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Double-Blind, Proof-of-Concept (POC) Trial of Low-Field Magnetic Stimulation (LFMS) Augmentation of Antidepressant Therapy in Treatment-Resistant Depression (TRD)

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Abstract

Background—Low-Field Magnetic Stimulation (LFMS) is a novel, non-invasive, sub-threshold neuromodulation technique, shown in preliminary studies to have immediate mood elevating effects in both unipolar and bipolar depressed patients.

Objective—We aimed to assess the antidepressant augmentation effects at 48 hours of LFMS administered on two consecutive days compared to sham treatment in treatment resistant depression (TRD) subjects, using the Sequential Parallel Comparison Design (SPCD).

Methods—Eighty-four eligible subjects with TRD were randomly assigned to double-blind treatment with LFMS 20 minutes/day for four days, sham treatment 20 minutes/day for four days, or sham treatment 20 minutes/day for 2 days followed by LFMS treatment 20 minutes/day for two days, using the pre-randomization version of the SPCD (randomization 1:1:1). The SPCD analyses used a repeated measures linear modeling approach with maximum likelihood estimation to use all

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available data, and using a 60–40 weighting of Stage 1 vs. 2 responses, with the primary outcome being measured after 2 and 4 days.

Results—Both primary and secondary outcome measures consistently showed no differences between LFMS-treated patients and those treated with sham, with the exception of a slight, non-significantly greater improvement than sham in the visual analogue scale (VAS) sad mood on LFMS-treated patients. LFMS treatment was relatively well tolerated.

Conclusions—We did not observe a significantly greater, rapid efficacy of LFMS compared to sham therapy. Future studies need to examine the possible therapeutic effects of more intensive forms of LFMS, as other forms of neurostimulation typically require longer duration of exposure.

Introduction

Treatment-resistant depression (TRD) typically refers to inadequate response (e.g., failure to achieve remission) despite at least one adequate antidepressant therapy among patients suffering from major depressive disorder (MDD) [1,2]. The findings of the largest clinical trial in MDD, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, demonstrated that approximately two thirds of MDD patients do not achieve remission following an initial adequate trial of antidepressant therapy [3], suggesting that TRD is highly common. When approaching TRD, clinicians typically consider switching to another antidepressant therapy [4] or adding a second antidepressant (combination strategy) or another psychotropic agent (augmentation strategy) to the ongoing antidepressant therapy [5]. However, the well-established therapeutic options are somewhat limited, as there are only four pharmacological treatments approved by the U.S. Food and Drug Administration (FDA) for adjunctive treatment in patients with TRD: aripiprazole [6], quetiapine [7], olanzapine-fluoxetine combination [8] and brexpiprazole [9]. In addition, only three non-pharmacological therapies have been approved for TRD: transcranial magnetic stimulation [10], vagus nerve stimulation [11], and electroconvulsive therapy [12].

The mood elevating effects of Low-Field Magnetic Stimulation (LFMS) were serendipitously discovered during an MRI study of bipolar depressed patients using echo-planar magnetic spectroscopic imaging (EP-MRSI), which uses specific time-varying gradient magnetic fields (similar to, but different from the pulse sequences used in functional MRI). LFMS was found in preliminary studies to have immediate mood elevating effects primarily in bipolar depressed patients (n=81) and in a small sample (n=22) of unipolar depressed patients [13,14]. LFMS has also been studied in the rodent Forced Swim Test (FST), a standard animal model of depression, showing comparable efficacy to two other antidepressant therapies (fluoxetine and desipramine) [15], and confirmed by other laboratories [16,17]. To investigate the potential physiological effects of LFMS in the brain, Volkow and colleagues measured regional brain metabolism using FDG-PET imaging before and after exposure to EP-MRSI/LFMS [18]. The electric fields induced by LFMS led to significant reductions in glucose metabolism in multiple brain areas, and modeling of the applied electric field showed that the magnitude of the decrease in metabolism correlated with the strength of the electric field.

In light of these promising, preliminary results, we aimed to assess the antidepressant augmentation effects at 48 hours of LFMS administered on two consecutive days compared to sham treatment in TRD subjects, using the Sequential Parallel Comparison Design (SPCD) [19]. The capacity to detect rapid-onset efficacy of the treatment was a priority in the study design.

Methods

This was a six-site, double-blind, sham-controlled, SPCD study of the acute efficacy of LFMS in the treatment of adults with treatment-resistant MDD, carried out at six sites (Massachusetts General Hospital, Yale University, Icahn School of Medicine at Mount Sinai, University of Texas Southwestern, University of Alabama at Birmingham, and Emory University). This trial was conducted according to FDA guidelines and the Declaration of Helsinki. IRB-approved written informed consent was obtained from all patients before any protocol-specified procedures were carried out. The subjects were drawn from an outpatient sample of MDD patients recruited through general advertisement and clinician referral. For study entry, all of the following criteria had to be met.

Inclusion Criteria

A subject was eligible for inclusion only if all of the following criteria were met:

1. Male or female, 18 to 65 years of age, inclusive, at screening.
2. Ability to understand/provide consent prior to screening, and to adhere to study protocol.
3. Diagnosis of MDD, single or recurrent, and currently experiencing a Major Depressive Episode (MDE) of at least eight weeks in duration, prior to screening, according to the criteria defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR™). The diagnosis of MDD was made by a site psychiatrist and supported by the Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P). The diagnosis was confirmed by remote, independent MGH Clinical Trials Network and Institute (CTNI) raters who administered the mood disorder module of the SCID-I/P, via teleconference, between the screen and baseline visits.
4. A participant had TRD of the current MDE, as assessed by the investigator and remote, independent MGH CTNI rater using the MGH Antidepressant Treatment Response Questionnaire (ATRQ). TRD was defined as failure to achieve a satisfactory response (e.g., less than 50% improvement of depression symptoms), as perceived by the participant, to at least one “treatment course” of a therapeutic dose of an antidepressant therapy of at least 8 weeks duration. The adequacy of dose and duration of the antidepressant therapy was determined as per the MGH ATRQ criteria. The TRD status was confirmed by remote, independent MGH CTNI raters who administered the MGH ATRQ, via teleconference, between the screen and baseline visits. Participants were required to be currently on a stable

(for at least 4 weeks) dose of ongoing antidepressant therapy, whose total duration had to be at least 8 weeks.

5. Participants had a total Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥20 for moderate to severe depression at both the screen and baseline visits, as confirmed by the remote, independent MGH CTNI rater between the screen and baseline visits.

6. Good general health as ascertained by medical history, physical examination (PE), clinical laboratory evaluations, and 12-lead electrocardiogram (ECG).

7. For females, status of non-childbearing potential or use of acceptable birth control.

8. Body mass index between 18–40 kg/m^2.

9. Concurrent psychotherapy was allowed if the type (e.g., supportive, cognitive behavioral, insight-oriented) and frequency (e.g., weekly, monthly) of the therapy had been stable for at least three months prior to screening and if the type and frequency of the therapy was expected to remain stable during the course of the study.

10. Concurrent hypnotic therapy (e.g., with zolpidem, zaleplon, eszopiclone, benzodiazepine hypnotics, and low-dose trazodone) was allowed if the therapy had been stable for at least 4 weeks prior to screening and was expected to remain stable during the course of the study.

Exclusion Criteria

A potential participant was not eligible for participation in this study if any of the following criteria were met:

1. Pregnancy or breastfeeding.

2. Participant had failed to achieve a satisfactory response to more than 3 treatment courses of a therapeutic dose of an antidepressant therapy of at least eight weeks of duration in the current major depressive episode (MDE).

3. Total MADRS score of < 20 at screening, or baseline, or as assessed by the remote, independent MGH CTNI rater between screen and baseline visits.

4. Participant had a current diagnosis of a Substance Use Disorder, with the exception of nicotine dependence, at screening or within six months prior to screening.

5. Current diagnosis of Axis I disorders other than Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, Specific Phobia, Post Traumatic Stress Disorder, or Complicated Grief (unless one of these was comorbid and clinically unstable, and/or the focus of the participant's treatment for the past six months or more).

6. Subject had a history of schizophrenia or schizoaffective disorders, any history of psychotic symptoms, or was on antipsychotic medication for treatment of psychotic symptoms.
7. Subject had a history of anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified, within five years of screening.
8. Subject had any Axis I/Axis II Disorder, which at screening was clinically predominant to their MDD or had been predominant to their MDD within six months of screening.
9. The participant was considered at significant risk for suicide during the study course.
10. Subject had had electroconvulsive therapy (ECT), Transcranial Magnetic Stimulation (TMS), or had received treatment with other experimental devices (e.g., cranial electrotherapy stimulation or CES) for the treatment of the current episode of depression.
11. Subject had received Vagus Nerve Stimulation (VNS) at any time prior to screening.
12. Dementia, delirium, amnestic, or other cognitive disorders.
13. Known history or current episode of uncontrolled hypertension, recent myocardial infarction (within one year) or a history of more than one lifetime myocardial infarction, syncopal event within the past year, congestive heart failure, New York Heart Association Criteria >Stage 2, angina pectoris, chronic lung disease, and a lifetime history of surgical procedures involving the brain or meninges, encephalitis, meningitis, degenerative central nervous system disorder, epilepsy, mental retardation, or any other disease/procedure/accident/intervention associated with significant injury to or malfunction of the central nervous system (CNS), or a history of significant head trauma within the past two years.
14. The following lab abnormalities: thyroid stimulating hormone (TSH) outside of the normal limits, or any other clinically significant abnormal laboratory result (as determined after evaluation by study investigator and MGH CTNI medical monitor) at the time of the screening exam.
15. Patient with any non-removable stimulation device such as neurostimulators, pacemakers and cochlear implants, or who have conductive or magnetic-sensitive metals present in the head or neck or within 18 inches of the coil and which were non-removable.

Study Design

Subjects were screened for eligibility as detailed above. Study participants were consented prior to the administration of any procedure. Following a baseline assessment and re-confirmation of study eligibility status by remote interview, eligible subjects were randomly assigned to receive LFMS or sham treatment. In accordance with the SPCD [19], the 5-day, double-blind treatment was divided into two stages (stage 1 and stage 2) of 48 hours each,

with assessments performed every day to assess the safety and efficacy of LFMS compared to sham therapy. Patients were randomized according to the pre-randomization format of the SPCD to double-blind treatment with LFMS 20 minutes/day for 4 consecutive days (n=30) (active-active sequence or AA), with sham therapy 20 minutes/day for 2 consecutive days and with LFMS 20 minutes/day for the following 2 consecutive days (n=30) (sham-active sequence or SA), or with sham therapy 20 minutes/day for 4 consecutive days (n=30) (sham-sham sequence or SS). The design involved a 1:1:1 ratio for random assignment to the treatment sequences active/active (AA), sham/active (SA), and sham/sham (SS). The data from all randomized subjects in stage 1 were pooled with the stage 2 data from all the sham non-responders in stage 1. Sham non-responders were defined as those patients who had failed to achieve at least a 50% decrease in their 6-item HAM-D (HAM-D-6) score at visit 2 (Day 2), and had a MADRS score > 16 at visit 2 (Day 2).

During Stage 1 of the study, the 20 minutes of LFMS/sham treatment occurred on treatment Day 0, immediately following baseline assessment. Patients returned for outcome assessments 24 hours after the first treatment (Day 1) and received another 20 minutes of LFMS treatment/sham therapy immediately thereafter. Patients returned for outcome assessments 24 hours after the second treatment (Day 2), that is 48 hours after receiving the first treatment. The Day 2 assessment represented the endpoint for Stage 1 and the baseline for Stage 2. During Stage 2 of the study, the 20 minutes of LFMS/sham treatment occurred on treatment Day 2, immediately following Day 2 assessment. Patients returned for outcome assessments 24 hours after the Stage 2 first treatment (Day 3) and received another 20 minutes of LFMS treatment/sham therapy immediately thereafter. Patients returned for outcome assessments 24 hours after the Stage 2 second treatment (Day 4), that is 96 hours after receiving the Stage 1 first treatment and 48 hours after receiving the Stage 2 first treatment.

During the follow-up period, patients were assessed at Day 7 (+/− 3 days) and Day 14 (+/– 3 days), in order to determine whether and for how long an antidepressant effect continued to build after the treatments, as well as to continue monitoring patient safety. Thereafter, follow-up assessment visits occurred at Days 21 (+/– 5 days) and 32 (+/– 5 days) for the purpose of determining whether and for how long antidepressant effects were sustained past the time of the acute treatments, and to monitor any changes in concomitant antidepressant therapy and whether any adverse events occurred during this extended post-treatment period.

LFMS Session

Active or sham (according to the randomization sequence) LFMS treatment was delivered to the study subjects through a device requiring the subject to lay flat on a bed for 20 minutes during each treatment session. The devices, with training and calibration, were provided to the study by Tal Medical Inc. The LFMS device consists of four main components: a standard commercial laptop computer, an electronic control system, a commercial power supply and a magnetic coil inside a plastic housing. The study subject ID number was entered into the software and the software referenced the preloaded randomization table to determine if sham or active treatment was to be applied. The patient and operator were blinded as to whether sham or active treatment was applied.

LFMS treatment is based on the gradient field used in echo-planar magnetic resonance spectroscopic imaging, consisting of repeated trains of oscillating magnetic stimulation broadly applied to the cortex. The trains comprise 1ms trapezoids of alternating polarity with 256 μs ramps, such that the peak-to-peak frequency is 500 Hz. Each 0.5 second train is delivered with a 2 second period for 20 minutes. LFMS utilizes low magnetic field strength (< 50 Gauss) with a peak induced electric field estimated to be 0.5 V/m. The electromagnetic fields produced by the device do not induce any sensation perceived by the patient and the study was determined to be a non-significant risk study by each site IRB. The only perception of the device by the patient is auditory, a cooling fan noise from the computer and amplifiers and a very low volume beeping sound from the coil. The coil sound was replicated with an audio system to maintain the study blind. To begin, the operator powered up the system and logged into the software. The patient lay down on an exam table or hospital bed and positioned his/her head inside the device with the assistance of the operator. Only the top of the patient's head (up to the eyebrows) was positioned inside the coil to preserve a significant field of vision for the patient. The operator then initiated the treatment by entering the study subject ID number, age and gender before clicking 'start' in the control software. Each treatment session was set to last 20 minutes.

Unblinding

In the event of a medical emergency, study clinicians at the site would have access to the randomization code for the patient involved.

Assessments

All subjects were evaluated by the study clinicians with respect to the efficacy and safety measures described below. In particular, the HAM-D-6 was administered at each visit by the site clinician and at baseline (Day 0), Day 2 and Day 4 by the independent, remote MGH CTNI rater. The follow-up sessions were conducted according to the method described by Fawcett and colleagues [20]. Sessions lasted between 20 and 30 minutes and involved a systematic inquiry into the presence, intensity, and features of the target symptoms that characterized the patient's depression.

Outcome and Safety Measures

Symptom improvement was evaluated by assessing changes in the primary outcome measure, the HAM-D-6 [21,22,23].

Secondary measures of depression, the Montgomery-Asberg Rating Scale (MADRS) [24], the Symptoms of Depression Questionnaire (SDQ) [25], and the global severity and improvement scales of the Clinical Global Impressions (CGI-S and CGI-I) [26] were administered with a time frame of the past three days for the MADRS and of the past 24 hours for the SDQ and CGI-S and CGI-I. Visual analogue scales (VAS) components assessing happy, sad, drowsy, irritated, alert, anxious, and restless [27,28] were also administered with a time frame of the past 24 hours. To measure within-session changes in mood, these VAS scales were administered with wording to capture immediate mood state, both immediately prior to starting and at 120 minutes post-initiation of each LFMS or sham treatment. The Suicidal Ideation and Behavior Questionnaire (SIBQ) is a clinician-rated

instrument designed to document the presence and nature of suicidal ideation and behavior of patients enrolled in clinical trials, as well as to document the clinical rationale for including or continuing a patient versus excluding or discontinuing a patient from a clinical trial on the basis of suicide risk. This scale, which is adaptable to each specific protocol as well as to incorporating any trial-specific standard operating procedures with respect to the management of suicidal ideation and behaviors, was used in the study to track suicidal ideation and behavior. Blood pressure and heart rate were measured at time 0 (right before starting LFMS or sham treatment), and at 30-min intervals for 120 minutes following the LFMS or sham treatment start. These vital signs were measured at every study visit. Blood pressure was measured while the patient was supine and sitting. At the screen visit, Day 4, and Day 32, patients had a physical examination and had blood drawn for chemistry and CBC blood tests, and also underwent an ECG. The presence of any potential side effects or adverse events were carefully documented at screen (for the past week) and at every subsequent visit (covering events since the last visit) using both the spontaneously reported adverse events and the Systematic Assessment for Treatment Emergent Events - Systematic Inquiry (SAFTEE-SI). The SAFTEE-SI [29] is a self-rated questionnaire assessing possible adverse events during the course of the trial. The time frame is the past 24 hours. The Massachusetts General Hospital (MGH) Cognitive and Physical Functioning Questionnaire (CPFQ) [30] was completed at the Screen Visit, Day 2, Day 4 and Day 32. The CPFQ is a brief (7-item), validated self-report inventory to assess rates of significant cognitive symptoms such as memory, attention and executive function difficulties. Reasons for premature discontinuation, including intolerable side effects, were recorded. Chemistry and CBC were obtained, as well as a physical examination performed at screen, Day 4, and Day 32. Weight and oral temperature were recorded at each visit.

Statistical Analyses

The primary aim of the study was to demonstrate superior outcome for LFMS compared to sham therapy on the 6-item Hamilton Rating Scale for Depression (HAM-D-6) in the acute treatment of patients with TRD within 48 hours, when added to ongoing and stable antidepressant therapy, using the pre-randomization format of the SPCD. Secondary aims were 1) to examine changes from baseline to 48 hours, as measured by the MADRS, the SDQ, CGI-S, CPFQ, and VAS self-ratings of mood, 2) to compare the sustainability of the antidepressant efficacy of LFMS to that of sham therapy during the four weeks after completing the acute double-blind phase, 3) to characterize the safety and tolerability of LFMS with sham therapy using the following information: vital signs, SAFTEE-SI, and 4) to characterize adverse events that occur following discontinuation of LFMS or sham.

The SPCD analyses used the approach detailed by Doros et al [31], which uses a repeated measures linear modeling approach with maximum likelihood estimation to use all available data, and using a 60–40 weighting of Stage 1 vs. 2 responses. To achieve power of 0.80, the goal was to achieve a sample size of n=82 for the primary endpoint, which was Day 3 (48 hours post treatment start), based on the assumption of a medium effect size. To this end, it was estimated that n=90 patients would need to be randomized, presuming a 100% retention rate during Stage 1 (Days 0–1), and a 90% retention rate during Stage 2 (Days 2–3). The

actual retention rate was higher than anticipated, thereby allowing study closure before randomizing n=90.

Results

Visit completion rates were 99% (n=84) on Days 1, 2, 3, and 4, 95% (n=81) on Day 7, and 96% (n=82) on Days 14 and 21, and 94% on Day 32. In total, n=6 patients terminated early. Thus, n=84 rather than the planned for n=82 were available for the primary endpoint analysis. Details on patient characteristics are summarized here in Table 1.

Primary outcome on the HAM-D-6 after 48 hours

Results of the SPCD analysis did not indicate superior outcome of LFMS compared to sham treatment within 48 hours (b=0.31, SE=0.61, p=0.61; where b is the combined maximum likelihood estimate of the repeated measures linear modeling approach by Doros et al. [31], pooling data from Stage 1 (all 84 randomized subjects) and Stage 2 (all 39 sham non-responders in Stage 1)). This result is depicted in Figure 1. The LFMS group decreased HAM-D-6 scores by −2.8 points in phase 1 (from 11.6 to 8.8), and −1.3 in phase 2 (from 10.9 to 9.6), while the sham group decreased HAM-D-6 scores by −3.2 points in phase 1 (from 11.3 to 8.1), and −1.5 in phase 2 (from 9.4 to 8.0).

Changes from baseline to 48 hours on secondary outcome measures

The same analytical approach as for the primary outcome was used to test changes within the first 48 hours of treatment start on the secondary outcome measures of interest. Table 2 provides descriptive details in terms of means and change scores for Stage 1 and Stage 2 of the SPCD, and the p-values of the SPCD test. Group differences were not significant on any of these secondary outcome measures.

Sustainability of effects over four weeks

In order to examine sustainability of effects, we compared the three randomized groups (Table 1) over time, as the stage-specific binary randomized group assignments were time-specific to the first four days. We used a repeated measures linear mixed model, where we modeled the effects of randomized group assignment (A:A:A:A vs. S:S:A:A vs. S:S:S:S), time (modeled continuously, days 4–32), and the group by time interaction effect. Observations were modeled as nested within persons using the PROC MIXED REPEATED statement and an unstructured covariance matrix.

Results (Table 3) indicate that for the primary outcome measure, HAM-D-6, no significant trends over time were identified. Group differences also were not significant.

The trends for the three randomized groups over time are shown descriptively in Figure 2. Error bars show standard deviations around the mean.

For secondary outcomes that were assessed during follow-up (CGI-S was not), results also did not indicate significant group differences, either in overall means, as measured by the ‘group’ effect, or in terms of slopes over time, as measured by the ‘group*day’ interaction effect. For two of the four secondary outcomes, however, the SDQ and CPFQ, there were

significant overall slopes over time, indicating a general increases in symptoms over time. Figure 3 depicts these trends over time.

Safety and tolerability

As shown in Table 4, there was only one serious adverse event in the randomized sample, and it was reported by one of the patients assigned to the sequence of four consecutive active treatments (A:A:A:A). The patient, who was recently started on glyburide by his primary care physician, reported lightheadedness when he returned home from his study visit. The patient reported to the emergency department, and was diagnosed with dehydration, hypoglycemia, and hypokalemia. The event resolved with no sequelae, and was judged, in the clinical opinion of the site investigator, to be unlikely to be related to study treatment.

Table 5 summarizes the spontaneously reported adverse events (AEs), ordered by decreasing rate of event overall for AEs reported ≥5% in at least one treatment arm. The rates of all AEs were generally similar across the treatment arms, except for hot flashes, which were reported by 15% of patients assigned to the sequence of four consecutive active treatments (A:A:A:A), and by none of the patients in the two other arms. A higher proportion of patients (82%) assigned to the sequence of four consecutive active treatments (A:A:A:A) reported AEs than the patients assigned to the sequence of four consecutive sham treatments (S:S:S:S) (62%).

Vital signs were measured six times on study days during the treatment stage (days 0–3), on arrival, immediately before treatment, and 30, 60, 90, and 120 minutes after treatment start. During follow-up, vital signs were assessed on all study visit days (i.e., days 4, 7, 14, 21, and 32). Table 6 provides an overview of how often blood pressures indicative of hypertension were observed. Systolic and diastolic blood pressure measures never exceeded hypertension cut-points during the active treatment phase. During the follow-up phases, participants rarely exhibited systolic blood pressure above 150 mmHg with no differences between randomized groups (Fisher's exact $p=0.09$). Diastolic blood pressure exceeding 95 mmHg was observed in 57% of participants at some point during follow-up, with no differences observed across randomized groups ($\chi 2(2)=1.42$, $p=0.49$). These numbers at follow-up are quite striking, compared to the acute treatment phase, and may be due to the fact that being recumbent for the treatment (which did not occur during follow-up visits) contributed to the difference.

The SAFTEE-SI was assessed every study day. Average scores per randomized group are presented in Table 7. SAFTEE-SI scores were highest at baseline. The results of a repeated measures linear mixed model, spanning days 0–32, did not indicate any group differences, either in overall levels of treatment emergent effects ($F(2,81)=0.82$, $p=0.44$), or in slopes over time ($F(2,81)=0.67$, $p=0.51$). Instead, there was a generally decreasing trend in treatment emergent effects over time ($F(1,81)=10.66$, $p<0.01$).

Table 8 provides details regarding suicidality, showing similar patterns across the three treatment arms. There were no patients with clinically significant suicidal ideation and/or behavior during the study.

Finally, there were no significant differences in rates of laboratory abnormalities across the three treatment arms.

Discussion

In our study of patients with unipolar TRD, we did not observe a significantly greater, rapid efficacy of LFMS compared to sham therapy. The original findings of the rapid efficacy of LFMS were obtained primarily in bipolar depressed patients (n=81) and only in a small sample (n=22) of unipolar depressed patients [13,14]. The initial observations of the mood-elevating effects of LFMS had in fact led to a follow-up sham-controlled study using bipolar depressed patients in which the subjects were administered the EP-MRSI sequence [13]. Sham treatment consisted of the full imaging protocol without the EP-MRSI pulse sequence. In this proof-of-principle study, 23 of the 30 subjects receiving active treatment reported an immediate (within minutes) improvement in mood as compared to only 3 of 10 subjects receiving sham treatment [13]. Rohan et al used a randomized, double-blind, sham-controlled treatment protocol to study the effects of LFMS in a larger group of stably medicated, depressed patients with either bipolar depression (n = 41) or major depressive disorder (n = 22) [14]. Improvement (>10% of baseline) in mood was observed following LFMS treatment relative to sham treatment for both diagnostic subgroups with respect to the primary outcomes, the visual analogue scale (VAS) and the 17-item Hamilton Depression Rating Scale (HAM-D-17). These differences were not statistically significant in primary analyses stratifying by diagnosis but were significant in secondary analyses combining data across the two diagnostic groups (p = .01 VAS, p = .02 HAM-D-17).

The failure to detect a signal of therapeutic activity is unlikely to be due to excessive sham response, as the mean changes in HAM-D-6 and SDQ were only 3.2 and 0.6 in Stage 1 and 1.5 and 0.1 in Stage 2. To put this in perspective, the average change from baseline in HAM-D-6 following antidepressant treatment across 23 short-term (of 5- or 6-week duration) trials was 6.93 points [32]. Both primary and secondary outcome measures consistently showed changes in LFMS-treated patients similar to those treated with sham. The only exception was a slight, non-significantly greater improvement in the VAS sad mood of 42.1 points vs 26.2 in stage 1 and 18.1 points vs 12.5 in stage 2 in LFMS-treated patients compared to those treated with sham. Our study suggests that LFMS is unlikely to provide robust efficacy after only two treatments of 20-minute duration in MDD, but does not exclude potential efficacy with either treatments longer than 20 min or repeated administration over longer term. In addition, it is possible that 20-minute duration LFMS may be sufficient dosing for bipolar depressed patients, as other neurostimulation treatments seem to require lower overall doses in BPD than MDD as well.

The LFMS treatment was very well tolerated and spontaneously reported adverse events and SAFTEE scores were comparable across treatment groups. Given the high morbidity associated with MDD [33], it is important to develop new treatments that are very well tolerated. There were no instances of clinically significant emergence of suicidal ideation/behavior in any of the treatment arms, and there were no significant laboratory or vital signs changes.

In light of the tolerability of the treatment, the small, non-significant benefit of LFMS on VAS sadness detected 120 minutes after the last LFMS in each stage, could perhaps suggest the need for higher dosing and duration. In fact, a possible explanation for our findings may be relative underdosing of LFMS in this study compared to neurostimulation approaches such as TMS. We administered LFMS for 20 minutes twice only, and it is quite possible that patients may require more intensive delivery of the treatment in terms of duration and/or number of administrations.

Contrary to clinical lore, those patients who did improve rapidly on sham therapy during Stage 1 appeared to maintain the improvement over time. One would have thought that the sham effect would be transient and would fade over time. This was certainly not the case in our study.

The main limitation of the study is the relatively small sample size; however, the use of the SPCD provided adequate power to detect a medium effect size. Another limitation of the study is related to the nature of the clinical sample. Our study was conducted only in unipolar patients, where the two previous positive studies included 81 bipolar patients and only 22 unipolar patients [13,14]. In addition, this was an augmentation study, and augmentation assumes a different mechanism of action than the oral antidepressants patients were on during the study, thus we cannot rule out the possibility that these treatments share a final common mechanism. Finally, we cannot exclude some recruitment biases that have led to relative unresponsiveness to the treatment, although the degree of change in MADRS scores on sham in Stage 1 and 2 (4–5 points) rule out the possibility that the sample was too refractory to treatment to demonstrate a treatment effect in this population. The population recruited into the study was required to have a history of one to three antidepressant treatment failures, and patients were excluded if they had failed four or more antidepressant therapies. In addition, study participants were drawn from an outpatient sample of MDD patients recruited through general advertisement and clinician referral, suggesting that this was not a particularly treatment refractory depressed population.

In conclusion, in our adequately powered SPCD study in 84 patients with MDD, LFMS administered twice for 20 minutes led to improvements in depressive symptoms that were similar to those observed followed sham administration. LFMS treatment was relatively well tolerated. Future studies need to examine the possible therapeutic effects of more intensive forms of LFMS, as other forms of neurostimulation typically require longer duration of exposure.

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Highlights

- Low-Field Magnetic Stimulation (LFMS) is a novel, non-invasive, sub-threshold neuromodulation technique, shown in preliminary studies to have immediate mood elevating effects in both unipolar and bipolar depressed patients
- In a four-day double-blind study of LMFS in treatment resistant depression (n=84), both primary and secondary outcome measures consistently showed no differences between LFMS-treated patients and those treated with sham
- Future studies need to examine the possible therapeutic effects of more intensive forms of LFMS, as other forms of neurostimulation typically require longer duration of exposure.

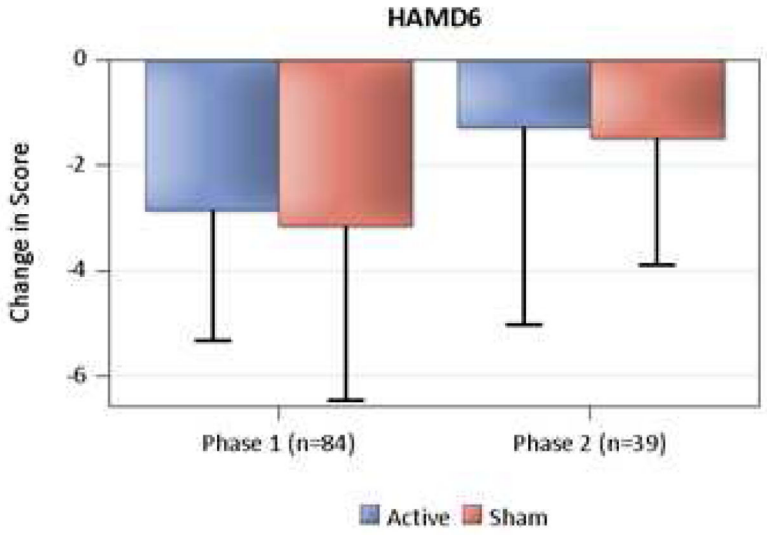

Figure 1.

Change in HAM-D-6 scores during phases 1 and 2 of the SPCD trial

Average change scores per treatment group per phase are shown. Each phase consisted of 2 treatments, one per day, on two consecutive days, so that the phase 1 treatment was delivered on days 0 and 1, and phase 2 treatment was delivered on days 2 and 3. Phase 1 change scores reflect HAM-D-6 scores assessed on day 2, the day after phase 1 treatment ended, minus HAM-D-6 scores on day 0, as assessed right before the start of the phase 1 treatment. Phase 2 change scores reflect HAM-D-6 scores assessed on day 4, the day after phase 2 treatment ended, minus HAM-D-6 scores on day 2, as assessed right before the start of the phase 2 treatment. Note that, as per the SPCD design, only scores of participants who were randomized to sham in phase 1, and who were non-responders to this sham treatment, are relevant to phase 2 outcomes. Thus, sample sizes are different for the effects shown for phase 1 (n=84) and phase 2 (n=39).

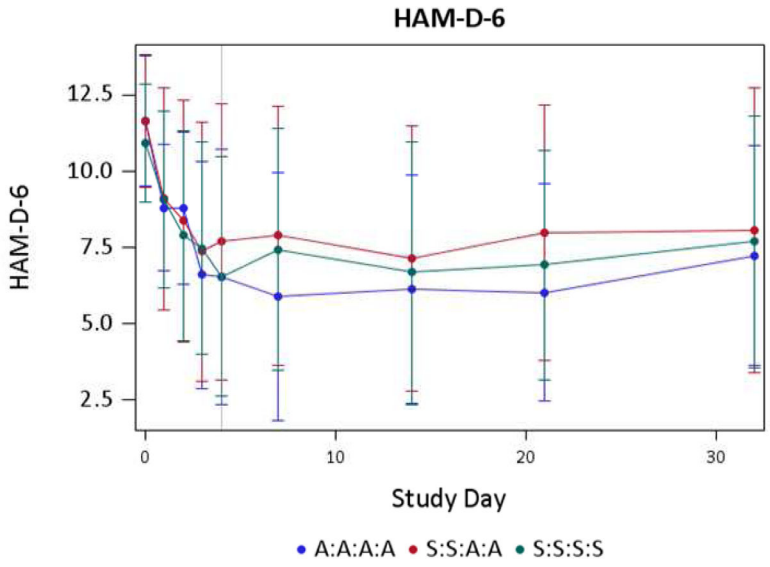

Figure 2.

HAM-D-6 scores over time

Average HAM-D-6 scores per randomized group are shown over time, using all available data (n=84 for days 1–4, n=81 for day 7, n=82 for days 14 and 21, and n=79 for day 32). As the SPCD design only applies to outcomes observed during the first 48 hours, trends over time are shown for all randomized and retained participants.

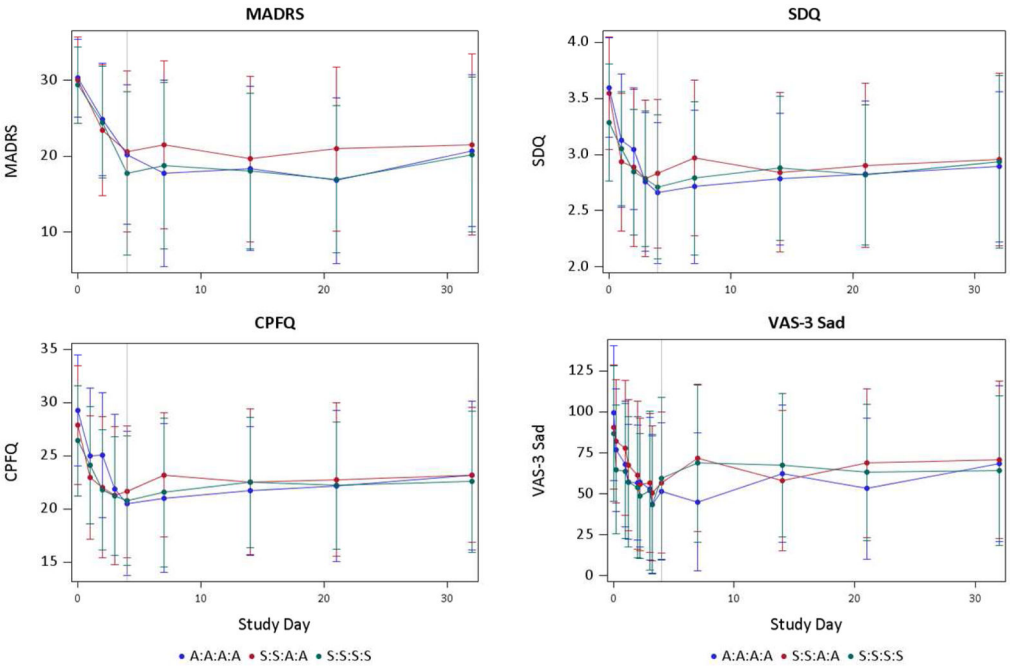

Figure 3.

Secondary outcomes over time

Average scores on the secondary outcomes (Montgomery-Asberg Depression Rating Scale (MADRS), Symptoms of Depression Questionnaire (SDQ), Cognitive And Physical Functioning Questionnaire (CPFQ), and the rating of a 0–100 visual analog scale for the adjective “sad”) per randomized group are shown over time. As the SPCD design only applies to outcomes observed during the first 48 hours, trends over time are shown for all randomized and retained participants.

Table 1

Sample Characteristics (n=84)

	A:A:A:A		S:S:A:A		S:S:S:S		
	N=26		N=29		N=29		
	mean / %	SD	mean / %	SD	mean / %	SD	*p*
Demographics							
Age	47.9	14.8	50.7	10	46.3	14.6	0.44
Gender (% female)	57.7		58.6		51.7		0.85
Hispanic (% yes)	3.9		3.5		0		0.58
Race							0.13
White	76.9		86.2		65.5		
African American	23.1		10.3		10.3		
Other	0		3.5		13.8		
Clinical Severity at Baseline							
HAMD6	11.7	2.2	11.7	2.2	10.9	1.9	0.33
MADRS	30.3	5.2	30	5.7	29.4	5	0.81
CGI-S	4.8	0.5	4.7	0.7	4.7	0.6	0.88

Table 2

Changes within the first 48 hours on secondary outcomes

	Stage 1				Stage 2				
	Active n=26		Sham n=58		Active n=18		Sham n=21		
	M	SD	M	SD	M	SD	M	SD	*p*
HAM-D-6									0.61
Baseline	11.7	2.2	11.3	2.1	10.9	2.2	9.4	2.3	
End of phase	8.8	2.5	8.1	3.7	9.6	3.9	8.0	3.7	
Score improvement	−2.8	2.5	−3.2	3.3	−1.3	3.7	−1.5	2.4	
MADRS									0.14
Baseline	30.3	5.2	29.7	5.3	27.8	7.2	27.8	5.7	
End of phase	24.8	7.4	23.9	8.0	26.2	8.6	22.2	9.1	
Score improvement	−5.4	7.3	−5.8	7.6	−1.6	5.4	−5.6	6.2	
SDQ									0.66
Baseline	3.6	0.4	3.4	0.5	3.2	0.7	3.0	0.5	
End of phase	3.0	0.5	2.9	0.6	3.0	0.7	2.9	0.6	
Score improvement	−0.6	0.5	−0.6	0.5	−0.2	0.5	−0.1	0.4	
CGI-S									0.29
Baseline	4.8	0.5	4.7	0.6	4.6	0.7	4.4	0.7	
End of phase	4.2	0.8	4.0	1.0	4.3	0.8	3.8	1.2	
Score improvement	−0.6	0.8	−0.7	0.9	−0.3	0.8	−0.6	1.0	
CPFQ									0.15
Baseline	29.3	5.2	27.2	5.4	24.7	5.8	23.9	4.3	
End of phase	25.1	5.9	21.9	6.1	23.9	6.0	22.8	5.4	
Score improvement	−4.2	4.9	−5.2	5.7	−0.8	5.5	−1.1	4.9	
VAS – sad									0.32
Baseline	99.3	41.2	88.7	39.5	76.6	46.0	68.4	39.6	
End of phase	57.2	35.1	62.5	39.8	58.5	43.9	55.9	43.7	

	Stage 1				Stage 2				
	Active		Sham		Active		Sham		
	n=26		n=58		n=18		n=21		
	M	SD	M	SD	M	SD	M	SD	*p*
	-		-		-		-		
Score improvement	42.1	54.0	26.2	37.6	18.1	40.3	12.5	26.2	

Note: M = mean, SD = standard deviation, *p* refers to the *p*-value of the SPCD combined contrast, using 60–40 weighting in the Doros linear mixed modeling approach [31]; phase 2 sample sizes are smaller, because only phase 1 sham non-responders are compared

Table 3

Trends over time (Days 4–32)

	Group			Day			Group * Day		
	F	***Df***	***p***	***F***	***Df***	***p***	***F***	***df***	***P***
Primary outcome									
HAM-D-6	1.03	(2, 81)	0.36	3.1	(1, 81)	0.08	0.19	(2, 81)	0.83
Secondary outcomes									
MADRS	0.72	(2, 81)	0.49	0.6	(1, 81)	0.44	0.45	(2, 81)	0.64
SDQ	0.66	(2, 81)	0.52	4.75	(1, 81)	0.03*	0.75	(2, 81)	0.47
CPFQ	0.47	(2, 81)	0.63	7.04	(1, 81)	0.01**	0.55	(2, 81)	0.58
VAS3-sad	0.84	(2, 81)	0.44	2.15	(1, 81)	0.15	0.79	(2, 81)	0.46

Note: Group refers to the treatment arm randomization (A:A:A:A vs. S:S:A:A vs. S:S:S:S); Day refers to study day, modeled continuously (days 4–32)

Table 4

Serious Adverse Events by Treatment Group

	Non Randomized[1] N = 121	A:A:A:A (N=27)	S:S:S:S (N=29)	S:S:A:A (N=29)	Total N = 206[3]
Number of subjects with a Serious Adverse Event	1	1	0	0	2
Percentage[2] of subjects with a Serious Adverse Event	1%	4%	0%	0%	1%
Total # of Serious Adverse Events	1	1	0	0	2

[1]Non randomized includes patients in screening and screen failure.

[2]Percentage= Number of subjects with a Serious Adverse Event / Number of subjects x 100.

[3]Non-randomized (n=121) plus randomized subjects (n=84) plus one subject who dropped out at baseline prior to randomization.

Table 5

AE Summary by Treatment Ordered by Decreasing Rate of Event Overall (for AEs reported =>5% in at least one treatment arm)

	A:A:A:A (N = 27)			S:S:S:S (N = 29)			S:S:A:A (N = 29)			Total (N = 85[4])		
Preferred Term	**N**	**E**	**%**	**N**	**E**	**%**	**N**	**E**	**%**	**N**	**E**	**%**
HEADACHE	6	9	22.2	10	17	34.5	5	7	17.2	21	33	24.7
DIZZINESS	1	2	3.7	2	4	6.9	2	2	6.9	5	8	5.9
IRRITABILITY	2	2	7.4	2	2	6.9	3	3	10.3	7	7	8.2
INSOMNIA	0	0	0.0	2	2	6.9	4	4	13.8	6	6	7.1
DISTURBANCE IN ATTENTION	2	2	7.4	2	2	6.9	1	1	3.4	5	5	5.9
PARAESTHESIA	0	0	0.0	1	3	3.4	2	2	6.9	3	5	3.5
SOMNOLENCE	2	2	7.4	1	1	3.4	1	2	3.4	4	5	4.7
UPPER RESPIRATORY TRACT INFECTION	2	2	7.4	1	1	3.4	2	2	6.9	5	5	5.9
DIARRHOEA	1	1	3.7	2	2	6.9	1	1	3.4	4	4	4.7
HOT FLUSH	4	4	14.8	0	0	0.0	0	0	0.0	4	4	4.7
MEMORY IMPAIRMENT	2	2	7.4	1	1	3.4	1	1	3.4	4	4	4.7
MYALGIA	1	1	3.7	0	0	0.0	2	3	6.9	3	4	3.5
NAUSEA	1	1	3.7	1	1	3.4	2	2	6.9	4	4	4.7
ABNORMAL DREAMS	2	2	7.4	0	0	0.0	1	1	3.4	3	3	3.5
CONSTIPATION	0	0	0.0	3	3	10.3	0	0	0.0	3	3	3.5
NASOPHARYNGITIS	2	2	7.4	1	1	3.4	0	0	0.0	3	3	3.5
POLLAKIURIA	2	2	7.4	1	1	3.4	0	0	0.0	3	3	3.5
BRUXISM	0	0	0.0	2	2	6.9	0	0	0.0	2	2	2.4
MUSCLE TWITCHING	0	0	0.0	0	0	0.0	2	2	6.9	2	2	2.4
Total	22	62	81.5	18	75	62.1	20	55	69.0	60	192	70.6

[1] N = Number of subjects with an AE.

[2] E = Number of AEs.

[3] % = Number of subjects with an AE / Number of subjects x 100.

[4] Randomized subjects (n=84) plus one subject who dropped out at baseline prior to randomization.

Table 6

Vital Signs

	A:A:A:A		S:S:A:A		S:S:S:S	
Total # of tx-phase assessments	**618**		**685**		**694**	
Total # of follow-up phase assessments	**127**		**142**		**140**	
	N	**%**	**N**	**%**	**n**	**%**
Tx Phase						
systolic blood pressure >150 mmHg	0	0	0	0	0	0
diastolic blood pressure >95 mmHg	0	0	0	0	0	0
Follow-up Phase						
systolic blood pressure >150 mmHg	1	0.8	3	2.1	7	5.0
diastolic blood pressure >95 mmHg	30	23.6	52	36.6	54	38.6

Note: N refers to the number of events/measures of blood pressure, and % to the percent of measures that were above stated criteria.

Table 7

SAFTEE-SI means over time

Phase	A:A:A:A		S:S:A:A		S:S:S:S	
Day	n=26		n=29		n=29	
	M	SD	M	SD	M	SD
Tx Phase						
0	39.3	14.5	40.7	24.3	36.8	24.0
1	31.1	15.2	33.5	20.7	28.5	18.5
2	28.8	12.7	32.6	23.6	27.3	20.4
3	24.6	13.6	27.3	20.0	27.6	24.0
Follow-up						
4	23.1	14.2	29.0	20.4	24.7	20.9
7	22.6	13.6	29.5	22.3	24.1	19.5
14	24.3	14.0	30.3	25.3	25.6	19.0
21	24.8	13.8	28.7	21.0	25.0	20.0
32	26.4	14.5	29.3	19.5	25.9	22.3

Table 8

Number of Patients Reporting Any Suicidal Ideation and/or Behavior by Treatment, Phase

Group	Phase[1]	Number of patients with suicidal ideation and/or behavior	Number of patients with clinically significant [2] suicidal ideation and/or behavior
Screen only (Non Randomized) (N=121)[3]	**Total**	**20**	**0**
Group A:A:A:A (N = 27)	**Total**	**12**	**0**
A:A:A:A	Screening	10	0
A:A:A:A	Treatment period 1	11	0
A:A:A:A	Treatment period 2	8	0
A:A:A:A	Follow-Up	7	0
Group S:S:S:S (N = 29)	**Total**	**15**	**0**
S:S:S:S	Screening	9	0
S:S:S:S	Treatment period 1	10	0
S:S:S:S	Treatment period 2	8	0
S:S:S:S	Follow-Up	14	0
Group S:S:A:A (N = 29)	**Total**	**17**	**0**
S:S:A:A	Screening	10	0
S:S:A:A	Treatment period 1	12	0
S:S:A:A	Treatment period 2	7	0
S:S:A:A	Follow-Up	12	0
All Groups (N = 206)	**Total**	**64**	**0**

Unit of observation is subject. Some subjects have multiple events.

[1] Screening Phase (before treatment): 7–14 days. Treatment Phase: Divided into 2 treatment periods of 2 days of treatment each (period 1 includes Day 0 and 1, period 2 includes Day 2 and 3). During the Treatment Phase, patients are assigned to one of 3 arms for the two periods: Active/Active, Sham/Active or Sham/Sham. Follow-up Phase: weekly for 28 days, starting with Day 4.

[2] As indicated and justified on the SIB-Q

[3] Including only screen-failures who completed the clinical interview (e.g., a patient screened out for hypertension would not necessarily complete a clinical interview)

Note: 1 SIBQ report is missing: 205-013 Day 4