Study Title: Repetitive transcranial magnetic stimulation as treatment for acute suicidality in adult patients

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PROTOCOL SUMMARY

Suicide was responsible for almost 40,000 deaths in 2011 in America. It is still singularly difficult to predict who is going to commit suicide and how to establish adequate interventions. Growing evidence supports the view that suicide is associated with poor decision making. Suicide is hypothesized to be triggered by stressful situations that create overwhelming psychological pain in an individual who chooses to terminate his/her own life, disregarding all future consequences. We have previously demonstrated rewarding impulsive choice common to both recent suicide attempters and suicidal depressed patients (1). Consistent with these findings, we hypothesize that high frequency repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal cortex will improve impulsive response tendencies as measured by the delay discounting procedure, and this in turn will be associated with a faster resolution of suicidal ideation. To these effects we will be using a randomized control trial of rTMS in adult inpatients at the Psychiatric Research Institute hospitalized for acute suicidality. At the conclusion of these studies, we will have tested the value of decision making in the development of suicide ideation and behavior, as well as piloted the use of rTMS in the treatment of these patients.

BACKGROUND AND RATIONALE

The proposed study seeks to improve the prevention of suicide by advancing our understanding of the neurobiology of suicide by using a randomized control trial of repetitive transcranial magnetic stimulation (rTMS) as a hypothesis driven intervention for acute suicidality. In 2010 suicide was responsible for more than 38,364 deaths in the United States and 447 in the state of Arkansas (2). Suicide represents the 10th leading cause of death in this country, and claims more deaths than chronic liver disease, hypertension, Parkinson's disease or homicide. Furthermore, suicide consequences extend beyond the termination of an individual's life to impact those that are left behind. These statistics are far more alarming because they are believed to be underestimates, with substantial numbers of suicides and suicide attempts undetected or misclassified. The high and rising prevalence of suicide is complicated by the clinical challenge of identifying those patients at highest risk for suicide. A variety of biological, psychological and social risk factors for suicide have been identified. However, we currently lack reliable predictors of suicide risk and must rely heavily upon self-report and clinical judgment. Thus, it remains singularly difficult to predict who is going to commit suicide. Therefore, there is an urgent unmet need to develop effective early detection methods and treatments for high-risk populations.

Suicide has been described as "a permanent solution to a temporary problem" (3), reflecting the view that suicide is the result of poor decision making. The strongest biological finding in suicide research is the association with reduced serotonergic neurotransmission, particularly within the ventromedial prefrontal cortex (VMPFC) (4). This deficit in serotonergic neurotransmission is thought to impair cognition, predisposing patients to become more impulsive, rigid in their thinking, and poorer decision makers. Decisions during depressed states are tainted by negative affect and distorted negative cognitions (5). However, suicide has been associated with cognitive impairments that go beyond those of depression. Asymptomatic patients with a history of suicide attempts exhibit significant cognitive deficits suggestive of generalized prefrontal cortex (PFC) dysfunction (6, 7), and corollary disruptions in risk assessment (8). Poor inhibition is found in suicide attempters when compared with patients with only suicidal ideation (9), and greater cognitive impairments are found in depressed patients with suicidal ideation compared to those without it (10). It is possible that cognitive deficits may be specific to suicidal behavior rather than to any comorbid or specific psychiatric diagnosis because this observation holds true for suicidal patients with depression, bipolar disorder, and even temporal lobe epilepsy. However, most of these studies were performed in symptom-free patients, often months or years after the presence of suicidal ideation or behavior. In a previous report (1) we demonstrated that inability to delay gratification (choosing smaller immediate rewards over larger delayed rewards) is shared by both recent suicide attempters and depressed patients with suicidal ideation. On a follow up assessment, 5-10 days after the suicide attempt, reduction of suicidal ideation and intent was correlated with decreased symptoms of depression

and recovery of delayed gratification impairments (1). These data are congruent with the hypothesis that stressful situations in combination with a biological and psychological predisposition may create a critical climate of overwhelming psychological pain in an individual who chooses an impulsive escapist strategy to terminate his/her own life discounting all future outcomes (11). However, the underlying neural mechanisms remain unknown and therefore not amenable to therapeutic interventions.

TMS is a noninvasive method to cause depolarization or hyperpolarization in the neurons in the brain using electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field. TMS is a novel intervention developed in the field of neurology that has been used in the treatment of patients suffering from migraine, stroke, Parkinson's disease, tinnitus and depression. In healthy subjects, high frequency rTMS over the left DLPFC has been shown to alter impulsive choice behavior (to decrease delay discounting) in healthy individuals and in smokers (12). On the other hand, a trial of TMS by one of the leaders in the field has shown it to be safe and well tolerated in recent suicide attempters suffering from depression with comorbid post-traumatic stress disorder and traumatic brain injury (13).

UAMS investigators have used repetitive transcranial magnetic stimulation (rTMS) to understand and treat phantom sound perception in subjects with tinnitus and to examine risky choices and impulsive behaviors using delay discounting in smokers. We propose to replicate a randomized controlled trial of rTMS over 3 days in a sample of well characterized acutely suicidal inpatients.

Our overall hypothesis is that 10 Hertz rTMS of the left dorsolateral prefrontal cortex (DLPFC) will correct impulsive choice behavior deficits found in acutely suicidal patients that in turn will translate into faster resolution of acute suicidal ideation. The current proposal will expand our understanding of the neurobiology of suicidal behavior by examining a potential neurocognitive mechanism of acute suicidality and test the value of rTMS as intervention for acute suicidal behavior. The current proposal will utilize behavioral assessments and rTMS in a randomized controlled trial in a group of adult patients hospitalized: a) following a recent suicide attempt with persistent suicidal ideation, or b) for severe suicidal ideation (n=20). To meet this goal we plan to recruit up to 28 individuals. Specifically, we propose:

The primary objective/endpoint of this study is safety. Adverse events will be collected throughout the duration of the trial. Any subject that meets the criteria for withdrawal (*Safety Assessments, page 14)* will be withdrawn from the study. The study will be stopped and all subjects withdrawn if two completed suicides by subjects receiving TMS occur during the active TMS treatment.

SA1. Determine the safety of repetitive transcranial magnetic stimulation (rTMS) in depressed patients with severe suicidal ideation.

Hypothesis 1: Given studies of rTMS for clinical depression, we predict that rTMS in patients with severe suicidal ideation will be well tolerated and not associated with significant side effects.

SA2. Determine the effect of rTMS on delay discounting on depressed patients with severe suicidal ideation.

Hypothesis 2: In depressed patients with severe suicidal ideation the rTMS active will reduce impulsive choice behavior (measured as delay discounting) compared with the non-treatment group

SA3. Determine the effect of rTMS on suicidal ideation on depressed patients with severe suicidal ideation.

Hypothesis 3.1: In depressed patients who had recently attempt suicide the rTMS active group will reduce suicidal ideation severity (measured by the Beck Scale for Suicidal Ideation) compared with the non-treatment group

Hypothesis 3.2: Suicidal ideation in depressed patients who recently attempt suicide will vary in function of

delay discounting.

SA4. Identification of biomarkers of positive response to rTMS in depressed patients with severe suicidal ideation.

Hypothesis 4: A composite of serum hormonal and inflammatory markers will predict positive response to rTMS in depressed patients with severe suicidal ideation.

Significance

Achieving the goals of this proposal will provide understanding of the neurobiological mechanisms of suicidality and proof of concept for the use of rTMS as adjunctive treatment for acute suicidality. This new knowledge would lead prospective studies testing the clinical value of rTMS to improve impulsive choice behavior to reduce suicide behavior in persons at high risk.

STUDY DESIGN AND PROCEDURES

Experimental design

A double blinded randomized controlled trial with assignment to active rTMS experimental treatments or sham will recruit adult patients (18-60 years old) of both genders voluntarily admitted to the PRI inpatient units following a recent suicide attempt with persistent suicidal ideation or because of severe suicidal ideation.

Recruitment/Screening: The patient population will be recruited from the 30-bed inpatient units at the PRI at UAMS. At least one member of our research team will be present during each day's morning report held at 7:45 am. Generally, in our inpatient unit, as new patients are admitted daily, their cases, specifically the circumstances surrounding the hospital admission are reviewed during the morning report meeting. At this time, the unit's psychiatrist(s) will discuss patients admitted within the past 24 hours for a recent suicide attempt or suicidal ideation and will provide our research team member with the names of potential eligible cases.

Potential research subjects will have an initial psychiatric interview with the inpatient treatment team for purposes of diagnosis and developing a treatment plan, as per standard procedures of the inpatient psychiatric unit. During the clinical psychiatric interview, the clinical staff will have gathered information that would generally indicate whether patient would be a candidate for this study. The clinical staff member conducting the initial interview will ask appropriate patients for approval to be approached by research staff. After the completion of the initial psychiatric interview with the patient, our research team member (PI, research nurse or study coordinator) will approach the patient to invite him/her to participate in a brief (15 minutes) interview.

During this interview, we will review the consent form and study procedures with the subject and complete the Informed Consent Capacity Checklist. Following consent, for those patients who meet inclusion and not exclusion criteria, their basic demographic and clinical information (past psychiatric history, past medical history, current diagnoses) will be collected. Next, the following assessments shown in Table 1 will be completed. Within these assessments, we will include pressure pain threshold which recent preliminary data have shown has been associated with acutely suicidal behavior. Hence, we include the pain threshold to attempt to measure severity of suicidality. The Young Mania Rating Scale (YMRS) was suggested by the FDA in order to monitor potential development of mania as consequence of treatment for depression, which may include active rTMS. The Delis–Kaplan Executive Function System (DKEFS) was added as a measure of verbal fluency to further control for cognitive effects of rTMS, as requested by the FDA. Lastly, a blood sample (equivalent to 6 teaspoons) will be collected by the research team. The samples will be centrifuged, serum isolated, and stored at -80 C in the freezers on PRI fourth floor until further processing. These samples will be used to identify biomarkers predictors (hormones (i.e. cortisol, testosterone, luteinizing hormone, and follicle stimulating hormone) and inflammatory markers (i.e. C reactive protein, interleukin 1, 2, 6 and 10, and tumor necrosis factor)) of positive response to rTMS.

Table 1. Assessments to be administered during the proposed study

Task	Administration time	Description
Columbia Suicide Severity Rating Scale (C-SSRS)	Approx. 10 min	Classification system that utilizes definitions of suicidality derived from empirical findings on the phenomenology of suicidality and identified predictive and risk factors (14)
The Hamilton Rating Scale for Depression (HAM-D)	Approx. 10 min	17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety (15)
Hamilton Anxiety Rating Scale *(HAM-A)*	Approx. 10 min	14 item widely used and well-validated tool for measuring the severity of a patient's anxiety (16)
Beck Scale for Suicidal Ideation	Approx. 5 min	21-item self-report questionnaire that may be used to identify the presence and severity of suicidal ideation. Items on this measure also assess the respondent's suicidal plans, deterrents to suicide, and the level of openness to revealing suicidal thoughts (17)
Beck Hopelessness Scale	Approx. 5 min	20-item scale that measures three major aspects of hopelessness: feelings about the future, loss of motivation, and expectations(18)
Delay discounting task	Approx. 5 min	Decision-making task in which subjects are presented a series of trials in which they will choose between a set of hypothetical rewards or losses to be received in variable time spans. Smaller sooner (SS) hypothetical reward/loss ($X) received today or a larger later reward/loss (LL) ($1000) received at a future delay (1wk, 1mo, 6mo, 1yr) (19)
N-Back Test	Approx. 5 min	N-back task. It is a computer based task is a non-verbal test of working memory, a cognitive process that generally facilitates other cognitions, which is correlated with strong lateral prefrontal cortex activity (20).
Stroop Test	Approx. 5 min	This computerized brief task, applicable for ages 15-90, is designed to measure conflict processing as a standard measure in neuropsychological assessment. (21).
Trail making A and B	Approx. 7 min	Timed measure of visual scanning ability and psychomotor speed that requires subjects to connect numbers in order. The measure used is the time, in seconds, to complete the task. Trail Making Part B is similar to Part A but is a more challenging task because it requires subjects to connect consecutively

		numbered and lettered circles by alternating between the 2 sequences. The measure used is the number of seconds to complete the test (22)
Pressure pain threshold	Approx. 3 min	Subjects will be placed supine. A point five inches below the patella in the medial border of the tibia will be identified in both sides. Pressure will be applied using a digital force gauge with a 1-cm^2 rubber tip (J-Tech Medical, Commander Algometer or equivalent) alternately to the left and the right tibia for a total of three times each. Participants are instructed to verbally report when their sensations change from pressure to pain.
Visual Analog Scale	Approx. 10 min	A custom developed Visual Analog Scale (VAS) questionnaire will be administered on a laptop computer pre and post each treatment session. Subjects are asked to rate their treatment experiences using the following descriptors: happy, irritable, angry, excited, confused, calm, sad, anxious, nervous, bored, relaxed, tired, distracted, discomfort, and suicidality (13) VAS scores are converted to a scaling of 0-99 points.
Sham validating measure	Approx. 2 min	Subjects are asked two questions regarding their perception of receiving treatment or placebo.
MINI International Neuropsychiatric Interview (MINI)	Approx. 30 min	Structured clinical interview for DSM-IV and ICD-10 psychiatric diagnoses. It is fully validated and is a more time-efficient alternative to the SCID.
Young Mania Rating Scale	Approx. 10 min	Used to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours.
Delis-Kaplan Executive Function System (DKEFS) Verbal	Approx. 3 min	A verbal fluency test that measures spontaneous production of words belonging to the same category or beginning with some designated letter.

C-SSSRS, HAM-D, HAM-A, MINI and other rating scales will be administered by a trained member of the research team.

Randomization

A predefined, computer-generated randomization sequence will assign participants in a 1:1 ratio to active vs. sham rTMS groups using a block size of 6. This sequence assignment will occur prior to the initiation of the study. Following completion of baseline assessments each subject will be assigned a sealed envelope with X or Y which will stand for active or sham stimulation.

The blind will be broken following completion of data gathering and analysis.

TMS

A NeuroStar TMS Therapy System and NeuroStar XPLOR Clinical Research System coil system (Neuronetics, Malvern Pennsylvania) will be used to deliver stimulation. The manuals for the stimulator and

coils are on file in the Office of Research Regulatory Affairs (ORRA) at UAMS. The NeuroStar TMS Therapy System has been cleared by FDA to treat major depressive disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode. It will be used in this study in conjunction with the NeuroStar XPLOR Clinical Research System to stimulate neurons in left prefrontal cortex in order to decrease suicidal ideation. The NeuroStar XPLOR Clinical Research System is not approved by the FDA.

After randomization each subject will be randomly assigned to an active or sham treatment. Both active and sham coils will be unmarked and appear identical. An open label coil will be used to determine a subject's motor threshold using the parameter estimation with sequential testing (PEST) algorithm and visible movement in the right hand (23-25). The characterization subject's motor threshold will indeed be adjusted in an individual basis by consultation between the PI and Dr. Prasad Padala, who is co-investigator and the director of the VA TMS laboratory, in the eventuality of changes in medications or in the neurological status that could affect seizure threshold.

For treatments, subjects will be seated in a semi-reclined chair. This chair will be located on the fourth floor of the Psychiatric Research Institute on the UAMS campus.

Active experimental treatment

Repetitive TMS (rTMS) will be delivered to the left PFC, defined as a location 6 cm (cm) anterior to the right hand motor thumb area. A research nurse will deliver the treatments. rTMS will be delivered with a figure-eight coil at 120% motor threshold, 10 Hertz (Hz), 5 s (s) train duration, 26 s intertrain interval for 50 min (6000 pulses) 3 times daily for 3 days (total 9 sessions, 54,000 stimuli). Similar parameters were previously used in a population of acutely suicidal veterans and military patients with even more severe comorbidity than our proposed sample because of comorbid posttraumatic stress disorder and traumatic brain injury without significant adverse effects (13). Variations will be allowed in the dosing schedule to accommodate the patient's inpatient schedule and staffing needs, with at least 1 hour between sessions. Treatments will be done on consecutive days, with the goal to deliver 9 sessions over three days. Adverse events will be assessed at each treatment session as well as daily. Prior to and then immediately after each rTMS session, subjects will complete visual analog scales (VAS) on a laptop computer located next to the rTMS chair. Patients will wear earplugs and will not be allowed to sleep. Counseling or other conversation during treatment will be discouraged.

Sham treatment

Parameters for sham rTMS are identical to those for active stimulation except that aluminum plate blocks the propagation of a magnetic field. The sound and physical sensation is the same as with the active coil while been biologically inactive.

Assessments

Trained and blinded study staff (raters) will administer assessments as described in Table 2. Additionally, menstrual cycle phase will be characterized for female subjects (i.e. date of last period, regularity of menstrual cycle).

Table 2. Assessments administration schedule during the proposed study						
Task	Intake & Pre rTMS Session 1 (day 1)	Pre rTMS Session 1 (day 2 & 3)	Post rTMS Session 3 (day 1 & 2)	Post rTMS Session 3 (day 3)	Before Discharge	3 & 6 month follow-up
Informed Consent Capacity Checklist	X					
Informed consent	X					
Demographic Data Form	X					
Columbia Suicide Severity Rating Scale (C- SSRS)	X				X	X
Hamilton Rating Scale for Depression (HAM-D)	X			X	X	X
Hamilton Anxiety Rating Scale (HAM-A)	X			X	X	X
Beck Scale for Suicidal Ideation	X			X	X	X
Beck Hopelessness Scale	X	X	X	X	X	X
Delay discounting task	X	X	X	X	X	X
N back test	X	X	X	X	X	X
Stroop Test	X	X	X	X	X	X
Young Mania Rating Scale	X	X	X	X	X	X
DKEFS Verbal Fluency Test	X	X	X	X	X	X
Pressure pain threshold	X	X	X	X	X	X
Sham validating measure				X		
Trail making A and B	X	X	X	X	X	X
Visual Analog Scales**	X	X	X	X	X	X
MINI International Neuropsychiatric Interview (MINI)	X					
Randomization	X					

** This assessment will be collected 3 times per day pre and post rTMS.

Safety Assessments

Research staff will use the MedDRA System Organ Class (SOC) and preferred term (PT) to document adverse events, which will be assessed at each treatment, and at follow-up visits.

This protocol will not modify patient care and our visits will not interfere with regular clinical care, except in the case of imminent danger to the patient or others in which appropriate measures will be taken, like contacting the primary treatment team and placing the patient on 1:1 observation until evaluation by the primary team.

STUDY POPULATION

Participant recruitment will occur at the inpatient units at the Psychiatric Research Institute (PRI). Target sample size is 20, which will be randomized into active or sham groups (1:1). Considering 40% attrition rate we plan to recruit 28 participants.

Recruitment: Recruitment will be facilitated by the PI's role of PRI inpatient attending physician. The success of this proposal depends heavily on the ability to recruit patients very soon after hospitalization for

suicide ideation or behavior.

All participants will be compensated $40 for their participation in each of the 3 rTMS sessions of the active phase of the study and the 2 follow-up sessions. Participants can earn a total of $200 for completing the entire study, including both follow up visits.

Inclusion Criteria

a) Age 18-60 years, of all races and ethnicities;
b) Admitted voluntarily to the adult psychiatric inpatient at PRI;
c) Suffering from a current depressive episode as defined by the DSM-V
d) Currently have diagnoses of major depressive disorder
e) Reason for hospitalization should be a recent suicide attempt or suicidal ideation
f) Current severe suicidal ideation defined by a score >7 in the Beck Scale for Suicidal Ideation
g) Must pass the TMS safety checklist (TASS)
h) Women of childbearing age must have a negative result on a pregnancy test
i) Ability to read, write and speak English.

Exclusion Criteria

a) History of dementia, neurovascular or neurodegenerative conditions
b) Physical disabilities that prohibit task performance (such as blindness or deafness)
c) Patients must not have increased intracranial pressure, which may increase seizure susceptibility.
d) Implanted medication pumps of any type
e) Intracardiac lines
f) Significant heart disease, defined as heart disease that causes moderate to severe symptoms and/or is characterized by moderate to severe pathology, including a recent history of myocardial infarction and heart failure with an ejection fraction of less than 30% or with a New York Heart Association Functional Classification of Class III or IV.
g) Choosing to opt out of the research study.
h) Additional exclusion criteria for rTMS include the following:
    i. a personal history or 1st degree relative with history of epilepsy ;
    ii. a personal history of head injury, aneurysm, stroke, previous cranial neurosurgery, neurological, or migraines;
    iii. recent use of cocaine or alcohol;
    iv. ferromagnetic metal implants in the head or neck, active or inactive implants(including device leads), deep brain stimulators, cochlear implants or vagus nerve stimulators;
    v. a pacemaker;
    vi. pregnancy (or the possibility of pregnancy);
    vii. Medications that lower seizure threshold (bupropion or tricyclic antidepressants, such as thorazine, clozapine, amitriptyline, amoxapine, Norpramin, Sinequan, Tofranil, Pamelor, Vivactil, or Surmontil). Other antidepressant and antpsychotic medications have been deemed exhibit a relatively low seizurogenic potential (Pisani et al. 2002).
    viii. Patients taking a medication for weight loss and depression called bupropion (Wellbutrin) they will be excluded because it may increase the likelihood of experiencing a seizure.

Of note, patients on a current depressive episode with a diagnosis of bipolar disorder will be eligible to participate in this study for several reasons. Many patients suffering from depression are not diagnosed with bipolar until an eventual manic episode. Bipolar disorder by itself has not been associated with higher risk for seizures. Many patients with major depression or bipolar depression receive antipsychotics not only for psychotic symptoms but also as adjuvant treatment. Lastly,

approximately half of hospitalized depressed patients are eventually diagnosed with bipolar disorder. Excluding this population not only hinder recruitment seriously but also would affect the generalizability of our results.

RISKS AND BENEFITS

Potential Risks

Risks Associated with TMS

A variety of potential risks of TMS have been identified during the last decade. The risks are not necessarily different for normal subjects and depressed patients; however, the risks for normal control subjects are lower than for clinical populations like in this study primarily because normal subjects only receive two days of active rTMS (versus 3 in our patients) and, secondarily, because normal subjects are not taking medications like depressed subjects. Procedures for minimizing these risks have been established (26). The following risks have been identified:

Likely: Subjects may feel anxious about participation. This typically abates after the first one or two sessions. Subjects may experience minor discomfort associated with scalp muscle twitching. Subjects typically tolerate the discomfort better as session's progress. The coil position is adjusted if pain occurs and stimulus intensity is reduced if pain persists.

Less likely: Head and neck pain related to stimulation of underlying muscle and nerves occurs in approximately 10% of subjects. The incidence and severity is a function of stimulus site and intensity but is most common over frontal-temporal regions. The symptoms are typically limited to the time of stimulation and can be treated with minor over-the-counter analgesics if necessary. A subject's symptoms could worsen (27). When this has happened, in subjects with tinnitus for example, their symptoms returned to a normal level after stimulation stopped. Occasionally, subjects have reported an increase in tinnitus followed by a reduction in tinnitus with subsequent treatment (28).

Rare: The following have rarely been identified:

1. Seizures: Seizure induction represents the most serious known risk of TMS (26). Seizures have been reported more frequently in subjects with brain lesions (e.g., stroke) but have rarely been reported in subjects with no history of seizures or neurologic disease. When seizures have been reported, they were almost exclusively in association with a stimulation frequency >1 Hz. Based on an extensive review of the literature, guidelines have been developed that specify the number of stimulations that may safely be given as a function of stimulus intensity (% of Motor Evoked Potential [MEP]) and frequency of stimulation (29). Using these guidelines, there have been few published reports, to our knowledge, of seizures or evidence of after discharge or spread of excitation in normal subjects receiving repetitive TMS who did not have an identified risk factor that is exclusionary for our study (26). We propose to adhere to the published guidelines. Furthermore, as subjects with a history of seizures are more likely to experience seizures due to TMS, these subjects will be excluded.
2. Effects on Cognition: A number of studies have been performed to identify possible adverse neuropsychological consequences of TMS. There have been several studies in which a number of cognitive tasks were administered before and after TMS (29, 30). Few adverse effects of TMS on cognition are reported, and there is a trend for performance to be better on measures such as delayed story recall. Two studies, however, have demonstrated possible adverse effects lasting up to one hour. Greenberg et al. (cited in (29)) reported that task switching was impaired after 20-Hz stimulation of the right compared to the left dorsolateral frontal lobe. As there was no untreated condition, this effect may reflect an enhancement of function after the left prefrontal TMS rather than a decrement after right TMS (see Grafman et al. (31)). Flitman et al. (32) reported a significant decrease in logical memory one hour after testing after extensive stimulation using

parameters that exceed guidelines for inter-train interval (150 trains of rTMS at 15 Hz, 750 msec duration, and 1.2 times the MEP).

3. Effects on Mood: Dysphoria with crying has been induced after left prefrontal stimulation (33). In contrast, high-frequency stimulation of the right prefrontal cortex may transiently improve mood as rapid-rate rTMS has been shown to be a safe and effective treatment in subjects with depression.

Since this study aims to assess the effect of rTMS on suicidal ideation, all subjects will be experiencing suicidality by definition. Hence, subjects will already be under ongoing intensive psychiatric inpatient care with suicide precautions. To assess worsening of suicidal ideation we will perform daily assessments and share with the treatment team in case of worsening of suicidal ideation.

There is a risk of worsening depression as a result of rTMS treatment. The subjects are inpatient and will be assessed daily by the treatment team and followed up 3 and 6 months after treatment. If worsening depression occurs during the study, the treatment will be stopped and the subject will be withdrawn from the study.

There is a risk of mania/hypomania in subjects with or without bipolar disorder. Also the use of rTMS may increase the risk of suicide or suicidal ideation. Subjects will be assessed daily for the development of mania or hypomania with the Young Mania Rating Scale. If mania/hypomania develops during the study, the subject will be withdrawn from the study and the treatment team will be informed in order to initiate adequate treatment. This would represent a relatively minor adjustment since all subjects will already be inpatient in the psychiatric ward.

4. Effects on Hearing: Animals have shown permanent increases of the auditory threshold after single-pulse TMS (34), and humans have shown transient increases. Foam earplugs were effective in avoiding changes in the auditory threshold in a safety study of TMS (30). As a precautionary measure, subjects will wear ear plugs during both control and active rTMS. In our preliminary studies, a decibel meter was used to test the click stimuli generated by the rTMS coil. These were between 65–75 dB; with the vacuum engaged, the most intense stimulus measured was 88 dB. Although OSHA guidelines allow exposure of individuals to 90-dB stimuli for up to 8 consecutive hours without protection, our subjects were given foam earplugs, which attenuate by 10 dB, to protect against noise trauma during the active and control treatments. Our studies using 1 & 10 Hz rTMS have shown no effect on hearing due to TMS stimulation (35-38). There is risk of permanent hearing loss if a patient's earplugs fall out. Each subject should immediately report any loosening or detachment of their earplug(s) during each rTMS session. If a subject reports that their earplug(s) has loosened or fallen out, the session will be immediately halted.

5. Scalp Burns: Rapid rate and high stimulus intensity TMS may cause the coil to heat and could possibly result in scalp burns in some situations (39). The NeuroStar stimulator that we use; however, is air-cooled and incorporates a temperature sensor in the coil; it will cease operation should the internal temperature of the coil exceed 140°C, which is cool to the touch externally. A thin insulating pad will also be inserted between the rTMS coil and scalp for all subjects, in addition to periodically checking the temperature of the coil during all treatment sessions and pausing the session if the coil becomes warm.

6. Histotoxicity: Studies from animals as well as a study of subsequently resected anterior temporal lobes of humans subjected to direct cortical stimulation or TMS have failed to demonstrate evidence of histotoxicity. For reasons reviewed by Wasserman 2002 (40), there appears to be very little chance of histotoxicity. It is also noteworthy that MRI examinations done minutes and hours after occipital stimulation with rTMS sufficient to cause phosphenes have failed to demonstrate edema or diffusion changes (41).

7. Kindling: Kindling is a process by which repeated administration of an initially subconvulsive stimulus results in a progressive intensification of induced neuroelectrical activity resulting in a seizure. This has not been reported with TMS and appears unlikely for several reasons. Kindling is most readily obtained with high-rate repetitive stimulation (e.g., 60 Hz), requires a pulse duration of 1 msec (longer than that of TMS), and is easiest to produce in

the amygdala and hippocampus. Kindling of the neocortex in animal models of epilepsy is very difficult to achieve. There is no evidence that kindling can be produced by TMS.

8. Exposure to Magnetic Fields: The maximal field strength generated by commercially available stimulators, such as the NeuroStar TMS Therapy System and NeuroStar XPLOR Clinical Research System machine to be used in our laboratory, is in the 2-Tesla range. We typically deliver between 50% and 70% of the maximum output in our studies. The field is induced for a brief period only, and the strength of the field falls off rapidly with distance from the coil (negligible at >2 cm). There is no evidence of adverse effects from magnetic field exposure during TMS.

9. A seizure caused by rTMS could place subjects at financial risk secondary to cost of medical care. Having a seizure might also influence driving privileges, employment, and the ability to obtain insurance. Subjects are informed of these risks in the consent process. The PIs would provide documentation that the seizure was triggered by rTMS, that it does not constitute epilepsy, and that seizures caused by rTMS have not resulted in future seizures. Seizures induced during electroconvulsive therapy (ECT) for depression, for example, do not cause driving privileges to be revoked in the state of Arkansas. Like ECT, a seizure occurring after rTMS would not cause driving privileges to be revoked.

10. There is a risk of a syncopal/convulsive syncopal event. Information regarding a history of syncope will be requested during the screening process. Subjects will be monitored for signs/symptoms during rTMS including blood pressure monitoring. Should an event occur, the treatment will be immediately stopped, subjects reclined and legs will be elevated.

11. Risk of vision changes. Temporary changes in visual fields may be noticed immediately after TMS. These visual abnormalities are not thought to be actual problems with the eyes, rather changes in brain functioning as a result of the TMS. Alterations in regional activation and neurotransmission may trigger things like blurred vision and/or eye floaters – both of which normalize in time.

12. All the above risks are increased by performing rTMS stimulation at an intensity higher than what the FDA considers as a safe limit. For 10Hz frequency and 120% of the motor threshold, FDA considers the maximum safe train duration to be 4.2 seconds, instead of 5 seconds. However, our parameters are less aggressive than the one used by George et al. 2014 in a very similar population that were well tolerated by their study participants.

Risks Associated with Loss of Confidentiality

Likely: None.

Less Likely: None.

Rare: Confidential information about subjects may be accidentally disclosed. All data will be safe-guarded in accordance with HIPAA. The investigators use codes to keep subject information secure. Data encryption software is required at UAMS for computers with confidential information.

Risks Associated with Interviews and Questionnaires

Likely: Subjects may experience frustration and boredom completing the questionnaires that measure subjects' response to this experimental therapy. Subjects may decline to answer any questions that may make subjects uncomfortable, including questions that may be asked of subjects by the study physicians.

Risks Associated with Blood Draw

Likely: Subjects my experience discomfort associated with venipuncture. Some bleeding and bruising may occur.

Rare: Infection at the site of blood collection and fainting are rare but possible risks associated with blood collection.

Protection Against Risks Associated with TMS

The following steps will be taken to minimize the risks associated with TMS. Additionally, subject exclusion criteria should eliminate subjects for whom risk is greater.

1. Subjects are fully informed of all risks during the informed consent process. .
2. The study physician or nurse will monitor the subject during and after rTMS for twitching of a hand muscle, such as the abductor pollicis brevis or the first dorsal interosseous muscle, on the side contralateral to the rTMS treatment site as this is the most sensitive procedure for detecting after discharges, muscle contraction persisting after stimulation. Subjects will also be monitored by inspection of other body parts that might be affected (e.g., the left arm after right frontal stimulation) or for symptoms that might occur (visual disturbance after occipito-temporal stimulation); should these be observed, the session will be terminated, and the subject will not be tested again using those stimulation parameters.
3. All subjects will wear ear plugs during testing sessions.
4. The study physician or nurse will be present when a subject is receiving TMS.
5. The PI, study physician, or nurse will stock and maintain the laboratory with the emergency supplies described below.
6. If a subject were to have a seizure during or immediately following the study, the study physician or nurse would attend to the subject and administer standard precautionary procedures for seizures. The following precautions will be performed:
    - Providing clear access to the subject.
    - Immediately terminate pulsing.
    - Rapidly remove the coil from the subject.
    - Place the patient in as close as possible a horizontal position on the floor onto a floor mat turning patient gently onto one side. This will help the patient to breathe.
    - Check patency of patient airway, verify adequate airflow.
    - Place a soft flat pillow under patient head (to help prevent injury).
    - Check circulation (peripheral pulses).
    - Time duration of the seizure. Most seizures last ≤ 2 minutes.
    - The PI will be notified.

    Knowing that all TMS-induced seizures to date have spontaneously resolved without interventions, the following will be done <u>only if the seizure or event persists past 5 minutes</u>:

    - Ativan 2 mg will be given IM.
    - The PI will notify primary clinical team for the PRI inpatient unit of the seizure occurrence.
    - The patient will be transported back to inpatient unit via stretcher to be placed under constant observation.
7. Prior to participation, subjects will be fully informed of the possibility of seizure, the plan for care in event of a seizure, and any foreseeable financial or medical consequences resulting from a seizure.
8. Pregnancy tests results from medical records will be obtained for women who are of childbearing age and for whom a possibility of pregnancy is indicated.

Protection Against Risks Associated with Loss of Confidentiality

All data will be safe-guarded in accordance with HIPAA. The investigators use codes to keep subject information secure. Data encryption software is required at UAMS for computers with confidential information. All study staff will have current documentation of HIPAA and CITI training.

Protection Against Risks Associated with Interviews and Questionnaires

Subjects may decline to answer any questions that may make subjects uncomfortable, including questions that may be asked of subjects by the study physician. Subjects may be excluded if the information is necessary to prevent adverse events associated with study procedures.

Protection Against Risks Associated with Blood Draw

Blood draws will be performed by trained staff in an appropriate setting to minimize adverse risks.

Potential Benefits

Suicidal ideation and behavior are very distressing and we anticipate that subjects will be eager to participate in this study with the hope of reducing suicidal ideation. This study will allow us to gather important data with regard to the anticipated efficacy of rTMS for the alleviation of suicidal ideation, thus being of benefit to all subjects who suffer from suicidal ideation.

SAFETY ASSESSMENTS

Safety monitoring will include the following: 1) the PI is the designated responsible entity; 2) subjects will be videotaped during rTMS in order to have a visual record of seizure activity if it occurs (we turn on a WebCam during each rTMS session and discard data if no adverse event occurs); 3) during and immediately following stimulation, subjects will be inspected for signs of twitching and movement indicative of seizure by the study physician or nurse; 4) in the event of seizure, the plan outlined under protection against risk will be followed by study personnel; 5) the PI will report any adverse events to the IRB and funding agency Any seizure resulting from this study would immediately be published so as to add to the collective body of information on TMS. The PI will prepare regularly scheduled reports to the IRB, as required, in a timely fashion.

Subjects will be withdrawn from the study if:

- they experience a seizure or a reaction to rTMS that looks like a seizure
- experience severe pain, like dental pain
- hearing gets worse during or after stimulation
- syncope during rTMS
- develop mania or hypomania during the TMS trial

The study will be stopped and all subjects withdrawn if two completed suicides by subjects receiving TMS occur during the active TMS treatment- as suggested by the FDA.

Adverse Events Reporting and Evaluation

All adverse events occurring during the course of the clinical study, whether device-related or otherwise, will be recorded on the Adverse Event Case Report Form. For all adverse events, the investigator will provide an assessment of the adverse event, its treatment and resolution, and its relationship to the investigational device. Special reporting procedures are required for certain adverse events.

Identification of Adverse Events

An adverse event is defined as any new medical problem, or exacerbation of an existing problem, experienced by a subject while enrolled in the study, whether or not it is considered drug/device-related by the investigator.

Relationship of Adverse Events to the Investigational Device

The investigator will assess the relationship of the adverse event to the investigational device. The relationship will be assessed using the following categories:

- Definitely Related: A direct cause and effect relationship between the investigational drug or device/experimental treatment and the adverse event exists.
- Possibly Related: A direct cause and effect relationship between the investigational drug or device/experimental treatment and the adverse event has not been clearly demonstrated, but is likely or very likely.
- Unlikely Related: A direct cause and effect relationship between the investigational drug or device/experimental treatment and the adverse event is improbable, but not impossible.
- Unrelated: The adverse event is definitely not associated with the investigational drug or device/experimental treatment.

Unanticipated Adverse Device Effects

An unanticipated adverse device effect is defined as "any serious adverse effect on health or safety, or any life-threatening problem, or death caused by, or associated with, a device; if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or application (including supplementary application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." If an unanticipated adverse effect occurs, the investigator will promptly notify the sponsor of such an event within 24 hours of first learning of the event using the FDA Medwatch 3500A form. The form can be found on-line at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/

Serious Adverse Events

Each adverse event will be assessed for its seriousness using the criteria outlined below. The term serious adverse event is not synonymous with a "severe" adverse event, which may be used to describe the intensity of an event experienced by the subject. An adverse event will be classified as serious if it meets any of the following criteria:

- Results in, or contributes to, a death
- Life-threatening (i.e., the subject was, in the opinion of the investigator, at risk of death at the time of the event, but it does not include an event that, had it occurred in a more severe form, might have caused death)
- Results in permanent disability or incapacity (i.e., permanent impairment of a body function or permanent damage to a body structure)
- Requires in-subject hospitalization or prolongs hospitalization
- Necessitates medical or surgical intervention to preclude a permanent disability or incapacity
- Results in a congenital anomaly or birth defect

Non-serious adverse events are all events that do not meet the criteria for a "serious" adverse event.

If serious adverse event occurs, the investigator will promptly notify the sponsor of such an event within 24 hours of first learning of the event using the FDA Medwatch 3500A form. The can be found on-line at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/

The investigator will also promptly notify the IRB of such an event as soon as possible, but no later than ten working days after first learning of the event.

Severity

Each adverse event will be assessed for its severity, or the intensity of an event experienced by the subject, using the following.

- Mild: Discomfort noticed, but no disruption to daily activity.
- Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Severe: Inability to work or perform normal daily activity.

Deaths

The investigator will notify the sponsor and IRB as soon as possible, preferably within 24 hours but in no event later than 48 hours, of learning of subject's death, regardless of whether the death is related or unrelated to the investigational drug or device. The investigator will attempt to determine, as conclusively as possible, whether the death is related to the drug or device. The cause of death and the investigator's discussion regarding whether or not the death was drug- or device-related will be described in a written report.

Pre-existing conditions

Pre-existing conditions will not be reported as an adverse event unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history.

Eliciting and Reporting Adverse Events

The investigator will assess subjects for the occurrence of adverse events at each study visit. All adverse events (serious and non-serious) reported by the subject will be recorded on the source documents and CRFs.

DATA AND SAFETY MONITORING PLAN

Recruitment and Informed Consent

Obtaining consent

The designated staff will discuss the informed consent form with the subject volunteer. The consent process will take place in a quiet and private room. Subjects may take as much time as needed to make a decision about their trial participation and may take the document home if desired. The consent discussion will not be timed but will be based on the participants level of understanding the informed consent and what is involved in consenting the subject to the research study. The person obtaining consent will carefully explain each element of the document and outline the risks and benefits, alternate treatment(s), and follow−up requirements of the study. Participation privacy will be maintained and questions regarding participation will be answered.

No coercion or undue influence will be used in the consent process. The steps that will be taken to minimize the possibility of coercion or undue influence include:

1. Stressing that the study is of a voluntary nature

2. Telling subjects they can leave the study anytime they choose.
3. Assuring the participant that there are no consequences to leaving the study and that acceptance or refusal to be in the study will not affect treatment.

We want to stress that the subject will be INFORMED of all the rights that go along with signing an informed consent to be in a voluntary study. The language used by those obtaining consent is English and the language understood by the prospective participant or the legally authorized representative will also be English. No research related procedures will be performed prior to obtaining informed consent. All signatures and dates will be obtained. A copy of the signed consent will be given to the participant. The informed consent process will be documented in each subjects' research record.

Following informed consent to participate, patient hospital and outpatient records may be reviewed to confirm appropriate candidates for the study. Any data obtained as part of the patient's clinical care may be reviewed to determine whether the subject meets inclusion and does not meet exclusion criteria. Data obtained specifically for research purposes are outlined in the experimental section. These include paper pencil testing and recording of subject's responses. Participant data will be de-identified using codes, personal identifiers will be kept separate from study data, and data will be locked in file cabinets or drawers in the Study Coordinator's office.

Each subject's name, SSN, birth date, address, and phone number and e-mail address will be obtained for purposes of follow-up and payment. We will ask for each subject's drug use history, medical history, and current drug use. Experimental data and questionnaire data will be collected. This information will be coded into the database. Each subject's personal information will be de-identified in the database by using codes. The PI and study nurse will have access to subject identities in order to arrange follow-up and to call them as part of the research project. If subjects prefer e-mail correspondence, they will sign a form authorizing research personnel to send e-mails for scheduling, follow-up, and research-related communication.

The PI is responsible for monitoring data confidentiality and the safety of our subjects. Confidentiality will be monitored through the use of checklists. Quality assurance will be monitored through a set of standard operating procedures that will be compiled and placed in study binders. Checklists will ensure that informed consent has been obtained, that identifying information is placed in a designated secure location, and that the subject has been de-identified in the database. Checklists also confirm what has occurred during each test session and during each phase of recruitment and follow-up. Checklists are signed and dated by the PI or relevant study personnel. Subjects will not be tested in any phase of the study until the appropriate checklists have been signed. Our safety monitoring plan includes the following:

1) the PI is the designated responsible entity;

2) subjects will be videotaped during rTMS in order to have a visual record of seizure activity if it occurs (this was a stipulation of the local IRB; we turn on a WebCam during each rTMS session and discard data if no seizure occurs);

3) during and immediately following stimulation, subjects will be inspected for signs of twitching and movement indicative of seizure by the study physician or nurse;

4) in the event of seizure, the plan outlined under protection against risk will be followed by study personnel;

5) the PI will report any adverse events to the IRB and funding agency

All staff involved in the conduct and/or monitoring of this study will have current UAMS Human Subject Protection and HIPAA Research Training.

Independent data safety monitoring.

1. The sponsor will conduct independent data safety and monitoring according to the ORRA Monitoring Plan.
2. The Data and Safety Monitoring Plan describes operating procedures that will be in place to monitor compliance, study data validity and integrity, participant safety, individuals and/or entities (e.g., IRB) that will be involved in monitoring these procedures, and the frequency/regularity of this monitoring.
3. UAMS IRB regulations will be strictly adhered to in the conduct of the proposed research. Specifically, prior to implementation of any protocol changes, amendments will be submitted to the IRB for approval. In terms of participant safety, if an adverse event occurs during the course of a study, UAMS IRB Policy 10.2 for adverse event and serious adverse event reporting will be followed. The PI will report all such activities to the IRB and the sponsor (as appropriate). Additionally, the PI will inform the sponsor of any actions taken by the IRB resulting from its continuing review of this study.
4. In terms of reporting mechanisms of IRB actions to regulatory agencies, the following UAMS IRB policy (#2.6) applies: The IRB reports any unanticipated problems involving risks to human participants or others; any instance of serious or continuing noncompliance with the IRB regulations, requirements, or determinations; and any suspension or termination of IRB approval to the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), and the Office of Research Oversight (ORO) according to appropriate regulations and the terms of the UAMS IRB Federal Wide Assurance (FWA).
5. Monitoring of the aforementioned procedures will also be overseen by the PI, study coordinator, and the IRB. These procedures will be reviewed regularly by the Project Investigator in a number of settings. For instance, issues pertaining to data validity and integrity and subject safety will be addressed during regular research staff meetings. Moreover, the study coordinator and PI will meet on a regular basis to discuss these topics further. In addition, the IRB, in collaboration with the Office of Research Compliance (ORC), during its yearly continuing review process, will evaluate procedures in place to effectively monitor data integrity and validity and participant safety.
6. A Data Safety and Monitoring Board will also be utilized.

DATA HANDLING AND RECORDKEEPING

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. To protect the identity of research volunteers, contact information will be stored in a separate file and locked cabinet, away from experimental data forms. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a locked file in the Study Coordinator's office. Only Dr. Caceda and designated research staff will have access to the code and information that identifies the subject in this study. All experimental data will be identified using a study code rather than a name, social security number, or other identifying information. All data collection forms will be kept in a locked cabinet in the Psychiatric Research Institute. Computer data records will remain on UAMS maintained password protected network drives.

DATA ANALYSIS

Cognitive tests and questionnaires

Data will be scored and analyzed/summarized according to instructions. Scores will be analyzed via t-tests, analysis of variance (ANOVA) or regression analysis.

The primary outcome (impulsive choice measured by delay discounting) will be analyzed using an MMRM (mixed model repeated measures) approach based on a modified intent-to-treat (mITT) population. The mITT population will be defined as randomized subjects who started at least one treatment. Participants from the mITT population who are included in the MMRM model will also require both a baseline and at least one post- baseline SSI score. The model will include as the dependent variable change from baseline in delay discounting indifference point (K) at each post-baseline visit during the acute phase. Independent variables in the MMRM model will include treatment, visit, treatment-by-visit interaction, delay discounting at baseline, gender, age at baseline and diagnosis. Visits (Days 0, 1, 2, 3) will be treated as a categorical variable. Unstructured variance-covariance structure will be used. This same analysis will also be repeated on the completers' population, defined as subjects who completed 3 days of treatment with the scheduled maximum 6000 pulses per session.

Analyses of VAS data will be conducted using a similar MMRM approach. Each VAS item will be analyzed separately. For the suicide, mood and anxiety items, the model included as the dependent variable change scores from pre-session 1 (session prior to intervention) to each post-session (sessions 1-9) during the acute phase. Independent variables included treatment, session, treatment-by-session interaction, VAS score at pre-session 1, gender, age at baseline, and diagnosis. Painfulness questions collected only at each post-session will be analyzed using an MMRM approach with post-session scores as the dependent variable. Independent variables will remain the same.

Descriptive analyses will be performed to compare baseline data between treatment groups. Categorical variables will be evaluated using Fisher's exact test. Continuous variables will be analyzed with Wilcoxon's rank sum test.

Safety data will be summarized overall and by treatment groups. Fisher's exact test will be used to compare the number of subjects between groups who experienced any adverse events. Length of hospital stay will be compared using Wilcoxon Rank Sum test. Time to re-admission will be analyzed with log-rank test.

The Stroop Test, N-Back scores and pain pressure threshold will be added as covariates in final analysis. Other secondary efficacy outcomes (HRSD, MADRS, CAPS and SSI) for the extended safety phase will be analyzed with MMRM model. The model will include the change from baseline at each follow-up visit as the dependent variable. Independent variables include treatment, visit, treatment-by-visit interaction and base- line score.

We will use repeated measures ANOVA (with appropriate statistical corrections) to compare measures obtained at baseline to those collected 3 & 6 months after all experimental treatment ends. This analysis will address long-term effects of rTMS experimental treatment on suicidal ideation.

The integrity of the blind will be analyzed by tables and Fisher's exact test.

All statistical analyses will be performed in R version 2.14.0. Because this is an early phase study, no adjustments will be made for multiple comparisons, and a *P*-value of 0.05 will be considered to be statistically significant.

Power estimation

Based on our previous results, we consider a meaningful clinical difference as one equal to or higher than that found between recent suicide attempters with persistent suicidal ideation (delay discounting rate (K)=0.122) compared to depressed patients with active suicidal ideation (K=0.099), thus d=0.23 (1).

Given these effect sizes, we determined that a sample of 10 experimental treatment responders will yield power of .80 or greater to detect change in tinnitus. We expect that the sample size proposed for this pilot study, 20 subjects, is sufficient to test our hypothesis as planned.

ETHICAL CONSIDERATIONS

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study. Given the transient state (severe acute suicidal ideation) targeted in this study, the earliest assessment of these patients is crucial in order to obtain a glimpse of the state of mind of the individual that led to engage in suicidal behavior or to ask for help in order to prevent doing so.

Vulnerable population: An ethical concern is that some patients may be receiving medical care involuntarily, and thus represent a vulnerable population with compromised ability to provide informed consent. Thus, no involuntary patients will be recruited in this study. We have ongoing projects [UAMS IRB#139056] and have executed successfully previously similar studies [University of Miami IRB# 20110619] with acutely suicidal patients in collaboration with IRB panels. Additionally, even though these patients have recently attempted suicide or are acutely suicidal, the fact that they would be hospitalized provides an additional layer of protection to this vulnerable population. We will work closely with the IRB to assure that all ethical concerns are addressed.

STUDY REGISTRATION AND PUBLICATION

The PI, Co-Is, and associates are active researchers and publish in a variety of academic journals. It is anticipated that results from this study will be published in similar academic journals. All manuscripts published in peer-reviewed journals will be made publicly available in PubMed Central as per the requirements for studies supported by NIH funding.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

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