An open-label trial of sequential bifrontal low frequency repetitive transcranial magnetic stimulation (r-TMS) in the treatment of primary insomnia.

NCT:02196025

Protocol document with SAP

4/19/2019

Protocol

1. Project Title:

An open label trial of sequential bifrontal low frequency repetitive transcranial magnetic stimulation (r-TMS) in the treatment of primary insomnia.

2. Investigator(s):

- Richard C Holbert, M.D
- Richard B Berry, M.D
- Herbert Ward, M.D.
- Gary Kanter, M.D.

3. Abstract:

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that has been approved as a treatment of depression in patients that have not responded to a trial of one antidepressant medication. We hypothesize that low frequency TMS exerts inhibitory effect on hyper excitable cortical state in patients with chronic insomnia and therefore is therapeutic. Therefore, we aim to undertake this exploratory study to test this hypothesis.
Aim: Compare the change in insomnia scores between baseline and end of treatment in an open label trial with bifrontal low frequency TMS stimulation in 20 patients with primary insomnia using daily stimulation of 3 weeks (15 week days). ***Methodology:*** We aim to study 25 patients with primary insomnia to get 20 patients who complete this open label pilot study. Patients between the ages of 21-65 years who meet DSM-IV criteria for Primary Insomnia will be studied. ***Results and Conclusions:*** Results will be analyzed and compared between the two groups. We will also analyze the predictive value of insomnia symptoms and severity in predicting treatment efficacy of TMS. This study is innovative and first of its kind in exploring the role of TMS in chronic insomnia.

Research Plan

Specific Aims:

Insomnia is a common clinical problem that affects about 25 million people in the US. Insomnia exacts health and economic consequences well beyond inadequate and non-restorative sleep. It increases healthcare costs, causes or adds to medical and psychiatric comorbidities, cognitive impairments, accidents, absenteeism and reduced quality of life.[1,2,3] Treatment of insomnia is difficult and usually needs a multimodal approach incorporating various cognitive and behavioral approaches in addition to medication treatment[15]. TMS and other neurophysiological studies have shown presence of a diffuse cortical hyper-arousal in patients with chronic insomnia.[6,7] High frequency TMS (>1 Hz) has been shown to be activating whereas low frequency TMS (<1Hz) has been shown to be inhibitory in clinical and neurophysiological studies.[8] TMS has been approved as a treatment of depression in patients who have not responded to a trial of at least one antidepressant medication. The goal of this study is to translate the knowledge learned from neurophysiological studies of insomnia to the clinical treatment of insomnia using TMS as the primary modality.

Specific Aim I:

Compare the change in insomnia scores on Pittsburgh Sleep Quality index between baseline and end of the study with sequential bifrontal low frequency TMS in patients with primary chronic insomnia using daily stimulation over a period of 3 weeks (15-week days).

Hypothesis I (Between Group Hypothesis):

Sequential bifrontal low frequency TMS (1 Hz), by exerting an inhibitory effect on cortical hyper-arousal, will lead to improvement in patients with chronic insomnia as measured by PSQI.

Subjective and objective sleep parameters may vary in patients with insomnia. Patients with insomnia tend to underestimate their total sleep time (TST)[11] To quantify a possible discrepancy between subjective and objective sleep parameters like sleep onset latency (SOL) and TST which may be affected by TMS, we propose to assess both objective and subjective measures of sleep onset, sleep continuity and total sleep time.

Specific Aim II:

Compare the change in Insomnia severity index (ISI), TST, SOL, wake after sleep onset (WASO) as measured on ISI, actigraphy and sleep diaries between baseline and end of treatment in subjects receiving low frequency TMS.

Hypothesis II (Objective vs. Subjective changes in sleep):

Because there are no data on TMS and insomnia, we are proposing the null hypothesis. TMS treatment does not differentially affect subjective and objective sleep parameters.

Significance: Insomnia is a clinical problem of significant public health importance. It is a huge burden on healthcare as it increases healthcare costs. Insomnia has also been invoked in causation of other medical and psychiatric disorders, cognitive impairments, accidents, absenteeism and reduced quality of life.[1,2] Effective treatment of insomnia involves multi-modal treatments that are not easily available.[10] Most medications used in the treatment of insomnia are associated with adverse effects and lose efficacy with long-term use.[10] There is need to develop treatments for insomnia that are easy to administer, safe and well tolerated by patients. A diffuse cortical excitability, as measured by various physiological parameters, has been seen in chronic insomnia. This inappropriate physiological arousal is seen as high frequency EEG activation, abnormal hormone secretion, high whole body and brain metabolic activation, elevated heart rate and sympathetic nervous system activation during sleep.[6]

TMS is a non-invasive brain stimulation technique that can be used to investigate directly the excitability level of human cerebral cortex. Van der Werf et al studied 16 patients with chronic insomnia and 14 matched controls using absolute and relative motor evoked potentials in response to single and paired pulse TMS. They found increased absolute response but reduced relative response to paired pulse stimulation at long interpulse intervals. This is indicative of diffuse cortical hyper-arousal but disturbed intra-cortical excitability in patients with chronic insomnia.[7] High frequency TMS (10 Hz) has been shown to be activating whereas low frequency TMS (1Hz) has been shown to be inhibitory.[8,9]

TMS has been shown to be safe and effective treatment.[10] It is approved as a treatment of depression in patients who have not responded to a trial of one antidepressant medication. Our preliminary studies have prepared us to undertake this new study. A review of clinical records from our sleep clinic revealed that insomnia is a common presenting feature. It was more commonly seen in patients with co-morbid depression. Presenting feature of insomnia alerts the clinician to look for co-morbid depression. [13] A review of preliminary data from 14 patients receiving treatment with high frequency (10Hz) left prefrontal cortex TMS for depression in our TMS therapy clinic shows that symptoms of depression and insomnia improve with TMS as seen on Montgomery Asberg depression rating scale (MADRS) scores. This improvement did not correlate with overall improvement in depressive symptoms in all patients. There was no worsening of depressive and insomnia scores with TMS as measured on MADRS scores. We think that current stimulation technique and parameters used in TMS therapy for depression will be counter-therapeutic or ineffective for insomnia, which is one of the rationales for proposed low frequency TMS.[14] Both high and low frequency TMS treatment has been found to be safe

and effective in our review of neuropsychiatric disorders other than depression, however, it is putative that bilateral low frequency TMS (1Hz) and not high frequency (TMS) will lead to improvement in patients with chronic insomnia by exerting an inhibitory effect on hyper-excitable cortical state.[15] If this pilot study shows effectiveness of low frequency TMS in insomnia, we will seek extramural funding and possibly additional multi-site collaboration to test our findings in a larger randomized placebo controlled clinical trial. This will lay the groundwork for establishing the role of low frequency TMS, an easy-to-administer, non-invasive treatment, for this huge clinical and public health problem.

Innovation:

This study offers a novel method to utilize the knowledge gained from neurophysiological studies of TMS in clinical treatment of insomnia. This study is the first of its kind that will explore sequential bifrontal low frequency TMS as a treatment modality for chronic insomnia.

Approach:

a) *Research Design and Methodology:*

This is a one year, prospective, open label pilot study to compare sequential bilateral low frequency TMS in patients with chronic insomnia. Subjects with chronic insomnia will be offered enrollment in this study to receive sequential low frequency (1Hz) bifrontal cortical TMS stimulation. We propose to enroll 25 patients so that we will have complete data on 20 patients with primary/chronic insomnia.

b) *Inclusion criteria:*

1. Patients referred for evaluation and management of insomnia to our sleep disorders clinic will be offered enrollment in this study.
2. Patients must meet DSM IV criteria for Primary insomnia.
3. Aged 21-65 years to target relatively healthy adults.

c) *Exclusion criteria:*

1) Patients with Major depressive disorder.
2) Substance abuse in last two weeks.
3) No Psychotropic medication changes 2 weeks before start of TMS treatment and no changes during the 3 week treatment period.
4) Patients with a major medical or psychiatric disorder that may be causing or contributing to insomnia: bipolar disorder, psychosis, anxiety disorders, dementia, seizure disorder and chronic pain.
5) Patients with ferromagnetic material in their head or within 30 cm of the coil will be excluded.

Subjects may withdraw from the study at any time. Subjects will be withdrawn who do not comply with the ratings and procedures or have an adverse event or a new clinical situation that necessitates their withdrawal from study as deemed necessary by PI.

d) *Procedure:*

Prior to any beginning any study activities subjects will sign the informed consent. Subjects will then be asked to sign a release of information so that the study team can review the medical record of each participant. Baseline clinician rating and clinical assessment and examination will consist of medical records review to obtain information about medical conditions, medications, and physical examination findings. This information will be documented in research files of the subjects. We will also record routine demographic information such as marital status and education as well as age, sex, height and weight. Patients will be assessed weekly to monitor and rate their symptoms. Patients who qualify for enrollment in this study will receive sequential

bilateral bifrontal low frequency TMS stimulation daily on weekdays for three weeks. Stimulation parameters are: 1Hz, 80-120% motor threshold, inter-train interval: 0, 40 minutes of treatment on each left and right prefrontal cortex. Insomnia has shown to be a disorder of hyperarousal. Neuroimaging studies of various brain areas have been shown to reflect this hyperarousal including hypothalamus, thalamus, amygdala, hippocampus and prefrontal cortices. Wake after sleep onset has been correlated with increased glucose metabolism in frontal cortices along with other subcortical areas. Frontal cortices have been more implicated in hyperarousal compared to other cortical areas. Transcranial magnetic stimulation is relatively safe and non-invasive method of stimulating cortical brain areas. Therefore, we are choosing stimulating frontal cortices with TMS to evaluate for effect on insomnia.

Motor threshold will be calculated on left side and right side and will be stimulated at approximately the same distance as the center of the coil from the midline. The primary outcome variable will be the change in Pittsburgh Sleep Quality Index (PSQI) between baseline and end of the treatment.[17]

For the TMS procedure all subjects will be asked to remove glasses, earrings or metal objects within 30 cm of the coil prior to treatment. Noise canceling ear plugs will be provided. A physician who is trained in TMS will administer and monitor the treatment. The study physicians will monitor closely for adverse events and will ensure that all rating scales are completed at the appropriate times.

e) Instruments:

Subjects will be rated weekly on PSQI, Insomnia severity index, CGI and MADRS. They will be requested to keep daily sleep diaries and wear actigraphy devices throughout the three week period of study.

Insomnia severity Rating Index: This instrument has been shown to be a reliable and valid to detect cases of insomnia in the population and is sensitive to treatment response in clinical population. It is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The usual recall period is the “last month” and the dimensions evaluated are: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0-7); sub-threshold insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28). Three versions are available—patient, clinician, and significant others—but the present paper focuses on the patient version only. Previous studies have reported adequate psychometric properties for both the English and French versions.[16,16]

PSQI: Pittsburgh Sleep Quality Index is 10-item scale evaluating various domains of subjectively reported sleep. The score can be between 0-21. A score of less than 5 indicates good sleep quality whereas a score greater than 5 indicates poor sleep quality.[17]

CGI: Clinical Global Impression is an easily administered clinician rating scale assessing overall clinical impression.[18]

MADRS: Montgomery Asberg Depression Rating Scale is a 10-item questionnaire used by clinicians to rate the severity of depression.[19]

Mini Mental State Exam (MMSE): assesses potential impairment in cognition (thinking)

Sleep diary: Sleep diaries are used both in research and clinical practice in the treatment of insomnia. Diaries will be completed daily by patients, reporting bedtime, wake up time, awakenings and various other daytime activities.[20]

Actigraphy: It is a wrist device that is worn like a watch. It records physical activity and light exposure. It provides objective information about the rest-activity cycle.[20] It is also useful to derive objective sleep parameters like sleep onset latency (SOL), total sleep time (TST) and wake-after-sleep onset (WASO).

Epworth Sleepiness Scale (ESS): 8-item self-administered questionnaire that provides a measurement of the general level of daytime sleepiness.[21]

Pittsburgh Insomnia Rating Scale (PIRS): 66-item self-administered questionnaire that assesses severity of insomnia. [22]

Schedule of Events	Day 1	Day 2-6	Day 7	Day 8-13	Day 14	Day 15-20	Day 21
Informed Consent	X						
Physical Exam	X						
Psychiatric interview	X						
Vital Signs	X						
Insomnia severity Rating Index	X		X		X		X
Pittsburgh Sleep Quality Index	X		X		X		X
MADRS	X		X		X		X
CGI	X		X		X		X
MMSE	X		X		X		X
Sleep diary	X	X	X	X	X	X	X
Actigraphy	X	X	X	X	X	X	X
TMS treatment	X	X	X	X	X	X	X
Adverse Events and Concomitant Medications	x	x	x	x	x	x	x

Potential problems:

A potential problem could be worsening of insomnia during TMS treatment. We will monitor subjects weekly and rate their insomnia and depressive symptoms. A MADRS score above 9 would necessitate a clinical interview to assess for depression. If subjects are found to have clinical depression, they will be released from the study and offered treatment in our outpatient clinic. We will study about 25 patients to get 20 completers. Patients with various sleep disorders including insomnia are referred to our sleep disorders' clinic. We see about 70 new patients a month. About 15% of these patients are found to have insomnia. These patients are of all ranges. We expect to enroll the requisite number of patients in the study period. We will hold regular study related meetings with all study personnel to document progress.

If a seizure or other medical condition arises during the course of TMS treatment, the study physicians will ensure appropriate medical evaluation.

Data Analysis and Statistical Methods: We shall compare baseline to post treatment via a one-sample t-test, using a two-sided P-value <0.05 to declare significance. The Total Pittsburgh Sleep Quality Index (PSQI) will be the primary outcome variables. Other outcomes will be analyzed in a similar manner, but the study is powered strictly around PSQI. Significant findings on secondary variables will not be considered as definitive.

Power for a sample size of N=20 completing subjects: Based on results from the study of a a large cohort of poor sleeping subjects had a cross sectional mean PSQI of 11.6 (SD=2.5).[23] Conservatively assuming that the repeated measures correlation is between 0.70 and 0.80 (Repeat measures assume 50-65% of the variation), the study has 80% power to detect 0.66 standard deviations of the paired difference. This translates to sensitivity to a 1.04 to 1.28 unit

difference in pre to post mean (9%-11% change in the mean PQSI).
Final sample size will be 25 subjects to allow for a dropout rate of 20%. Every attempt will be made to collect the PSQI on both days, whether the subject is compliant or not. We shall approximate intent-to-treat as closely as possible, including attempts to get non-compliers to do the post-test and carrying the last observation forward.

Other sleep parameters will be evaluated as secondary endpoints, and a descriptive analysis of responders (reduction by at least 30%) to non-responders will help identify subgroups to be targeted in future. We will analyze the differences in outcome between subjective (PSQI scores, ISI, SOL on PSQI and sleep diaries, TST on sleep diaries and PSQI) and objective measures (actigraphy computed SOL, TST and WASO) between the baseline and end of treatment. We will also analyze the predictive value of insomnia symptoms and severity in predicting treatment efficacy of TMS as a secondary variable. Given the small sample size, we may see differences/trends in this regard that will need to be studied in larger studies. Last Observation Carry Forward (LOCF) strategy will be used to study dropouts. We will also contact those subjects that drop out to ask for the reason for drop-out.

Design Decisions and Limitations

The sample size is small but necessarily constrained by the cost of the SenStar Treatment Links. We chose to conduct an open label efficacy and feasibility trial based on our clinical and research experience indicating that 1) insomnia is associated with cortical hyper-arousal and low dose TMS is inhibitory. This design will assess effectiveness of the low dose regimen while probing for a possible mechanism for effectiveness. We have proposed recruiting subjects between the ages of 21 and 65. While this is a very broad age range, cortical hyper-arousal is implicated regardless of age. Effectively, the incidence of insomnia increases with age so that our sample is more likely to include middle-aged and older adults.

Conflict of Interest:

None

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