrument for assessment of depressive symptoms. Administered at the baseline, at the end of month 1 and month 2 of tDCS/sham application. Administration time is about 20 minutes (Hamilton, 1960; Williams, 1988).

- tDCS User Survey is an 8-item questionnaire on user's satisfaction with the use of tDCS. Administered at the end of tDCS use. Administration time is about 5 minutes.

- Occurrence of side effects and adverse events through the study. Tolerability will be determined from occurrence of side effects and adverse events related, probably related or possibly related to tDCS, through the study.

SAMPLE SIZE DETERMNATION AND DATA ANALYSIS

The sample size calculations are based on responder rates from previous studies of non-invasive neurostimulation in migraine (Lipton et al., 2010; Saper et al., 2011). The numbers used were 15% for sham, based on published trials and 55% for the supraorbital neurostimulation inferred from the pilot study (Gerardy et al., 2009; Lipton et al., 2010; Saper et al., 2011) and 12.1% for sham vs 38.1% for verum in the RCT (Schoenen et al., 2013). To detect a significant difference between the 2 treatments (5% significance level) with an 80% power, the minimum size of each treatment group was estimated at 26 patients, 52 in total who get randomized and initiate the intervention. To account for possible dropouts in the category "randomized, but never started the intervention", we plan to randomize in total 60 patients. To account for patients who do not meet the eligibility criteria at screening, we anticipate we will need to consent about 75 patients.

Statistical analysis will be carried out on an intention-to-treat basis, as well as per protocol for comparison. For Aim 1, the primary comparison will be the between-group comparison at the end of month 2 of the tDCS/sham intervention for the primary and secondary outcomes measures (listed in detail on pgs 7,8). Secondary exploratory comparisons will include between-group comparisons at the month 1 (Day-30) of the 2-month intervention, and within groups comparisons across the study time-points (the baseline, month 1, month 2), as well as comparison of efficacy in patients with chronic and episodic migraines and comparison of efficacy in patient taking abortive migraine medications on 10 or more days with those taking them on 9 or fewer days.
For Aim 2, (Satisfaction with the device and procedure), the primary analysis will include the between-group comparison of at the end of month 2 of the tDCS/sham intervention, evaluating the percentage of patients stating at the end of the trial that they are very satisfied, moderately satisfied, or not satisfied with the device use and procedure, determined from the 8-item tDCS User Survey at the end of the intervention. (We anticipate significant group differences in Survey items pertaining to being more confident in symptom management at home, but no significant group differences in items pertaining to satisfaction with tDCS training and ease of use of the device). In addition, the

process data - number of delivered applications and the protocol fidelity in each study group will be analyzed, in order to support evidence on feasibility of the procedure.

DATA MANAGEMENT AND CONFIDENTIALITY

Each participant will be assigned a study ID consisting of the participant's numerical code. Subjects name will not be recorded on study materials, except on the consent form. Signed Consent forms with the participant's full name and signature will be kept by the study coordinator separately from other study files double-locked and secured at the research offices. In the electronic database, the data will be saved and identified with an assigned study number; patient's name or data that can potentially lead to identification of the patient will not appear in the database. The results of this study may be used for publication but will not include subjects' name. The study materials and documentation will be kept for 3 years after closure of the study.

SAFETY MONITORING PLAN

tDCS safety data

As per FDA determination, tDCS is considered a non-significant risk technique, and was exempt from the IDE requirement.

The safety of this technique has been addressed and tested by multiple researchers. To date, more than 100 studies have been reported in electronically accessible databases (MEDLINE, PUBMED) on effects of tDCS, underlying mechanisms, and safety in humans (Ardolino et al., 2005; Lang et al., 2005; Nitsche et al., 2003a,b; Liebetanz et al., 2006). Notably, tDCS has been shown to comply with general safety considerations as delineated for all types of non-invasive transcranial electrical stimulation (Agnew and McCreery, 1987; Nitsche et al., 2003a,b). Beyond the general safety parameters of the tDCS technique, safety considerations pertaining to tDCS stimulation parameters has been observed to ensure the safety of participants undergoing tDCS stimulation. Major safety parameters of electrical stimulation utilizing direct current (as opposed to devices producing alternating current), are Current Density [A / cm2] = stimulation strength [A] / electrode size [cm2], and Total Charge [C/cm2] = stimulation strength [A] / electrode size [cm2] x total stimulation duration [s]) (Nitsche et al., 2003a,b). Therefore, these major safety parameters are determined by the size of the electrodes, the intensity of the current and the duration of the stimulation. A comprehensive review on safety of tDCS in human subjects by Sundaram et al. (2009) evaluated all existing tDCS protocols involving human participants for the aforementioned safety parameters, Current Density and Total Charge, as well as available data from animal studies identifying potentially damaging values for each parameter: the threshold for potentially damaging Current Density was at 25 mA/cm2. The threshold for potentially damaging Total Charge was 216 C/cm2. Notably, tDCS protocols involving human subjects typically apply tDCS at the intensity of 1-2mA, for 10-30 minutes, with electrodes of size 25-36 cm2. This translates into Current Density 0.03-0.08 mA/cm2 and Total Charge 0.018-0.096 C/cm2, thus orders of magnitude below the potential safety threshold. The parameters in our study will be: the current intensity 1.5 mA, for 20 minutes, with electrodes of size 25cm2. Thus, Current Density will be 0.06 mA/cm2 and Total Charge 0.072 C/cm2, which is within the parameter range delivered in other tDCS studies and well within safety limits.

Researchers at the National Institute of Neurological Disorders and Stroke (NINDS) conducted a safety study on tDCS, investigating 20-minute sessions of 1 mA and 2 mA current stimulation with healthy controls (n=103), and no negative effects were identified (Iyer et al., 2005).

In a review of 567 tDCS sessions conducted over a period of two years, Poreisz et al. (2007) reported that during tDCS, a mild tingling sensation was reported by 70.6% subjects and a light itching sensation under the stimulation electrodes occurred in 30.4% cases (Poreisz et al., 2007). It is important to note that a mild tingling/itching non-painful sensation during tDCS is a natural sensation pertaining to passing the electrical current through the skin, similarly as water-flow elicits non-painful sensation on the skin surface. Other events reported in Poreisz' study were transient headache, and infrequently reported nausea and insomnia. Some subjects in Poreisz study also reported fatigue during and after tDCS, while subjects in another study experienced a fatigue improvement (Bocci et al., 2013).

Overall, the most common side effects reported in tDCS studies were: headache, dizziness, nausea, itchy sensation as well as transient irritation under the area of the electrodes (Brunoni et al., 2011; Brunoni et al., 2012; Iyer et al., 2005; Poreisz et al., 2007). Thus, a growing body of research from different laboratories support the notion that tDCS is a noninvasive technique for modulating neural excitability, with favorable safety profile.

Monitoring of Subjects and Criteria for Withdrawal of Subjects

Adverse Events (AEs): Study personnel will monitor study participants for AEs thorough the course of the study, and in 30-day post-study safety follow-up by phone.

Any AE that is ongoing at the time of the participant's study completion or withdrawal will be followed by the study physician and PI until the event resolves or stabilizes.

AEs will be captured, by the Investigator or designee, in the subject's source documents and on the case report form (CRF). AEs will be followed by the study physician and Principal Investigator and reported to the IRB in accordance with regulatory requirements.

Fluctuation of intensity and frequency of symptoms evaluated in the study is expected due to natural course of the chronic illness. If the patient reports significant worsening of any symptom during treatment, this will be conveyed to the study physician, who will assess the patient's report and offer the patient appropriate follow-up.

The participant may withdraw from the study at any point for any reason.

Participants may be removed from the study for the following reasons:

- Not following the study protocol or instructions from study personnel.
- Participants who during familiarization (Visit 2) find the sensory sensation associated with the stimulation unacceptable.
- Participants who after instruction are not able to perform tDCS in accordance with the procedure described in the patient's instructional booklet.

- If a serious adverse event related or potentially related to the study procedure occurs.
- If the study closes.

Provisions for Research Related Injury
Because the risk profile of tDCS is very low, no research-related injury is anticipated. In the unlikely event that a patient reports clinically-relevant harm from the study, this information will be conveyed to one of the study physicians (R.K. Portenoy, MD; A. Mauskop, MD), who will evaluate the patient. The physician will ensure that the patient has appropriate medical follow-up. The IRB guidelines for reporting will be followed.

REGULATORY AND ETHICAL OBLIGATIONS
General
This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and under applicable regulatory requirements; the Code of Federal Regulations (CFR), CFR Title 21, International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) E6.

Protocol
A copy of the protocol, proposed informed consent, research authorization and any further documentation will be submitted to the Institutional Review Board (IRB) for written approval. All subsequent protocol amendments and changes to the informed consent document will be submitted to the IRB for written approval.

Informed Consent
Each qualified participant will voluntarily sign and date the informed consent and research authorization after the study purposes, procedures, and potential risks and benefits of the study and all other aspects have been fully explained to them. The consent form must be signed prior to performance of any study-related activity.

Confidentiality
All medical information collected from study participants, and documentation related to their participation in the study will be kept in a locked cabinet at MJHS Institute for Innovation in Palliative Care. Unique patient identifiers will be used to label all data. Strict standards of confidentiality will be upheld at all times.

Alternatives to Participation
The alternative to participate in this study is not to participate. Participants are free to withdraw at any time without penalty. Participants may elect to discuss possible approaches to symptom management in chronic illness with their medical providers.

Prompted Action
If the score on the Hamilton Depression Scale (Ham-D) is 17 or higher [moderate or severe depression], the study personnel will ask the patient whether he/she would like to have study personnel contact the patient's physician to inform him/her about this score.

If the score on item #3 of the Ham-D scale is 3 or 4 [Suicidal ideas, gestures or attempts], the patient will be told that the study physician will be informed, and that the study physician will make a determination about whether to inform the patient's physician that this score was elicited.

ADMINISTRATIVE ISSUES

Compensation

Participants who undergo the study intervention in accordance with the study protocol (daily active/sham tDCS with completed Daily Diaries and completed outcome assessment questionnaires), will receive monetary compensation for their time and effort up to $150 in cash dispensed at Visit #3.
Participants not adhering to the study protocol will not receive the compensation.
Participants who do not start the at-home stimulation phase will not be compensated. This means that participants who complete the 30-day Baseline phase and do not qualify will not be compensated for their time.

Participants who start the at-home stimulation phase, but leave the study early, will receive prorated compensation as it follows:

- If they leave the study before completing the first month of stimulation, they will receive $50, if they followed the study procedures (tDCS daily applications, Daily Diaries and questionnaires).

- If they complete the first month of at-home stimulation, but not the second month of at-home stimulation, they will receive $100, if they followed the study procedures.

- If they complete both the first and second month of at-home stimulation, you will receive $150, if they followed the study procedures.

Study Registration

The study will be registered at the publicly accessible website ClinicalTrials.gov. in accordance with the U.S. regulatory requirements.

Study Documentation and Storage

A list of all persons authorized to perform study procedures will be maintained in the Regulatory Binder. All study related essential documentation will also be kept in the Regulatory Binder. Participant's study files and source documentation will be maintained by the assigned study staff. Study files will be kept locked in the research offices. Following completion or termination of the study, all study documents will be kept for a minimum of 3 years as required by the IRB.

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