Maintenance Transcranial Magnetic Stimulation in Major Depressive Disorder
NCT04076644
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BIOMEDICAL RESEARCH PROTOCOL
UNIVERSITY OF MISSOURI

Project Title: Maintenance of response to Transcranial Magnetic Stimulation (TMS) in Major Depressive Disorder (MDD) using monthly TMS treatment
IRB Number: 2013884
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Principal Investigator: Dr. Muaid Ithman
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Clinical Trial Phase: *IV*
Clinicaltrials.gov Number:
Study Drug/Study Device: *Magventure/Magvita TMS machine*

I. Research Objectives/Background

Transcranial Magnetic Stimulation (TMS) has been established as an effective and safe method to treat Major Depressive Disorder (MDD). Large randomized sham controlled trials (1,4), and over a decade of clinical use since it was FDA approved for acute treatment of MDD in 2008, has shown TMS to be a promising treatment after medications and psychotherapy have failed to alleviate depressive symptoms. TMS is non-invasive, and uses a small but powerful pulsed magnetic field placed over the dorsa-lateral-prefrontal-cortex (DLPFC), a part of the brain thought to be associated with depression. In general, treatments are given 5 times for week for 4-6 weeks. This treatment protocol results in an effectiveness of roughly 2/3 of patients seeing a clinically significant benefit, while 1/3 of those patients experience a complete remission of their depressive symptoms (2). TMS is also a relatively safe treatment and has very little if any side effects, the most common being a slight headache after the treatment (5,6).

Given that treatment resistant MDD is a chronic disease with no known cure, management of symptoms mostly consists of trialing and failing medications whose positive effects on symptomology are of limited time course. TMS is no different. Patients that respond or remit after a TMS course will most likely see a relapse in their depressive symptoms at some point after their acute TMS treatment course is completed (3,7,8). The time course of response or remission after acute TMS treatment varies between individuals from weeks to years, and there is no way to predict the length of positive outcomes. Research has shown that close to 40% of patients will see symptom worsening, and another 10% will have a relapse within 6 months post-acute treatment course (3). Interestingly, data and clinical evidence has shown that if a patient responds to TMS and relapses back into a depressive episode, a new TMS treatment course will provide the same benefits as the original TMS course (3). In other words, if TMS works for the patient, it will most likely work again. Given the relative safety and the fact the TMS is equally effective after a positive acute response, many clinicians and researchers

have questioned the current clinical protocol of waiting for a relapse to start treating with TMS. Succinctly, should we be using TMS to maintain response?

Research using TMS as a maintenance therapy has shown that remission and response have been extended out for longer periods after the acute treatment, however there has been a multitude of parameters, populations, and treatment protocols used which has led to mixed results. These maintenance protocols studies include: as needed (10), use as a rescue (11), regular weekly or monthly intervals (10), and clustered treatments where multiple treatments are given in the same day (12).

More recently, new acute TMS protocols, called theta-burst have been FDA cleared on some TMS machines for treating depression (9). Both the original 10hz stimulation approved by the FDA in 2008, and the newer theta-burst stimulation are excitatory in nature, but little research has been completed to determine if newer theta-burst protocols are as effective and safe in maintenance of the response compared to acute TMS treatment. Further, no work has been completed on how they compare to the clinical standard 10hz during a maintenance course of treatment.

Hence, the main purpose of this study is to use TMS treatment to maintain patients that have responded or remitted from their depressive symptoms from the use of clinical TMS treatment, while off their antidepressant medication. A secondary objective is to see how the safety and effectiveness of this newer treatment protocol (theta-burst) is compared to prior treatment protocols in a maintenance regime, by comparing the theta-burst to traditional 10hz TMS treatment protocols. An additional tertiary purpose is to see if maintenance therapy treatment performed by a certified TMS technician can be performed without the need of TMS Attending supervision. Given the relative safety of TMS, that TMS technicians are CPR certified, and highly experienced in understanding the safety of TMS, this particular objective would help to show the feasibility and possible economic benefit to patient and provider of not needing Attending supervision for TMS maintenance treatment.

II. Drugs/Biologics/Devices

The device used in this study is a Magventure/MagVita Transcranial Magnetic Stimulation device. It is a FDA approved for treating Major Depressive Disorder in an acute treatment protocol. The normal acute clinical treatment protocol consists of 36 treatments given over 6 weeks with a 3 week taper (totaling 9 weeks). This study will be looking at a maintenance protocol and treating monthly, so there will be much less treatments comparatively. There is no IDE required for this study since it is a FDA approved device and we will use FDA cleared treatment protocols. More specific inclusion criteria are listed in the inclusion/exclusion section of the protocol.

TMS is an electromagnet that uses a small precise, but powerful magnetic pulse delivered to the head corresponding to an area over the brain thought to have some role in the depressive symptoms associated with MDD. This study will use the exact same protocols used in the acute treatment setting, except that treatments will be given monthly not daily (see methods section for reference).

There are currently 3 FDA cleared treatment protocols for acute clinical treatment associated with this device. They consist of a 37 minute treatment, a 20min treatment, and a

3 minute treatment. The 37 and 20 min treatment have similar treatment protocols and total 3000 stimulations for each treatment. Both of these protocols consist of a 10Hz stimulation for 4 secs with either 27 or 11 sec intertrain break with no stimulation respectively. The 3 minute protocol is different than the other two protocols and consists of 600 stimulations per treatment. It's parameters consist of a 50Hz triplet burst stimulation for 2 seconds with a 8 second intertrain break with no stimulation.

Dosage (or % of machine output) is determined by Motor Threshold which is described in the methods section of this protocol.

This device will be used in this study because it is the current device used to treat patients for acute MDD in the UMHC Neuromodulation clinic, and the Neuromodulation clinic is where the subjects for the study will be recruited from.

This study is open-label with no sham group used as a comparative group. However, we will use a study arm that *does not* use a TMS treatment for maintenance and follow them for similar time frame as other study TMS treatment arms noting durability/length of response measures compared to other study treatment groups.

III. Recruitment Process

Subjects will be recruited from the UMHC Neuromodulation clinic. All subjects will already have completed an acute TMS treatment regime in the clinic. This study will be looking at treating in the maintenance phase only, meaning they must previously have completed the acute clinical protocol (36 treatments). Subjects will only come from the UMHC clinic, and must have responded or remitted from their depressive symptoms due to the TMS acute treatment. No participants will be allowed into the study who were acutely treated outside the UMHC Neuromodulation clinic.

As patients come close to the end of their acute clinical TMS treatment, they will be screened to see if their depressive scores have shown a clinically significant improvement, or if their symptoms have remitted (we already collect these scores clinically). If their clinical scores show this inclusion criteria then they will be approached by study staff either through face to face or by letter in mail, letting them know we have a study looking at the efficacy of using TMS treatment to maintain their improvement they have attained in their clinical course of TMS treatment.

If a potential subject is interested in learning more about the study a copy of the consent will be given or sent to them in the mail for them to review, and a consent appointment will be setup to meet with the study staff.

IV. Consent Process

When a potential subject is identified and after a copy of the consent is given to the potential subject for review, a consent appointment will be setup. At the appointment an approved study team member will go over the privacy practices, HIPAA, and consent thoroughly, allowing the potential subject to ask questions and stressing that the signing of the consent is not a contract only a process, and that they can discontinue the study at

any time for any reason. Then if the subject is interested in starting the study the approved team member will have the subject sign and date the HIPAA and consent. Then a copy of each signed document will be given to the subject. A baseline visit will then be setup, or if time allows a baseline visit commence immediately following the signing of consent.

V. Inclusion/Exclusion Criteria

Inclusion Criteria:

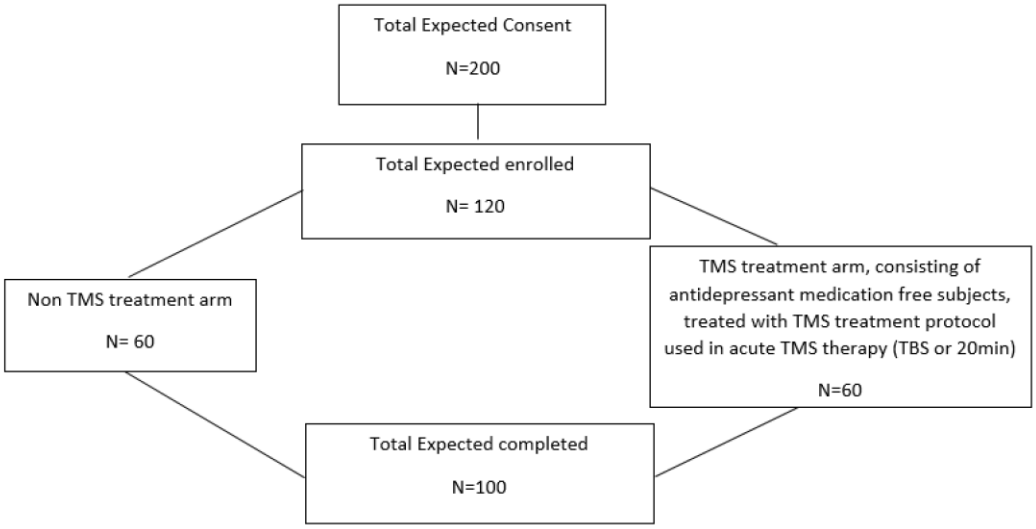
- Must have recently (within 4 weeks) completed an acute TMS course (full 36 treatments) at the UMHC Neuromodulation clinic
- Must have clinically responded to the acute TMS treatment course (≥50% improvement according to the clinical depressive scale used - usually the PHQ-9)
- Must be able sign consent
- Must have a current address and phone number
- Must have current mental health care provider, either psychiatrist or general practioner who they see for mental health symptom management
- Must be able to taper off antidepressant medication within 2 months of signing consent of study (treatment group only)

Exclusion Criteria:

- Subject that has not completed a full acute treatment course, including taper
- Subjects that have changed anything that may not make them safe for TMS, which are (all changes will be reviewed by study MD, and will not necessarily be excluded possibly depending on severity):
    - Any new metal near head
    - Any new medical devices that cannot be removed
    - Any new pregnancies (verbally confirmed)
    - Seizures that occurred post-acute TMS treatment
    - Any uncontrolled cardiovascular disease
    - Any new head trauma
    - Any new illness causing injury to brain
    - Any new medications which cannot be altered or lowered that may be contraindicated for TMS treatment
    - Any drug or alcohol use deemed by the study doctor as unsafe for TMS treatment
- Subjects unwilling to sign consent or follow study procedures
- Subjects with known extended travel plans which may affect study procedures and scheduled TMS treatment

VI. Number of Subjects

For this study we are looking to enroll 120 subjects broken down between 2 different treatment arms in the following way:



The number of subjects we expect to enroll is based on our current UMHC Neuromodulation clinic patient flow. The average patient clinic flow is 100 per year and using these numbers the study should be able to complete within 1-2 years. We expect that at least 20% of our expected enrolled may drop out of study for varies reasons (moved, loss of interest, unexpected reasons) hence the total expected completed being 100. 60 subjects in each arm will allow for a balanced study.

VII. Study Procedures/ Design/Treatment Plan

This is an open-label non-blinded study, for patients that have already completed an acute TMS course of therapy and have responded or remitted from their depressive symptoms according to their routine care clinical assessments (PHQ-9, or QIDS). There is no sham treatment in this study, but we will be using a study arm that does not receive TMS treatment in order to compare to an active TMS study arm.

All subjects will complete 3 non-treatment visits (consent, baseline, end of study visit) and if a subject is in the treatment arm and additional 60 visits (over the course of year). Additionally, a subject that is in the treatment arm will completed a PHQ-9, and IDS at baseline visit, and the beginning and end of each monthly treatment block. If a subject is in the non-treatment arm they will complete 15 total visits consisting of a consent, baseline, 12 assessment visits (for PHQ-9 & IDS testing) and an end treatment visit. For these individuals, a PHQ-9 and IDS will be completed at the baseline visit and at each monthly assessment visit.

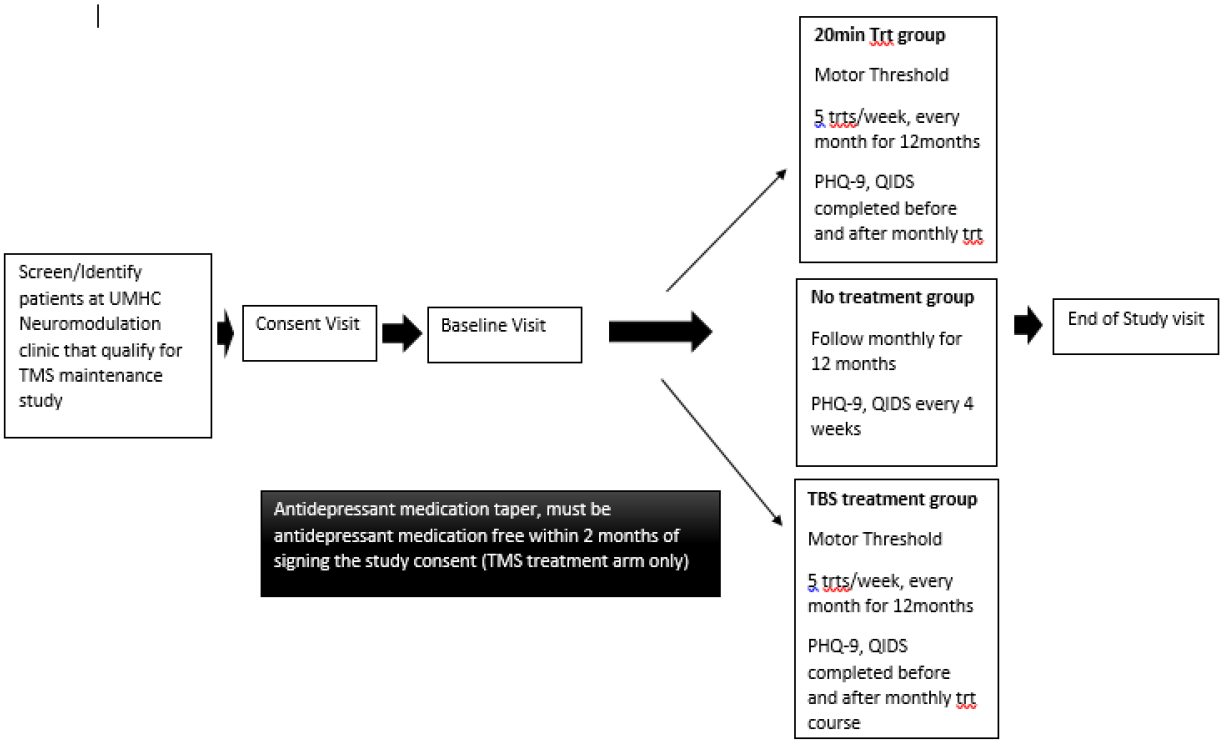
Subjects in the active TMS treatment arm will be tapered off their antidepressant medication as soon as they have signed consent according to the study doctor's direction. Subjects in the TMS active arm will remain antidepressant medication free for the duration of the study. If these subjects deteriorate during course of the study they will be removed from the study and normal clinical care will resume. They will complete a PHQ-9 and QIDS at this time. Their data will be used in the final analysis of study. Deterioration or relapse will be determined by the study doctor clinical judgement.

For subjects in the active TMS treatment arms, a dosing procedure (Motor Threshold) will need to be performed by any person the study PI delegates this authority to, each month immediately before the first treatment of each monthly treatment block. The Motor Threshold (MT) is used to determine the % TMS machine output or dosage, needed to treat. The procedure consists of the TMS certified operator placing the TMS machine treatment coil on the patient's head, corresponding to an area over the patients left Motor Cortex of his/her brain. Then the TMS machine intensity is turned up or down and the coil is moved around on patient's head to determined how much energy is need to elicit a muscle twitch in the right abductor pollicis brevis muscle (APB). Then a computer algorithm helps determine the correct intensity that should be used for the next 5 treatments. An additional computer algorithm uses head measurements of circumference, Nasion to Inion, and Tragus to Tragus, to determine where the TMS treatment coil will be located to treat over the Dorsolateral Prefrontal Cortex (DLPFC). This procedure must be completed each month prior to the monthly treatment block.

If a patient drops out of the study for any reason their data up to that point will be retained and used, this will be discussed with the potential patient during the consent process, and described in the consent itself.

The last treatment visit when a patient completes the treatment portion of the study or has finished their last monthly assessment visit if they are not in an active treatment arm, will be an end study visit (this could be the last treatment/assessment visit if time allows). At this visit the TMS MD will discuss end of study and possible future clinical care that maybe necessary for subject when they switch back over to clinical realm and are no longer part of the study.

Study procedure plan is below:



Study visit completion for TMS active arms form is below, subjects that are in non-active arm will not have the TMS treatment visits, but will do the monthly assessment visits:

Visit	Consent	Hipaa	Inclusion/Exclusion	TASS	PHQ-9*	QIDS*	AE **
Consent	x	x					
Baseline			x	x	x	x	
Trt 1-5 (1 Month)					x	x	
Trt 6-10 (2 Month)					x	x	
Trt 11-15 (3 Month)					x	x	
Trt 16-20 (4 Month)					x	x	
Trt 21-25 (5 Month)					x	x	
Trt 26-30 (6 Month)					x	x	
Trt 31-35 (7 Month)					x	x	
Trt 36-40 (8 Month)					x	x	
Trt 41-45 (9 Month)					x	x	
Trt 46-50 (10 Month)					x	x	
Trt 51-55 (11 Month)					x	x	
Trt 56-60 (12 Month)					x	x	
* Completed before and after each monthly TMS treatment block							
** Adverse Event form to be filled out as needed							

VIII. Potential Risks/Adverse Events

The machine and treatment protocols are the same used in the clinical setting, therefore the risks are the same. The most common side effect/ risk is headache, superficial pain under treatment site, dental pain, eye pain, or facial muscle twitching. These seem to well tolerated, and can occur during or after treatment. These can be treated with over-the-counter pain medication (Tylenol, Ibuprophen).

Another rare but serious risk is seizure. Seizures are very rare and are thought to occur about 1in 30,000 treatments. Subjects will have already gone through safety screens in order to get TMS treatment clinically, but nevertheless, another Transcranial Adult Safety Screen (TASS) will be done prior to starting treatment phase of study. Study staff are trained in seizure occurrence during TMS and are also CPR certified.

The study doctor will determine if patient participation should start or continue from these or any other subject problems that may occur, such as failure of TASS question throughout the study.

If an adverse event, UP, or deviation occur study staff will fill out a study adverse event form, the AE event log, and will notify the MU IRB if required within 5 days of awareness of the event.

IX. Anticipated Benefits

It is not known whether TMS used in a monthly maintenance protocol will be beneficial in helping to extend out the subject's acute response or remission, but it may be a possible benefit. Additionally, this study will help add to the work of clinical and scientific community in this area of interest. This data may also help future patients that have MDD and are trying to maintain their response.

X. Compensation

No compensation will be given for this study.

XI. Costs

There are no costs associated with this study either for the research or to participants. The TMS machine is already part of the Neuromodulation Clinic.

XII. Data Safety Monitoring Plan

No DSMB is required for this study. All adverse events will be reported on the AE study report form, the AE log, and local IRB protocol will dictate what needs to be submitted to MU IRB. Because this is an internal study (no other sites), AEs and UP will immediately be known to study doctor. He will determine if AEs are in the normal range

for TMS treatment, comparing to clinical experience and TMS safety data. If they are found not to be, the he may pause the study to review protocols and procedures.

All study data will be captured on paper then transferred over to an electronic database on a secured approved UM computer. All data will coded so no patient data will be identifiable. Study Consents and HIPAA that are signed will be stored in locked cabinet behind a locked door. The key linking subject consent and subject codes will not be stored in same place as consents and coded data. All coded data on paper will be placed in subject binder and stored in locked cabinet behind locked door. All study data will be stored for length of time in accordance with UM IRB research data rules.

XIII. Multiple Sites

1. NA

XIV. References/Appendices

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