PROTOCOL and ICF COVER PAGE:

Accelerated Repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment for post-stroke depression in the subacute phase: an open label pilot study

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Protocol Number & Study Protocol Title

Accelerated rTMS as a treatment for post-stroke depression in the subacute phase: an open label pilot study

IRB # 1804090922

PI Signature_____ Date _____

Abbreviations List

AAQP = Amino Acids, Quantitative, Plasma

AIS = Acute Ischemic Stroke

ASRM = Altman Self-Rating Mania Scale

BP = Blood Pressure

CT = Computed Tomography

DLPFC = Dorsolateral prefrontal cortex

DSMB = Data Safety Monitoring Board

EKG = electrocardiogram

FDI = First Dorsal Interosseous

FIM = Functional Independence Measures

HAMD = Hamilton Depression Rating Scale

HR = Heart Rate

Hz = Hertz

IR = Interventional Radiology

MINI = Mini International Neuropsychiatric Interview

MRI = Magnetic Resonance Imaging

mRS = Modifed Rankin Scale

NIHSS= National Institutes of Health Stroke Scale

NLR = Neutrophil to Lymphocyte Ratio

PSD = Post Stroke Depression

RMT = Resting Motor Threshold

rTMS = repetitive Transcranial Magnetic Stimulation

tPA = tissue Plasminogen Activator

Section I: Team and Research Summary

Study Team Composition

Role: Principal Investigator
1 Amelia Karen Adcock
Contact information: akadcock@hsc.wvu.edu 304-598-6127

Role: Co-Investigator
2 Jessica Elizabeth Frey Role: Co-Investigator
3 Ashley Brooke Petrone Role: Co-Investigator
4 Umer Najib Role: Co-Investigator

Role: Study Coordinator:
1 Jay Michael Sherman
2 Louise Ann Moore

Role: Study Personnel:
1 Padmashree Srinivasan Tirumalai

Research Summary

Study Population –

Goal subject recruitment N for this study = 20 patients

Patients are NOT recruited from vulnerable populations (eg children, prisoners, pregnant women, and/or mentally handicapped individuals). Selection of subjects will be equitable addressing gender, race, and ethnicity because all patients who have radiographic evidence of stroke and meet eligibility criteria will be considered for enrollment.

All patients must meet the following inclusion criteria:
1. Ages 22-85 years old.
2. Radiographic evidence of acute or subacute ischemic stroke (typically on MRI or CT).
3. Ischemic stroke diagnosed within the last 2 weeks to 6 months.
4. HAMD depression score 8 or greater.
5. Agrees and is able to provide written informed consent.
6. Agrees and is able to participate in all study procedures.

Exclusion Criteria:
1. Metallic objects or neurostimulators implanted intracranially.
2. Stroke in the Left DLPFC.
3. Known history of epilepsy or seizure disorder.
4. Clinically significant EKG abnormalities including QTC prolongation >450 ms in men or > 480 ms in women.
5. A woman who is pregnant or breastfeeding.
6. History of psychiatric hospitalization unrelated to current PSD
7. Current SI or MINI suicide scale > 8.
8. ASRM > 6
9. Current illicit drug use.
10. History of head trauma resulting in loss of memory >5 minutes or requiring hospitalization.
11. Evidence of hemorrhage in the brain at the time of study.

12. Have other mental or physical conditions that are inappropriate for study participation at PI's discretion.

Study Design –
This is an open label trial meaning that all participants (stroke patients with depression) will be given the intervention, which in this case is rTMS.

The purpose of this study is to find alternative treatments for patient's suffering from depression after having a stroke. The specific treatment this study will be looking at is Transcranial Magnetic Stimulation (TMS). TMS is a non-invasive process where a patient reclines in a chair and a magnetic coil is placed near the patient's head. The coil will be pointed at specific target in the patient's brain and will give pulsations to that area of the brain. These pulsations can change the patient's brain activity. After the pulsations are done, the patients will be immediately able to resume their normal daily activities. After the TMS sessions, the patients' quality of life, measure of depression, and stroke deficits will be assessed. The patients will then follow up at their regularly scheduled stroke follow up appointments in the outpatient clinic and these same measures will be reassessed. Past studies have shown that TMS is safe and effective for treating major depression as well as motor recovery in stroke, but there are fewer studies looking at TMS in post-stroke depression. This study aims to show that accelerated rTMS is a safe, effective, and convenient treatment for patient's suffering from post-stroke depression in the acute to subacute phase. This will be an open label trial and thus all participants will receive the active rTMS intervention. This is a pilot study with a small sample size (20 patients) and the information gathered from this study will help to generate future randomized controlled studies on similar topics.

Study Duration –3 years total, with patients accrued and data analyzed on a rolling basis.

Section II: Design

Background & Significance

TMS has been well studied in major depression and has shown significant benefit for patients suffering from MDD, with more benefit seen in younger patients who already respond well to antidepressants (Dumas, Brunelin). TMS has also been well studied as an effective treatment for post-stroke motor recovery by either stimulating the affected hemisphere or sending inhibitory pulsations to the unaffected hemisphere in order to promote plasticity (Hoyer). Post-stroke depression (PSD) is a phenomenon that affects up to 30-50% of stroke survivors (Paolucci). It is a prevalent condition that not only affects mood but can translate into poorer motor recovery and overall quality of life. As acute

stroke management continues to improve through the use of tPA and IR thrombectomy, there are more stroke survivors and as a consequence, a higher population of survivors suffering from PSD. Currently the mainstay of treatment for PSD is the use of antidepressants. However, many patients cannot tolerate antidepressants due to side effects or drug-drug reactions. In addition, antidepressants are not always effective for patients. Therefore, an alternative treatment for PSD such as rTMS as needed. However, the downside for TMS is that it typically takes 4-6 weeks of nearly daily session before a clinically significant benefit is seen and this is a barrier due to patient location, transportation, and compliancy (Janicak, Holtzheimer). Thus, a new protocol that accelerates the time period in which the patient receives the rTMS sessions within a reasonable time frame is needed. Studies have shown that an accelerated protocol is a safe and effective treatment tool for patients suffering from major depressive disorder as well as in patients suffering from alcohol withdrawal craving symptoms (Baeken, Herremans). Studies have also shown that rTMS is safe in the acute stroke period (Conforto, Khedr, Rossi). It follows then that an accelerated rTMS protocol would also be effective in patients suffering from post-stroke depression. Please see attachments section for cited references.

Objectives

Purpose *– Overall purpose is to improve an otherwise poorly and incompletely treated common complication of stroke; PSD. rTMS is a promising alternative as an effective and practical tool to combat PSD.*

Primary Objective –
Determine the feasibility and tolerability of repetitive transcranial magnetic stimulation (rTMS) in patients with post-stroke depression (PSD) in the subacute recovery period.

Hypothesis: This study design and its execution will support the feasibility of a 4 day accelerated rTMS protocol and that PSD patients will tolerate this accelerated protocol in the subacute recovery period following an ischemic stroke.

Secondary Objective(s) –
Determine the efficacy of repetitive transcranial magnetic stimulation (rTMS) in patients with post-stroke depression (PSD) in reducing depressive symptoms during the subacute recovery period.

Hypothesis: PSD patients who are treated with rTMS in the subacute recovery period following an ischemic stroke will experience amelioration of their depressive symptoms compared with PSD patients who do not receive rTMS.

Tertiary objective-
Investigate the role the immune system plays in patients who undergo rTMS for PSD.

Hypothesis: The NLR will be positively correlated with the HAM-D scale score and is an accurate prognostic marker to identify stroke patients at risk for PSD. Second, rTMS will decrease the NLR in stroke patients with PSD, and this reduction in NLR will correlate with a decrease in depression symptoms, as measured by the HAM-D scale score.

Study Design & Methodology

This is an open label study. The intervention that is being studied is rTMS in PSD patients.

1. Patients will have a radiographic study of the brain that shows evidence of ischemic stroke (this step represents routine care in their stroke evaluation).
2. Patients who meet the inclusion/exclusion criteria and have a HAMD or ≥ 8 will be offered to participate.
3. Enrolled patients will be scheduled for their 4 day sessions of neurostimulation.

Prior to stimulation (typically on Day 1):

a. Screen subject with:
    a. ASRM
    b. MINI
    c. NIHSS
    d. mRS
    e. FIM
    f. HAMD
    g. Vitals (EKG and BP)
    h. Blood draw
    i. Assess whether psychiatric medication was changed within the preceding 10 days
    j. Mapping procedure (where to place the stimulator):
        i. the patient's resting motor threshold (RMT) will be identified visually as muscle twitching in the First Dorsal Interosseous (FDI) muscle in 5 out of 10 stimuli provided. RMT can vary between patients, so this will be used to ensure that patients are all getting the same strength of TMS treatment.

4. The following protocol will be applied on days 1-4:
   High frequency (20 Hz)- rTMS will be applied to the patients. There will be five sessions per day over the course of 4 days for a total of 20 sessions. Neurostimulation will be applied with a figure of eight coil. There will be 40 trains of 2.0 second duration (39 pulses) with a 12 second intertrain interval for a total of 1560 pulses per session. Each session will be separated by 10-20 minutes (based on subject discretion). Stimulation will be provided at up to 110% of the resting motor threshold over the left DLPFC. Patient will be able to immediately resume normal activities after the stimulation session and their safety will be monitored throughout the study.

5. Subjects' vitals will be checked prior to 1st rTMS stimulation session of the day as well as after the day's last session.

6. General adverse event screens will be conducted following each day. Self-harm will be assessed before and after each stimulation treatment. In addition to general and mood-related significant adverse events will be defined as hospitalization that was a result of a psychiatric condition throughout the 12 months of enrollment (per subject).

7. Following day 4's stimulation, a follow up HAMD, FIM, mRS, NIHSS, ASRM and MINI will be conducted and bloodwork obtained.

8. A follow up phone call within 24-72 hours following Day # 4 to further assess for any adverse events will be completed.

9. Subjects will return for follow-up visits at 3, 6 and 12 months post stimulation. Patients will be surveyed with the HAMD scale, FIM scale, NIH stroke scale, mRS, MINI suicide scale, and ASRM prior to the intervention and then directly afterwards at the end of the 4th day as well as at their stroke follow up appointments at 3 months, 6 months, and 1 year. Patients will additionally have CBC/diff, Pax Gene tube, Sodium EDTA tubes, green top tube for AAQP drawn prior to TMS treatment, after TMS treatment, and at their 3 month follow up appointment to measure neutrophil-lymphocyte ratios and arginase levels, in addition to glutamate levels and validation of any unique proteins (included in the kits) in order to characterize the immune response in patients with acute stroke and PSD.

10. The blood samples will be drawn before the 4 days of TMS, after the 4 days of TMS sessions, and during their 3 month follow up. Four tubes of blood will be collected during the blood draws described: CBC/diff (lavender top), PaxGene tube, Sodium EDTA tube, and AAQP (green top). The samples will be given a de-identified sample number and then stored for processing serum and WBC isolation. Once fully processed, the sample will be stored in a locked -80 freezer in a locked room to complete analysis of blood work. Patients will have the ability to opt out of the blood storage portion and this will be specified in the consent form.

11. General variables about the subject's background will also be recorded in our de-identified secure database (RedCap): age, gender, ethnicity, handedness, stroke risk factors, etiology of stroke, mRS prior, antidepressant use prior and if an SSRI was initiated post stroke.

12. In addition to the specific tools used to monitor for adverse events describes above, eg the ASRM (for mania) and the MINI (for suicidality), adverse events will include any hospitalization for psychiatric disease. Any death and cause, when known, occurring during the study period of 12 months, will be recorded. Tolerability of the study will be assessed by asking participants to report any discomfort or side effect to the treatments during the 4 days of active rTMS treatment.

13. Concomitant medications: all psychiatric medications will be recorded at each study visit. A participant will not undergo rTMS if a modification in their psychiatric medications in the preceding 10 days or less has occurred.

14. rTMS administration will be supervised by adequately trained personnel and the number of pulses and times received will be documented in the subject's binder.

15. Prespecified stopping rule: if 1) a seizure in a patient or 2) a patient attempts/completes suicide occurs. Either of these events would trigger a Data Safety Monitoring Board Review. This would also generate an IDE supplement for FDA review.

    The address of the DSMB is as follows:

    West Virginia University Cancer Institute

    1801 Health Sciences South

    PO Box 9300

    304-293-0781

The Data Safety and Monitoring Board is comprised of 3 WVU faculty who all have extensive research experience and have committed to serving in the role as monitors for this study. They are familiar with the protocol and specifically with the prespecified timelines and events necessary that will trigger their analysis. While they all have expertise conducting research; both in the clinical and pre-clinical arenas, as well as trial design and data analysis, none of these members have any involvement in this trial or stake in its outcome. They are completely independent and impartial.

1. Muhammed Alvi, M.D.: Dr. Alvi is a vascular neurologist. He has been Co-I or PI in multiple investigator-initiated institutional studies as well as large multi-center clinical trials and is currently PI on 4 multicenter trials .

2. Ann Murray, M.D.: Dr. Murray specializes in treating people with inflammatory disorders of the CNS and is director of our neuromodulation center with a focus on Deep Brain Stimulation (DBS). She has been involved with multiple clinical trials and is currently PI on 3 clinical trials.

3. Cheryl Smith, M.D.,PhD: Dr. Smith earned her doctorate in neuroanatomy. Clinically, she is a neuromuscular specialist. She has over 20 years of research experience. Dr. Smith heads the Department of Neurology's research division and is currently PI/Co-I of 6 active clinical trials.

Schedule of Activities

Procedures	Screening Day 1 to 170	Enrollment/Baseline Visit 1, TMS Day 1	Study Visit 2 TMS Day 2	Study Visit 3 TMS Day 3	Study Visit 4 TMS Day 4	Follow up Phone Call (within 72 hours of Day 4)	Study Visit 5 3 month follow up	Study Visit 6 6 months follow up	Final Study Visit 7 12 month follow up
Informed consent[#]	■	■							
Demographics	■								
Medical history	■								
Variable Collection[a]		■							
Administer rTMS		■	■	■	■				
Concomitant psychiatric medication review[1]	■	■	■	■	■	■	■	■	■
Depression Screen (HAMD or PHQ 9)[#]	■	■			■		■	■	■
Vital signs[1,2]		■	■	■	■		■	■	■
mRS [a,b]		■			■		■	■	■
FIM [a,b]		■			■		■	■	■
NIHSS [a,b]		■			■		■	■	■
MINI [a,b]		■			■		■	■	■
rTMS documented[2]		■	■	■	■				
EKG (as indicated)[1,2]	■	■	■	■	■				
Pregnancy test[a]		■							

Procedures	Screening Day 1 to 170	Enrollment/Baseline Visit 1, TMS Day 1	Study Visit 2 TMS Day 2	Study Visit 3 TMS Day 3	Study Visit 4 TMS Day 4	Follow up Phone Call (within 72 hours of Day 4)	Study Visit 5 3 month follow up	Study Visit 6 6 months follow up	Final Study Visit 7 12 month follow up
Adverse event review and evaluation (post treatment)[1,2]									
ASRM [a,b]									
Other assessments(e.g., bloodwork)[a,b]									
Psychiatric medication review									

Key:
#: can either be completed during screening phase or during visit 1, prior to TMS
a: before TMS on day 1
b: after TMS on day 4
1: before each TMS treatment
2: after each TMS treatment

Target Population & Recruitment Methods

See above.
Goal subject recruitment N for this study = 20 patients.

Patients are NOT recruited from vulnerable populations (eg children, prisoners, pregnant women, and/or mentally handicapped individuals). Selection of subjects will be equitable addressing gender, race, and ethnicity because all patients who have radiographic evidence of stroke and meet eligibility criteria will be considered for enrollment.

Inclusion & Exclusion Criteria – All patients must meet the following inclusion criteria: 1. Ages 22-85 years old. 2. Radiographic evidence of acute or subacute ischemic stroke (typically on MRI or CT). 3. Ischemic stroke diagnosed within the last 2 weeks to 6 months. 4. HAMD depression score 8 or greater. 5. Able and agrees to provide written informed consent. 6. Able and agrees to participate in all study procedures. 7. If subject has child bearing potential will have a negative urine pregnancy test prior to enrollment. Exclusion Criteria: 1. Metallic objects or neurostimulators implanted intracranially. 2. Stroke in the L DLPFC. 3. Known history of epilepsy or seizure disorder. 4. Clinically significant EKG abnormalities including QTC prolongation >450 ms in men or > 480 ms in women. 5. A woman who is pregnant or breastfeeding. 6. History of psychiatric hospitalization unrelated to current PSD 7. Current SI or MINI suicide scale > 8. 8. ASRM > 6 9. Current illicit drug use. 10. History of head trauma resulting in loss of memory >5 minutes or requiring hospitalization. 11. Evidence of hemorrhage in the brain at the time of study. 12. Have other mental or physical conditions that are inappropriate for study participation at PI's discretion.

Recruitment – 1. Patients who have radiographic evidence of an acute stroke and are currently on the stroke service (or in the outpatient clinic) will be screened for depression with the HAMD scale during routine stroke care, including admission to the hospital and at their follow up stroke appointments or other outpatient appointments. Potential candidates are pre-screened by the study coordinator via the electronic medical record. MyChart messages may also be sent to qualified candidates and West Virginia Practice Based Network providers are aware of this study. They may refer an appropriate candidate for more information. Participants may also be pre-screened over the phone for those patients who were identified as potential study subjects. 2. The study will be explained to patients that meet the inclusion/exclusion criteria. 3. Patients who wish to enroll and participate and who have decision making capacity will be consented during their hospitalization, at their outpatient neurology follow up appointment, depending on the timeline for that particular patient. TriNetX will also be used to identify potential candidates via chart review. Families will be invited to participate in the discussion regarding enrollment in this study.

Risk & Benefit

Risk – Currently there are no standard safety guidelines for TMS in stroke, although it is generally thought that high frequency TMS carries a higher risk of seizure since high frequency (>1 Hz) generates cortical excitability (Rossi). However, it has also been reported that TMS is a focal process and if the area of seizure susceptibility (whether that is an ischemic stroke or epileptogenic focus) is not directly stimulated by TMS, the risk for seizure is not any higher in the stroke population that in the regular healthy adult population (Rossi, Jorge, Fregni). In addition, there have been several studies looking at various high frequency, high stimulation intensity protocols in stroke patients (for various outcomes such as motor recovery and grip strength) that have been shown to be safe, with similar side effect profiles to the general population (Guo, Sasaki, Hosomi, Guan). These studies have been summarized in the table below references. Of note, the only major adverse effect reported in all of the aforementioned studies was one patient with attempted suicide- it should also be noted that this adverse effect was in a study that was specifically studying suicidal ideation and thus all patients in the study were at high risk for suicidal ideation. All other reported side effects summarized in the table below involve transient pain or feelings of discomfort at the site of stimulation. Accelerated rTMS has not been tested for PSD, which is part of the novelty of our proposed study. However, given the above studies demonstrating safety and efficacy of accelerated protocols for depression and high frequency, high stimulation protocols in acute stroke timelines (as early as 5 days post-stroke), it follows that an accelerated rTMS protocol would also be an effective and safe method in patients suffering from post-stroke depression (when stimulation will be performed much later, in the subacute period). Lastly, the most current and complete meta-analyses of rTMS in our population of interest (PSD) which compared 25 RCTs (n = 1,804 patients with n = 520 with safety data available) failed to show any significant incidence of a serious adverse event (including seizure) in the actively treated patients (Shen 2017, McIntyre 2016).
Due to the theoretical risk of higher seizure risk in a patient with stroke, we will follow similar protocols for clinical monitoring of seizure signs and symptoms as outlined in the studies mentioned above. Our study will have vitals closely monitored before and after each TMS session. Patients will be clinically monitored for signs of seizure and clinicians trained to diagnose and manage seizures will be immediately available at the study site. AEDs will also be immediately available should any patients have a seizure during the study.

Study	Site of Stimulation	Frequency	Trains per session	Sessions per day	# of days	Total # of pulses	Intertrain interval	Intersession interval	# of patients	AEs
Baeken 2014 (Unipolar depression)	Left DLPFC	20 Hz	40	5	4 consecutive	31,2000	12 sec	15-20 min	15	Transient headache and transient fatigue
Herremans 2015	Right DLPFC	20 Hz	40	5	3 consecutive	23,400	12 sec	15 minutes	26	1 dropped out due to temporary

(cravings of alcohol dependent patients)										pain at stimulation site
Seok 2015 (MDD)	Not available	Not available	Not available	5	3 consecutive	Not available	Not available	Not available	20	No major AEs
Holtzheimer 2010	Left DLPFC	10 Hz	20	5 on day 1 and 10 on day 2	2 consecutive	15,000	25 sec	0	14	1 patient had possible increase in SI
Guo 2017 (acute stroke for motor recovery)	Ipsilesional motor cortex (same side as acute stroke)	10 Hz	30	1	10	15,000	25 sec	NA	15	none
Fitzgerald 2018 (MDD)	Left DLPFC	10 Hz	83-84	3	6	63,000	15 sec	15-30 min	58	2 withdrew due to treatment discomfort and 1 withdrew due to migraine
Duprat 2016 (medication resistant depression)	Left DLPFC	iTBS	54 triplet bursts	5	4 consecutive	32,400	8 sec	15 min	50	3 dropped out due to discomfort at stimulation site
Desmyter 2016 (suicide risk in refractory MDD)	Left DLPFC	iTBS	54 triplet bursts	5	4 consecutive	32,400	8 sec	15 min	50	1 suicide attempt (patients had SI prior to study enrollment because study was assessing suicide risk)
Conforto 2012 (acute stroke treatment of hemiparesis)	Contralesional motor cortex	1 Hz	Not reported	1	10	15,000	Not reported	NA	15	Transient head pain, no serious AEs
Khedr 2005 (acute stroke for motor recovery)	Ipsilesional motor cortex	3 Hz	10	1	10	15,000	50 sec	NA	52	none
Hosomi 2016 (subacute stroke for upper limb paresis)	Ipsilesional motor cortex	5 Hz	10	1	10	50,000	50 sec	NA	39	none
Sasaki 2017 (acute stroke for leg weakness recovery)	Ipsilesional motor cortex	10 Hz	10	2	5	10,000	50 sec	Not reported	21	none
Blesneag 2015	Contraslesional motor cortex	1 Hz	Not reported	1	10	12,000	Not reported	NA	16	None reported
Young Gu 2017 Population: PSD	Left DLPFC	10 Hz	20	1	10 (consecutive)	10,000	60 sec	NA	24	None
Jorge 2004 Population: PSD	L DLFPC	10 Hz	20	1	10 (consecutive)	10,000	60 sec	NA	20	Transient headache, local pain and anxiety.

										Insomnia in one patient. No serious AE
Carey 2008 Population: PSD	Contraslesional motor cortex	6 Hz	20	1	1	1000	25 sec	NA	10	Transient fatigue, headache, neck pain. No serious AE reported.
El Etribi 2010 Population: PSD	L DLPFC	1 Hz	10	1	10	1000	2 sec	NA	20	Transient mild headache
Narushima 2010 Population: PSD or at least 3 vascular risk factors)	L DLPFC (excluded patients with stroke at this location)	10 Hz	20	1	10	18,000	60 sec	NA	31	None

Benefit **-**The current options for treating post-stroke depression include stroke support groups, cognitive therapy, and anti-depressants. Although these options are available and will be offered to all the patients in this trial, there is not one particular option that is currently considered the standard of care. There was one trial which showed that fluoxetine showed mild improvement in motor recovery for stroke patients, so fluoxetine is often prescribed for stroke patients to enhance motor recovery, though it is not specifically used for PSD. Thus, patients previously on antidepressants or that have been started on antidepressants, particularly fluoxetine, will not be excluded from the study. However, patients will be asked to remain on current treatment (not to stop, start, or change antidepressants) throughout the duration of the study, unless medically necessary to adjust, so as to not influence results of the study. If a patient changes their antidepressant regimen within 10 days of TMS (pt will be rescheduled if possible for stimulation sessions to begin or, if this change occurs within the 10 days following TMS treatment, it will be noted in our statistical analysis). Patients will also be informed of all the options available to them to treat their post-stroke depression, and support groups, cognitive therapy, and antidepressants will be offered to all patients in addition to the TMS therapy to patients in this study.

Participants in this study may note a benefit in their mood, functional status, and motor recovery. Prior studies have shown TMS to improve motor recovery after stroke and prior studies have also shown TMS to improve depression in patients with major depression as well as post-stroke depression (Dumas, Brunelin, Shen). It follows then that some form of TMS in the acute to subacute phase will additionally benefit patient's mood, motor recovery, and cognitive recovery.

In order to compensate for time spent or transportation costs, participants will be reimbursed with a $50 gift card following completion of all 4 sessions. If a participant lives remotely or cannot reasonably drive to Morgantown daily for 4 days of treatments, hotel accommodations locally will be provided.

The potential benefits to society include novel and efficient approaches to treating post-stroke depression. The goal is to find an alternative treatment to post stroke depression since many patients cannot tolerate antidepressants due to side effects or drug-drug interactions. Thus TMS potentially represents a safe and convenient alternative or adjunctive therapy to antidepressants for patients with post-stroke depression. It also represents an alternative or adjunctive treatment to therapy or support groups, treatments that rely heavily on a patient's intrinsic motivation for recovery, whereas TMS does not depend on patient's motivation for effectiveness. This data will be used to support a larger, randomized controlled project comparing accelerated rTMS to sham TMS.

Statistical Analysis Plan

Analyses will be conducted using SPSS, version 22. Descriptive and frequency data will be analyzed for Adverse Events. T-tests will be used to determine differences in BP/HR pre- and post-rTMS. While not sufficiently powered to provide

conclusive results, mixed-model, repeated measures analysis of variance (ANOVA) will be used to evaluate preliminary efficacy effects of rTMS on HAMD score, FIM score, and NIH scores. This latter analysis will serve as pilot data for future studies.

Sample Size –This is an open label, pilot study intended to gather data about safety and logistics of using accelerated rTMS in the subactue stroke phase as a treatment for post-stroke depression. We hope to gather data about subjects' response to accelerated rTMS in preparation to eventually conduct a larger, randomized controlled trial comparing rTMS to sham rTMS. However, this study will look at a smaller sample size of intervention only patients to monitor safety and efficacy in this population.

Safety Monitoring & Unanticipated Event Reporting

If an adverse event is noted or any other question surrounding the eligibility of a patient, the PI will be immediately contacted. Any IRB reporting is done as a study team including the PI, the study coordinator (s) and regulatory liaison in accordance with the requirements outlined by the IRB/IDE.

Data Safety Monitoring –
This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

Relationship to TMS Procedure:

Definitely related – the AE can be fully explained by administration of theprocedure.
Probably related – the procedure is more likely the cause of the AE than other factors.
Possibly related – there is a reasonable possibility that the procedure is the cause of the AE, including that the procedure and another factor(s) are equally likely as causes of the AE.
Unrelated – another factor is clearly (incontrovertibly) the cause of the AE.

Severity Rating	Definition
Grade 1 = Mild	Usually transient, requiring no special treatment Does not interfere with usual status or activities Awareness of the event, but easily tolerated
Grade 2 = Moderate	May be ameliorated by simple therapeutic measures May cause enough discomfort to interfere with usual activities
Grade 3 = Severe	Causes inability to perform usual activities Requires close monitoring and/or intervention
Grade 4 = Very Severe/ Life Threatening	Significantly debilitating or incapacitating despite symptomatic therapy Requires immediate intervention or emergency treatment May be life threatening

Participants who meet 4 AE severity criteria will be medically monitored and then discontinued from the study. Participants who meet Grade 1, 2, or 3 AE severity criteria will be medically monitored and determination of continuation/discontinuation will be made at the discretion of the study physician.

Adverse events will be monitored via the adverse events screening forms and patients will be routinely asked if they are experiencing any side effects during the treatment process. Any of the following scenarios would trigger an immediate review with the Data Safety Monitoring Board:

-a seizure in a patient

-a patient who attempts or completes suicide

The Data Safety Monitoring Board will also meet when 50% target patient accrual is achieved, and quarterly thereafter. The Board will review adverse events and trial progress. All serious adverse events will be immediately discussed and if at any time the Board determines one of the above 4 criteria have been met, the study will be stopped prior to its completion.

Study Duration & Timeline

Nov 2018-Nov 2021: Study recruitment and execution. Parallel data analysis and dissemination.

Protected Health Information (PHI)

Yes, this research will deal with protected health information (PHI). However, participants will be "de-identified" and assigned a participant number in our secure database (RedCap).

Confidentiality & Privacy

Confidentiality *– All data collected must be kept for a minimum of 3 years after the conclusion of the research project. It may be decided upon by the research team to keep the data for a longer time frame. Physical copies of data collected must be locked in a drawer or file cabinet, within a locked room or office. Digital data should be encrypted or on a password protected database. All participant identifiers should be stored separately from the data collected (ex. ICFs should not be in the same locked drawer as the survey results collected).*

Data will be kept for 3 years. The data will be secured in a password protected database on a password protected tablet in a locked office. The Department of Neurology has a protocol in place for destroying PHI if in paper form. It is a locked box in a staff only area. Electronic data will be deleted from the protected files.
Data is only accessible to the PI, research team members, or IRB.

Participants will be "de-identified" and assigned a participant number. Their information will be kept on an encrypted drive. Consent forms will be kept in a separate, locked cabinet in a separate, locked room. Participants will be consented in their individual hospital rooms where nonessential personnel will not be given access during the consenting process. Similarly, all questionnaires and the TMS procedures will be completed in a private, secure room in individual sessions with no other participants and/or nonessential staff present.

Section IV: Other Considerations

Conflict of Interest

NONE

Publications, Presentations, & References

North American Conference on Neuromodulation (NANS) Las Vegas Jan 2019. Poster presentation. Study Design.
Van Liere Research Day. West Virginia University, Morgantown, WV. Poster Presentation, first place award.
CTSI Annual Conference. Greenbrier Resort, WV, April 2019. Poster presentation. Preliminary Results.

References

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WestVirginiaUniversity.
OFFICE OF HUMAN RESEARCH PROTECTION

Key Information for:
Accelerated Repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment
for post-stroke depression in the subacute phase: an open label pilot study

You are being asked to participate in the research described below. This page provides key information thatmay help you to make this decision; more detailed information can be found after this section.

Why is this research being done and what is involved?

The purpose of this study is to find alternative treatments for patient's suffering from depression after having a stroke.

The specific treatment this study will be looking at a procedure called Transcranial Magnetic Stimulation (TMS). During an TMS session, an electromagnetic coil is placed against your scalp. The electromagnet painlessly delivers a magnetic pulse that stimulates nerve cells in the region of your brain involved in mood control and depression.

In this study, you will receive 5 sessions of TMS per day over the course of 4 days for a total of 20 sessions, each day lasting for a 2-4 hours.In addition you will have blood draws, ECG, vital signs, and tests to assess yourstroke and depression status. You will then follow up at regularly scheduled stroke follow up appointments at, 3, 6 and 12 months in the outpatient clinic and some of these same measures will be reassessed. There may be phone calls following your treatment.

Do I have to participate and what are the risks, benefits and alternatives?

Participation in this research study is completely voluntary and you are free to withdraw from the research at any time. You may or may not directly benefit from participating in this research.

Side effects such as headache and light headedness are generally mild to moderate and improve shortly after an individual session and decrease over time with additional sessions.

Rare but serious risks from participation in this study include temporary or permanent hearing loss, seizure, and mania. There may be other study related risks that are currently not known.

You do not have to participate in this study and your post-stroke care will not be affected if you choose not to participate. Alternative treatment options for post-stroke depression include antidepressants and counseling/therapy.

Who can I talk to if I have questions or concerns?

If you have any questions or concerns about this research or would want to withdrawal from the study, you can contact Dr. Amelia Adcock at 304 598 -6127 or AKADCOCK@hsc.wvu.edu from the Dept. of Neurology at West Virginia University.

For more information, please see the Informed Consent Form.

Informed Consent | More than Minimal Risk Research(Version date December 20, 2018)

Site Version 25 Sept 2019

Principal Investigator (PI) | Amelia Adcock, MD

Department | Neurology

Co-Investigator(s) | Jessica Frey, MD; Ashley Petrone, PhD; Umer Najib, MD, Patrick Marshalek, MD

Coordinators Jay Sherman, RN Louise Moore, RN, Jennifer Krupp, MPH

Funding Source | None

WVU IRB Protocol # | 1804090922

Study Title | Accelerated Repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment for post-stroke depression in the subacute phase: an open label pilot study

Contact Persons

If you experience any injury or side effects from being in this research, you should contact Dr. Adcock at 304 598 -6127.
If an injury occurs outside of business hours and is related to your participation in this research, please contact Dr. Adcock at 304 598-6000.
If you have any questions, concerns, or complaints about this research, you can contact Dr. Amelia Adcock at 304 598 -6127.

For information regarding your rights as a person in research or to talk about the research, contact the WVU Human Research Protection Program (HRPP) at (304) 293-7073 or by email at IRB@mail.wvu.edu.

Introduction

You,_____, have been asked to participate in this research study, which has been explained to you by_____. This study is being conducted by Dr. Adcock in the Department of Neurology at West Virginia University, along with Jessica Frey, MD; Ashley Petrone, PhD; Umer Najib, MD, Patrick Marshalek, MD.

Purpose

The purpose of this study is to determine if repetitive Transcranial Magnetic Stimulation (rTMS) is an effective treatment for post-stroke depression (PSD). Post-stroke depression affects up to 30- 50% of stroke patients. TMS may reduce depressive symptoms in stroke patients by changing electrical activity in the brain, and may additionally improve strength and thinking in stroke patients. WVU expects to enroll up to 20 subjects.

Description of Procedures

If you are enrolled in this study, you will be evaluated with several scales:

Hamilton Depression Screen (HAMD): measures level of depression
- Functional Independence Measures (FIM): measures level of independence
- NIH stroke scale: measures severity of stroke symptoms using a neurologic exam

MINI Suicide Scale: measures risk of suicide
- Altman Self-Rating Mania Scale (ASRM): measures tendency toward mania

After that, you will receive an experimental protocol using TMS. The protocol involves 20 total sessions over the course of 4 consecutive days. A brief description of the actual rTMS procedure is as follows:

- Step One: You will recline comfortably in the treatment chair, awake and alert
- Step Two: A small curved device containing the magnetic coil rests lightly on your head

Step Three: The device delivers pulses directly to the target areas of your brain
- Step Four: You can immediately resume normal activities

During treatment, you will hear a clicking sound and feel a tapping sensation on the head.

Study Procedures

The study procedures will be as follows:

- After reviewing and signing this consent form, you will be screened with a survey to ensure you meet all inclusion and exclusion criteria as well as the surveys listed above
- Any personal information will be de-identified
- Bloodwork will be drawn along with your routine labs to check for signs related to post stroke depression.

We will obtain basic vital signs including EKG, blood pressure, and heart rate prior to the start of the TMS sessions.

All participants will receive rTMS using the following experimental protocol:

- 5 sessions of TMS per day over the course of 4 days for a total of 20 sessions, each day lasting for approximately 2-4 hours.
- Prior to the first session, we will determine the correct TMS settings for you by looking for a twitch of the hand muscles.
- Prior to and following all TMS treatments, your blood pressure and heart rate will be monitored and EKGs will be performed

You are asked to report any side affects you may experience throughout this protocol. Within 72 hours of your Day 4 visit you will receive a follow-up phone call to determine if you experienced any side effects following the treatments. After the 4 total days of TMS, you will again be evaluated based on the HAMD, FIM, and neurologic exam. The same assessments will be measured during your routine outpatient stroke follow-up appointments at 3 months, 6 months, and 1 year. Treatment will be stopped at your request or if your physician determines that this treatment is not in your best interest.

You will have routine blood work drawn at specific time points in this study. Blood samples will be drawn before the 4 days of TMS, after the 4 days of TMS sessions and during your 3 month follow up appointments. Once these samples have been processed, the samples will be given a unique identification number, will not be labeled with your name or any other personally identifying information and stored for future testing. The testing will look at gene and protein markers of depression. You can opt out of having the samples stored for future testing and will still be able to participate in the main study.

Please indicate if you would like us to store your sample for testing.

1 I do want to have my blood sample stored for future testing.

1 I do NOT want to have my blood samples stored for future testing.

Risks and Discomforts

Common Side Effects:

- Temporary pain or discomfort at stimulation site
- Headache
- Eye pain
- Toothache
- Muscle twitch
- Facial pain
- Neck stiffness

Acetaminophen or other medications for treatment will be available and provided to you if the above side effects occur.

Uncommon Side Effects:

- Temporary or permanent hearing loss
- Seizure (less than 0.1% of the time)
- Mania

In order to minimize the rare risk of hearing loss, the following procedures will be followed:

You will wear earplugs during the TMS sessions

- Study staff will discuss with you the risk of permanent hearing loss if earplug falls out
- Study staff will ask you to immediately report any loosening of an earplug duringTMS
- Investigators will immediately stop TMS if you report or if an investigator observes that an earplug has loosened or has fallen out.

In order to minimize the rare risk of seizure, the following procedures will be followed:

- You will be monitored at all times for signs of seizure by a trained physician or nurse who has experience treating seizures

- Equipment such as oxygen, suction, blood pressure monitor, CPR equipment, and anti seizure medications will be available on site if needed
- Given the social implications of seizure and convulsive syncope (i.e. adverse impact onfuture employability, insurability, and/or eligibility to drive), in the event of seizure, the investigators will provide you with a letter documenting that the event was experimentally produced.

In order to minimize the rare risk of mania, you will be monitored with the Altman Self-Rating Mania Scale anda score concerning for manic symptoms will halt further TMS trials and you will be provided with appropriate psychiatric care should these symptoms occur.

There is no known adverse effect of TMS on cognitive functioning. The long-term effects of TMS are unknown.

If you are a woman of child bearing age, you will be asked to provide a pregnancy test prior to enrollment in the study.

Starting any treatment for depression, you may become more depressed before getting better. Your depression symptoms will be closely monitored throughout the study. Any signs of self-harm or suicidal ideation will lead to removal from the study and immediate and appropriate psychiatric care for these symptoms. Any increased risk of self-harm will be assessed via a standardized questionnaire known as the M.I.N.I. Suicide Scale.

You will be asked to report any adverse reactions you may experience throughout the study. You may choose to discontinue the study at any time.

In addition, this study will involve some routine blood draws. Some adverse reactions to blood draws include pain from inserting a needle under the skin surface (common), fainting at or about the time of blood drawing (infrequent), bruising at the site (infrequent), and infection at the site (rare).

Alternative

You do not have to participate in this study and your post-stroke care will not be affected if you choose not to participate. Alternative treatment options for post-stroke depression include antidepressants and counseling/therapy, which have been discussed with you and you are welcome to partake in as well.

Benefits

Possible benefits include the improvement of your health, including improvement of your depression as well as motor recovery and improved quality of life. Since this study is using TMS in a novel way, it is not known whether rTMS will be effective in your case, and you may not receive any benefit or your condition may worsen. The knowledge gained from this study may eventually benefit others.

Financial Considerations

There are no special fees for participating in this study.

All participants will a receive card to compensate for their time ($10 for each TMS procedure completed with an additional $10 for subjects who complete all four TMS). Additional compensation is available for lodging

and or transportation for all participants who either live more than 1 hour away or have significant barriers securing transportation to trial appointments (including the TMS session days).

You may be asked to provide your Social Security Number and/or verification of U.S Citizenship or Permanent Resident Status to receive payment.

Your information may be provided to the appropriate parties for billing and/or payment purposes. Please be advised that any compensation received for participation in a research study, including a gift card, is considered taxable income and must be reported to the IRS. If you are a WVU employee or a WVU student-employee, youare required to report the total amount of compensation received for your participation in a research study to theWVU Tax Services Office upon receipt of payment.

Voluntary Compensation

In the event that you are physically injured as a result of participating in this research, care will be available and we will connect you with a medical professional who will examine and treat you if needed. Unless an injury happened because of an error directly related to the study, we will not compensate for any medically related charges. You should realize, however, that you have not released this institution from liability for negligence. Please contact the investigator, Dr. Amelia Adcock at 304 598-6127 if you are injured or for further information.

Confidentiality

Any information about you that is obtained as a result of your participation in this research will be kept as confidential as legally possible. Information or bio specimens collected as part of the study will not be used or distributed for future studies, even if the identifiers are removed. Your research records and test results, just like hospital records, may be subpoenaed by court order or may be inspected by the study sponsor or federal regulatory authorities, including the Food and Drug Administration (FDA), without your additional consent.

In addition, there are certain instances where the researcher is legally required to give information to the appropriate authorities. These would include mandatory reporting of infectious diseases, mandatory reportingof information about behavior that is imminently dangerous to your child or to others, such as suicide, child abuse, etc.

In any publications that result from this research, neither your name nor any information from which you might be identified will be published without your consent.

Voluntary Participation

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time. If you choose to withdraw your participation from the study, the data collected on you up until that time remains a part of the study database and may not be removed. No additional information will be added to the study database after your withdrawal.

Refusal to participate or withdraw will not affect your future care at West Virginia University.

In the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether or not to continue your participation.

Genetic Information Nondiscrimination Act (GINA)

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009. Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

West Virginia's genetic discrimination laws protect patients from discrimination by health insurers or employers. This means that a health plan or insurance company cannot raise your rates based on genetic information about you or commit any other form of illegal discrimination, nor can employers in West Virginia use your genetic information to inform decisions related to hiring or firing you.

HIPAA Authorization

We know that information about your health is private. We are dedicated to protecting the privacy of that information. Because of this promise, we must get your written authorization (permission) before we may use or disclose your protected health information or share it with others.

You can decide to sign or not to sign this authorization section. However, if you choose not to sign this authorization, you will not be able to take part in the research study. Whatever choice you make about this research study will not have an effect on your access to medical care.

Persons/Organizations Providing the Information

Patient (data are from the participant)/West Virginia University Hospitals/ WVU Medicine/ WVUHS (data arefrom records)

Persons/Organizations Receiving the Information

The research site(s) carrying out this study. This includes UHA or UHA Affiliates, WVU, WVUHospitals, WVUHS. It also includes each site's research staff and medical staff.

- Health care providers who provide services to you as part of this research study.
- Laboratories and other people and groups that look into your health information as part of this study in agreement with the study protocol.
- The members and staff of any institutional review board that oversees this research study.
- The West Virginia University Human Research Protection Program and/or Compliance and the Officeof Sponsored Programs.
- WVCTSI Clinical Trials research staff

The Following Information Will Be Used

Information from your existing medical records, and new information about you that is created or collected during this study, such as: history and physicals, clinic visit notes, nursing and staff notes, laboratory results, x-rays, EKG results, demographic data, pulmonary tests, imaging scans, and study forms.

The Information is Being Disclosed for the Following Reasons

- Review of your data for quality assurance purposes

Publication of study results (without identifying you)

- Other research purposes such as reviewing the safety or effectiveness of the study drug and other products or therapies; conducting performance reviews of the study drug; evaluating other products ortherapies for patients; developing a better understanding of disease; improving the design of future clinical trials

You may cancel this Authorization at Any Time by Writing to the Principal Investigator:

Amelia Adcock
1 Medical Center Drive
Morgantown, WV 26505 Email:
akadcock@hsc.wvu.eduPhone:
304 598-6127

If you cancel this authorization, any information that was collected already for this study cannot be withdrawn. Once information is disclosed, according to this authorization, the recipient may re-disclose it and then the information may no longer be protected by federal regulations.

You have a right to see and make copies of your medical records. You will not be able to see or copy your records related to the study until the sponsor has completed all work related to the study. At that time, you may ask to see the study doctor's files related to your participation in the study and have the study doctor correct anyinformation about you that is wrong.

This authorization will expire at the end of the study unless you cancel it before that time.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summaryof the results. You can search this Web site at any time.

Signatures

You have been given the opportunity to ask questions about the research, and you have received answers concerning areas you did not understand. Upon signing this form, you will receive a copy.

I willingly consent to participate in this research.

_____

Signature of Subject or Subject's Legal Representative

_____

Printed Name Date

The participant has had the opportunity to have questions addressed. The participant willingly agrees to be inthe study.

_____

Signature of Person Obtaining Informed Consent

_____

Printed Name