

INFORMED CONSENT

Open Label Study of the Efficacy, Durability, Safety and Feasibility of Intermittent Theta Burst Stimulation (iTBS) in Adolescents with Major Depressive Disorder: Effect Duration, Suicidality, and Non-Suicidal Self Injurious Behavior

NCT number NCT04485455

Document Date 09/29/2020

University of North Carolina at Chapel Hill
Parental Permission for a Minor Child to Participate in a Research Study

Consent Form Version Date: Version 2 , September 29, 2020

IRB Study # 19-1100

Title of Study: Open Label Study of the Efficacy, Durability, Safety and Feasibility of Intermittent Theta Burst Stimulation (iTBS) in Adolescents with Major Depressive Disorder: Effect Duration, Suicidality, and Non-Suicidal Self Injurious Behavior

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CONCISE SUMMARY

The purpose of this study is to evaluate the safety and feasibility of providing Intermittent Theta Burst Stimulation (iTBS) to adolescents for treatment of depression. This is a new treatment for kids but has been used in adults. Participation lasts 16-17 weeks, including a screening phase, 20 iTBS treatments, and 3 follow-up visits. A screening visit will take approximately 2-4 hours, the treatment visits will last approximately 20 minutes, but once a week they will last 1-2 hours, and follow-up visits will last 1-2 hours. This is an open label, pilot, feasibility study.

Potential benefits include treatment of depression and/or depressive symptoms. Other potential benefits include additional monitoring of symptoms. Participants can continue their regular care (most medications, therapy, etc.) in addition to participating. Potential risks include mild discomfort, headaches, or scalp pain around the treatment area. Other potential risks include breach of confidentiality, though we take all measure to protect you and your child's information. Safety information known thus far resembles that of adults. iTBS has shown to be an effective treatment for adults with treatment resistant depression.

There is no cost to participate. There is a low risk of seizure from receiving iTBS. This is described more thoroughly in the section of this consent form titled "What are the possible risks or discomforts involved from being in this study?"

What are some general things you and your child should know about research studies?

You are being asked to allow your child to take part in a research study. To join the study is voluntary.

You may decide to not allow your child to participate, or you may withdraw your permission for your child to be in the study, for any reason, without penalty. Even if you give your permission, your child can decide not to be in the study or to leave the study early.

Research studies are designed to obtain new knowledge. This new information may help people in the future. Your child may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your or your child's relationship with the researcher, the health care provider, or the University of North Carolina-Chapel Hill. If your child is a patient with an illness, your child does not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you and your child understand this information so that you and your child can make an informed choice about being in this research study.

You will be given a copy of this consent form. You and your child should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this research study is to learn if Intermittent Theta Burst Transcranial Magnetic Stimulation (iTBS) can be used on adolescents for the treatment of depression, as it is currently used for adults. This procedure is not FDA approved in children. This is an open label, pilot, feasibility study. That means we will be looking at safety and tolerability of iTBS. We will use this data to potentially research a larger number of participants in the future if there is evidence that iTBS helps subjects with depression in this study. So far, data shows that safety data for minors is similar to that of adults. We will be tracking and evaluating changes in depression, monitoring effects of iTBS on any suicidal ideation or non-suicidal self-injury impulses, and examining duration of effect of this treatment (in other words if the change in symptoms, if any, last through our follow-up visits). We will also be examining safety and side effects at each study visit. This is an open label study, meaning everyone participating will receive iTBS treatment in addition to their regular care. We will be using questionnaires to evaluate treatment outcomes and safety. In addition, other safety, medical, and cognitive testing will be done to evaluate outcomes and ensure safety.

Transcranial Magnetic Stimulation (TMS) has been used to treat depression in adults for years and is FDA approved. However, there are fewer options for treatment of depression for kids and adolescents. We aim to provide an alternate treatment for depression with this study. iTBS is like TMS, but sessions are 3 minutes instead of 37 minutes long. iTBS is FDA approved for adults with treatment resistant depression.

iTBS is a type of TMS. TMS works by using a treatment coil to send an electromagnetic pulse into a specific region of the brain. Research shows that for depression, the electromagnetic pulse should be sent to the left-dorsolateral-prefrontal cortex (DLPFC) region of the brain. The DLPFC connects to other brain areas to form a circuit, and when this circuit does not work well, people develop major depression. The electric pulse will only go 2-3 centimeters into the brain under where the treatment coil is placed. The result of the electric pulse is a change in the electrochemical activity of the brain cells. Since depression is thought to be a result of an imbalance of chemicals in the brain, TMS can work to restore this balance. Various types of TMS use various frequencies of electromagnetic pulses, for a various amount of time. iTBS,

which will be the type of TMS used in this study, uses electromagnetic pulses that are similar to the theta-frequency waves already present in the brain, for close to 3 minutes. Adult studies have shown that iTBS is non-inferior to repetitive slow wave TMS, which means that in adults iTBS works as well as a type of TMS that has been FDA approved for a longer time. We are using iTBS as the treatment lasts 3 instead of 37 minutes, which we feel will lead to easier treatments and less side-effects. iTBS uses stimulation that looks like theta waves, naturally occurring electrical signals in the brain.

Your child is being asked to be in the study because he or she is seeking treatment for depression and may be eligible to participate.

Are there any reasons your child should not be in this study?

Your child should not be in this study if they have any of the criteria listed below:

- Past or current diagnosis of bipolar disorder, psychosis, seizures, or traumatic brain injury.
- Presence of intracranial metallic implants or fragments, which is a contraindication for TMS.
- Current diagnosis of substance abuse, eating disorder, PTSD, or intellectual disability.
- Current imminent suicide ideation or other clinical reasons for inpatient psychiatric hospitalization.
- Currently pregnant.
- Any reason the investigator determines may cause noncompliance with study rules or is unfit for receiving treatment.
- Currently taking benzodiazepines, certain antipsychotics, antidepressants, or stimulants, for 7 days prior to screening. Medications will be reviewed by a licensed study team investigator.
- Any positive drug testing from a urine drug test unless medically indicated with a valid prescription.

*Those with marijuana/cannabis positive results may retest at a later date if they do not meet criteria for substance abuse at screening and agree to refrain from use for the duration of study participation. Decision to be made by Investigator discretion.

How many people will take part in this study?

Approximately 5 people at this institution will take part in this study.

How long will your child's part in this study last?

Participation lasts 16-17 weeks total. There are 3 different phases of the study. A screening phase will typically last 2-4 hours over the course of one visit. However, we will allow screening period to last up to 1 week to ensure eligibility. The treatment phase includes iTBS treatment Monday-Friday for 4 weeks. This is a total of 20 treatment sessions. Treatment sessions should only last 20 minutes or less, while the actual iTBS lasts 3 minutes. Once per week during the treatment phase, we will do additional examinations and questionnaires, which will make the study visit last longer, about 1-2 hours. There are 3 planned follow-up visits. These will happen 1 week, 4 weeks, and 12 weeks after the last treatment day, and will be about 1-2 hours long each visit. There is a total of 24 study visits planned for participation. If needed, we can create an “unscheduled” safety visit should concerns arise that may be related to the study. Please see the next section for more detail about what happens at each study visit.

What will happen if your child takes part in the study?

Screening visit: (2-4 hours, up to 1 week)

- Informed consent and assent for study participation with an investigator.
- A clinical interview and confirming depression diagnosis.
- A neurological exam and consultation by a trained clinician.
- The following scales will be administered:
 - o Diagnostic: A SCID-5 interview for diagnosis of major depression and rule out exclusionary psychiatric disorders.
 - o Efficacy scales to establish a baseline:
 - Children's Depression Rating Scale Revised (CDRS-R): a commonly used questionnaire to evaluate level of depression.
 - Hamilton Depression Rating Scale (HAM-D): a commonly used questionnaire to evaluate level of depression.
 - o Cognitive / Safety: also used for baseline:
 - Mini Mental Status Exam, Trails B and List Generation: brief assessments to evaluate cognitive functioning.
 - Columbia Suicide Severity Rating Scale (C-SSRS): evaluates suicidality for safety.
 - A semi-structured interview and questionnaire for self-harm behavior evaluation.
 - Self-Injurious Thoughts and Behavioral Interview (SITBI): evaluates self-harm behavior and thoughts.
 - A medical review of symptoms, metallic implants, general medical history, and medication review. This includes a physical exam, vital signs (temperature, respiratory rate, blood pressure, heart rate, oxygen saturation), urine pregnancy test for females of childbearing potential (meaning has begun menstruation), and a urine drug screen test. Urine samples will be immediately discarded after use. We will also ask to speak with your child's regular provider.

Subjects must pass our screening phase in order to be eligible to participate.

Treatment Phase: (20 visits, Monday-Friday)

- Establish motor threshold by a trained clinician. This is done prior to receiving iTBS.
- 20 iTBS treatments by a trained clinician. iTBS treatment lasts 3 minutes.
- Once weekly, we will use cognitive, safety, and efficacy scales listed above in "screening" section to evaluate progress of the patient's treatment.
- Every visit will include a medical review of symptoms by a trained clinician and review of medications.

Follow-up Phase: (3 visits)

- These will occur once at 1 week, 4 weeks, and 12 weeks after the last iTBS session.
- Cognitive, safety, and efficacy assessments and questionnaires (listed in "screening" section) will again be used to evaluate duration of treatment effect and safety. The last follow up visit will also include a patient/caregiver satisfaction questionnaire.
- Medical review of symptoms, a physical exam, vitals, and medication review will occur.

For any questionnaires used, participants and parents may choose to not answer any questions without reason. However, if enough information to determine safety for iTBS participation is unable to be collected, this may require study withdrawal per investigator discretion.

At any time during the course of study participation, per investigator discretion, we may perform additional urine pregnancy tests or urine drug screen tests for immediate safety concerns. In addition, we can also make “unscheduled” safety visits for a medical, cognitive, and safety evaluation should there be concerns about receiving iTBS.

We ask all participants to refrain from drinking alcoholic beverages or using drugs not prescribed by a doctor during participation of the study. Participants who drink alcohol, use any drugs not prescribed by a doctor, or think they may be pregnant must immediately inform the study doctor.

The name of the clinician responsible for patient safety during this study is the Principle Investigator, Dr. Shahzad Ali, M.D. His contact information is listed on the first page of this document.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. The benefits to your child from being in this study may be a reduction in depressive symptoms. The additional follow-up and monitoring may seem therapeutic for some participants. It is possible this treatment may not cause direct benefit to your child.

What are the possible risks or discomforts involved from being in this study?

There may be uncommon or previously unknown risks. You should report any problems to the researcher.

Pregnancy tests will be done on all females who might be able to get pregnant at the start of the study. This is paid for by the study. We do not know if TMS effects on fetal development, pregnancy, delivery or infant health. Studies of TMS treatment in just a few pregnant women do not show any problems with fetal development during pregnancy, delivery or infant health, but there could be TMS effects not yet discovered. So, we are not including pregnant women in this study. A pregnancy test will be performed at screening and will be repeated if we become concerned that your child is pregnant. If your child does become pregnant during the study, your child will have to be withdrawn from the study, but the study doctor will discuss other treatment options with you and your child to ensure proper continuation of care.

The potential risks and discomforts involved from being in this study are listed below:

Breach of confidentiality: With all research, there is a potential for breach of confidentiality. With stigma regarding mental illness, broken confidentiality regarding diagnosis and treatment may cause embarrassment or discrimination.

Side effects: iTBS is new for adolescents and kids. So far, however, safety data is extremely similar for that of adults. We looked at current safety data for iTBS used in anyone under 18 years old. The below information summarizes safety data.

- Mild side effects that are brief and resolve on their own without intervention (headaches, local discomfort, pain, tingling, dullness, scalp pain, nausea, loss of appetite, change in hearing, neck stiffness, finger twitching, fatigue, musculoskeletal problems) : 9-12.4 % of participants
- Moderate side effects (headaches, ringing in ears, neurocardiogenic syncope) : 1.3%
- Serious side effects (seizures): 0% in kids treated with iTBS in studies performed so far. The risk for seizure increases if someone has central nervous system disorders or history of epilepsy. In regular Transcranial Magnetic Stimulation (TMS), the risk is .06%

If you choose not to give permission for your child to be in the study, what other treatment options does your child have?

Your child does not have to be in this research study in order to receive treatment. The other procedures or treatments that are available include medications, therapy, a combination of both, and ECT. Please ask the study doctor if you have questions about these.

What if we learn about new findings or information during the study?

You and your child will be given any new information gained during the course of the study that might affect your willingness to continue your child's participation in the study.

How will information about your child be protected?

Our study team will only discuss your child's participation in private, clinical environments. In addition, all electronic communication will be through encrypted and secure means. Any paper documentation will include a subject ID number that will not include Protected Health Information (PHI). There will be a key that links ID numbers to PHI. All study documentation will be kept in a locked cabinet/ closet in a locked office in a secure building. Only study staff will have access to this information on a need-to-know basis. Per regulations, we are required to keep study materials up to 6 years before documents are destroyed. It is possible research collaborators such as statisticians may have access to PHI during data analysis. However, all effort will be made to remove PHI and minimize PHI exposure to these persons.

Participants will not be identified in any report or publication about this study. We may use de-identified data from this study in future research without additional consent.

Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your child's information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

A copy of this consent form will go in to your child's medical record. This will allow the doctors caring for your child to know what study medications or tests he/she may be receiving as a part of the study and know how to take care of him/her for other health problems or needs during the study.

By signing this informed consent document, you agree that some of the information generated by your child participating in this study and/or a copy of the consent form may be included in your child's medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to your child. This will allow the doctors caring for your child to know what study medications or tests they may be receiving as a part of the study and know how to take care of them if they have other health problems or needs during the study. Additionally, the information may be shared with their medical insurance plan if the research services provided are billed to insurance.

You will be asked to sign a separate form ("HIPAA Authorization") to allow researchers to review your medical records.

What will happen if your child is injured by this research?

All research involves a chance that something bad might happen to your child. If your child is hurt, becomes sick, or develops a reaction from something that was done as part of this study, the researcher will help your child get medical care, but the University of North Carolina at Chapel Hill has not set aside funds to pay you or your child for any such injuries, illnesses or reactions, or for the related medical care. Any costs for medical expenses will be billed to your child, you, or your insurance company. You/your child may be responsible for any co-payments and your child's insurance may not cover the costs of study related injuries.

If you think your child has been injured from taking part in this study, call the Principal Investigator at the phone number provided on this consent form. They will let you know what you and your child should do.

By signing this form, you/your child do not give up your right to seek payment or other rights if your child is harmed as a result of being in this study.

What if you or your child wants to stop before your child's part in the study is complete?

You can withdraw your child from this study at any time, without penalty. The investigators also have the right to stop your child's participation at any time. This could be because your child has had an unexpected reaction, or has failed to follow instructions, has not provided enough information to the study team to evaluate safety (refusing to answer certain questions), or because the entire study has been stopped.

If you withdraw your child or your child is withdrawn from this study, all data collected up until the point of withdrawal will be retained, however no additional information will be collected

unless you provide additional written permission for further data collection at the time of your child's withdrawal.

If your child withdraws from the study, or the study stops, we ask to complete a termination visit to ensure proper follow up and safety. This may include efficacy, cognitive, and safety assessments, as well as a medical review. We will ensure proper follow-up care is obtained. This termination visit is optional.

Will your child receive anything for being in this study?

Your child will not receive payment for being in this study. On an as needed basis the study team has set aside funds to assist with transportation. Any payment provided for participation in this study may be subject to applicable tax withholding obligations.

Will it cost you anything for your child to be in this study?

If you allow your child to enroll in this study, you or your child will not have to pay to participate. We have allocated a set amount of funds to cover the cost of anticipated expenses below:

Transportation and parking: Research visits are planned to occur at our outpatient clinic where there is free parking. However, screening, follow-up, and unscheduled visits may occur at the main hospital on campus. We have set aside funds to reimburse for this parking cost. If subjects have unique situations that require other assistance for other transportation costs, the study team will do everything we can to allow participation and cover these expenses for you. It is your responsibility to discuss this with the study team immediately if you anticipate assistance needed for transportation-related costs.

It will not cost anything extra to be in this study. However, you will be billed for your child's routine medical care. All tests, visits or procedures other than what is done for this study will be related to medical care that is part of the usual care for your child's condition. These would be suggested even if you decided not to allow your child to be in the research study. Here are some examples of routine medical care that may be performed within this study: psychotherapy, medication management, clinic visits with your child's other providers, etc..

What if you or your child have questions about this study?

You and your child have the right to ask, and have answered, any questions you may have about this research. If there are questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, contact the researchers listed on the first page of this form.

A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S.

Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if there are questions about your child's rights as a research participant?

All research on human volunteers is reviewed by a committee that works to protect your child's rights and welfare. If there are questions or concerns about your child's rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Parent's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily give permission to allow my child to participate in this research study.

Printed Name of Research Participant (child)

Signature of Parent

Date & Time

Printed Name of Parent

Signature of Research Team Member Obtaining Permission

Date & Time

Printed Name of Research Team Member Obtaining Permission

Signature of Witness (if applicable; e.g. literacy issues, visually impaired, physically unable to sign, witness/interpreter for non-English speaking participants using the short form)

Date & Time

Printed Name of Witness