Efficacy and Safety of Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression

AF Leuchter, IA Cook, D Feifel, JW Goethe, M Husain, LL Carpenter, ME Thase, AD Krystal, NS Philip, MT Bhati, WJ Burke, RH Howland, YI Sheline, ST Aaronson, DV Iosifescu, JP O'Reardon, WS Gilmer, R Jain, KS Burgoyne, B Phillips, Y Jin, P Manberg, J Massaro, SH Lisanby, MS George

Department of Psychiatry and Biobehavioral Sciences, and the Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at UCLA, Los Angeles, CA; and NeoSync, Inc., Newton, MA and Newport Beach, CA.

ABSTRACT

Objective: This study tested the efficacy and safety of transcranial magnetic stimulation synchronized to the individual alpha frequency (IAF) for treatment of MDD (synchronized TMS, or sTMS).

Methods: Six-week double blind sham controlled treatment trial of a novel device that used three rotating neodymium magnets to deliver sTMS treatment. IAF was determined from a single-channel EEG prior to first treatment. 120 unmedicated adult subjects with moderate MDD (mean baseline 17-item Hamilton Depression Rating Scale ($HamD_{17}$) score of 21.5) completed six weeks of treatment per-protocol. Antidepressant Treatment History scores ranged from 0-6.

Results: Subjects who received sTMS per-protocol (N = 59) had significantly greater mean decrease in $HamD_{17}$ scores after six weeks than those receiving sham treatment (N = 61) (-9.00 versus -6.56, p=0.033). There was significant interaction between prior history of antidepressant treatment and efficacy: subjects with history of treatment resistance or intolerance in the current episode showed greater differential improvement (-8.58 vs. -4.25, p=0.017) and higher response rates (34.2% vs. 8.3%, p=0.017) to sTMS than sham. Treatment-naïve subjects had high response rates to both active and sham treatment, with no difference in mean decrease in $HamD_{17}$ between the treatments. No serious adverse events were attributable to sTMS.

Conclusions: Results indicate that sTMS is a safe and effective treatment for MDD. Future studies should examine longer-term benefits of sTMS treatment.

INTRODUCTION

Repetitive Transcranial Magnetic Stimulation (rTMS) is a safe and effective treatment for MDD in patients who have failed to benefit from antidepressant medication (1). rTMS commonly is administered using a high-field strength electromagnet that causes neuronal firing in the brain at a fixed stimulation frequency. Repetitive entrainment of neuronal firing at the stimulation frequency is hypothesized to reset thalamocortical oscillators and lead to recovery from MDD (2,3).

We developed a novel device that used rotating neodymium magnets positioned close to the head to stimulate the brain through magnetic induction (4). We hypothesized magnets rotated at the IAF would entrain and reset thalamocortical oscillators while imparting much less energy to the brain than rTMS, because the technique would take advantage of the brain's natural resonance at the IAF (2). This study tested the safety and effectiveness of this method, called synchronized transcranial magnetic stimulation (sTMS), as a treatment for MDD.

METHODS

This six-week double-blind sham-controlled study was performed at 17 sites in the United States (NCT01370733). The sTMS device was reviewed by the FDA and classified as a Non-Significant Risk (NSR) medical device, and IRB approval was obtained at each site before start of the study.

Subjects

202 subjects ages 22-65 with moderate MDD [17-item Hamilton Depression Rating Scale ($HamD_{17}$) score ≥ 17] and free of CNS active medications for at least one week were enrolled. Exclusion criteria included another primary Axis I disorder, serious medical illness, illicit substance use, treatment with rTMS within six months, ECT within one year, duration of illness > 2 years, or presence of implanted medical devices or any metal object near the head.

Fifteen subjects in the ITT completer sample had incorrect IAF measures due to artifacts or technical difficulties and were excluded from the PP study population.

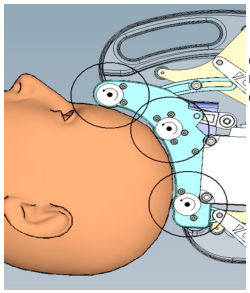

Figure 1. *Diagram of sTMS device. Cross-sectional drawing of the arm of the sTMS device showing the location of the rotating magnets (indicated by cylinders with arrows) in relation to subjects' head.*

METHODS (continued)

sTMS device and treatment

The sTMS device contained three diametrically magnetized cylindrical neodymium magnets, 1-inch in diameter and length, with a surface field of 0.64 Tesla. Subjects were treated while supine with the magnets in close proximity to the head (Figure 1). The IAF was determined from a single- channel EEG (Fpz-Oz electrodes) built into the sTMS device. Magnets were rotated at the IAF for 30 minutes per treatment session, with subjects observed to ensure that they remained awake and in position. The sham device used non-magnetic rotating shafts and was indistinguishable from the active device. Treatment was scheduled five days per week for six weeks (30 treatments). Subjects who did not remit during blinded treatment could enter a four-week open label extension phase.

Assessment instruments

-MINI structured diagnostic interview for the DSM-IV, ATHF $HamD_{17}$, $HamD_{24}$, and $HamD_{28}$, MADRS, CGI-S, CGI-I, and IDS-SR

Study procedures

Subjects were randomized 1:1 to receive sTMS or sham. Primary endpoint was mean change in $HamD_{17}$ from baseline to six weeks. Subjects who did not enter remission (final $HamD_{17}$ score ≤ 7) were eligible to receive four weeks of open-label treatment. Subjects who did not complete 80% of treatments, in whom a reliable IAF could not be measured, or who were otherwise non-compliant were excluded from the per-protocol (PP) population.

Statistical analyses

Analyses were performed on the intent-to-treat (ITT) and PP populations, defined prior to unblinding. Tests of statistical significance were two-sided at a significance level of 0.05. Adverse events (AEs) were calculated for each treatment group, and incidence of AEs with a frequency of greater ≥ 2% and any serious adverse events (SAEs) were compared using Fisher's Exact test.

RESULTS

Subject characteristics

202 subjects were randomized and 135 subjects completed treatment. The PP study population included 120 subjects (59 active, 61 sham). There was no difference in the age, gender, length of the current depressive episode, or treatment history in the ITT or PP populations.

Efficacy analyses

In the ITT population, there was no difference between sTMS and sham in the mean change in HamD17 at the primary endpoint. Subjects receiving active treatment in the ITT population and who complied with protocol (received >80% of treatments) had significantly greater improvement than subjects assigned to sham; those who were non-compliant with active treatment showed no difference from sham (Figure 2).

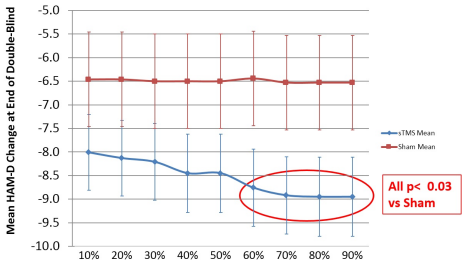

Figure 2. Compliance Criteria (minimum % of treatments) versus Mean HAM -D_{17} Change at End of Double-Blind

RESULTS (continued)

In addition, subjects in the ITT population who were treated at the incorrect IAF (and therefore excluded from PP population) had significantly less improvement on the HamD17 than those treated at the correct IAF (mean decrease -3.82 ± 7.36 vs. -9.00 ± 6.54, respectively, p=0.002).

In the PP population, the sTMS group had a significantly greater decrease in $HamD_{17}$ at week 6 than did the sham group (-9.00 ± 6.54 vs. -6.56 ± 5.85, p=0.03) (Figure 3). There was a numerically but not statistically significantly higher response rate in active versus sham subjects using the final $HamD_{17}$ score at Week 6, although a significantly higher response rate was seen with active treatment using the MADRS rating scale in the PP population (Table 1). Active treatment during the four-week open label extension was associated with significant improvement (mean decrease of $HamD_{17}$ = 2.63, p<0.001).

Outcome	Active treatment (n=59)	Sham treatment (n=61)	Statistic
HamD17 (±S.D.)	-9.00 (±6.54)	-6.56 (±5.85)	p=0.033
HamD24 (±S.D.)	-12.61 (±9.02)	-8.30 (±7.50)	p=0.006
HamD28 (±S.D.)	-13.93 (±9.93)	-9.48 (±8.46)	p=0.013
MADRS (±S.D.)	-12.07 (±8.84)	-8.34 (±8.61)	p=0.014
IDS-SR (±S.D.)	-16.78 (±14.83)	-11.67 (±12.35)	p=0.056
Response Rate HamD17	33.9%	29.5%	ns
Response Rate MADRS	39.0%	21.3%	p=0.036

Table 1. Week 6 outcomes in active and sham treatment groups in the per-protocol population.

Efficacy in the PP population was statistically significant overall but with a significant interaction between ATHF and change in $HamD_{17}$ (p=0.025). Subjects who attempted or completed prior antidepressant treatment in the current episode (ATHF 1 - 6) demonstrated significantly greater benefit from sTMS treatment compared to sham (-8.58 vs. -4.25, p=0.005), while treatment-naïve subjects (ATHF 0) showed no significant difference between active and sham (-9.76 vs. -10.08; p=0.28) (Figure 4). Mean decreases in depressive symptoms in treatment-naïve subjects were numerically larger, both for active and sham, than average decreases in subjects with treatment intolerance or resistance in the current episode.

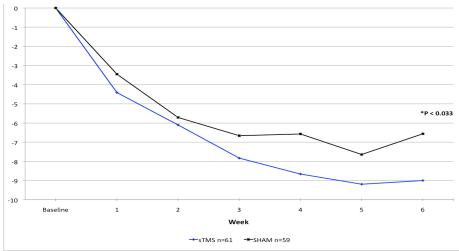

Figure 3. *Change in $HamD_{17}$ score from baseline by treatment group for each week during the double-blind phase.*

Safety and tolerability analyses

Active and sham treatments were well tolerated, with no significant difference between the active and sham arms in the incidence or severity of adverse events and no difference in treatment discontinuation.

RESULTS (continued)

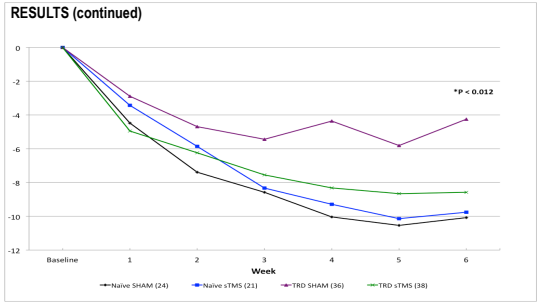

Figure 4. Change in $HamD_{17}$ score from baseline by treatment group, separated by those who are treatment naïve in the current episode (ATHF 0) and those who have attempted or completed at least one adequate treatment (TRD, or ATHF 1-6).

CONCLUSIONS

This double-blind study showed that sTMS was safe and significantly more effective than sham for the treatment of MDD of at least moderate severity in the PP population. The greatest difference in efficacy was seen in the treatment non-naïve population. In addition, subjects showed continued improvement during four weeks of open-label sTMS. The FDA classified sTMS as NSR, consistent with the very low rate of adverse events and the absence of any serious adverse events attributable to sTMS treatment in this study.

sTMS was associated with significant improvement regardless of treatment history, although secondary analyses revealed no significant difference between active and sham treatments in subjects who were treatment-naïve in the current episode. The large degree of symptom improvement in treatment-naïve subjects treated with sham suggests that they have a tendency to improve with both specific and non-specific treatments.

The results of this study are consistent with the previous pilot study showing that low-field magnetic stimulation synchronized to each subject's IAF is an effective treatment for MDD (4), and with other studies indicating that low intensity magnetic fields improve mood in patients with treatment-resistant depression (5).

The absence of difference between active and sham treatment in the ITT population reflects effects of non-compliance as well as treatment at an incorrect IAF in subgroups of subjects assigned to active treatment. Subjects who received >60% of active treatments at the correct IAF showed significantly better outcomes than those treated with sham.

The current results demonstrate that sTMS is effective across a broad range of subjects with MDD. Future studies should examine stimulation frequency, length of treatment, and number and placement of magnets to optimize treatment delivery. Because sTMS can be administered with a low rate of adverse events and without significant risk, it constitutes a valuable addition to the armamentarium of neuromodulation treatments for MDD.

REFERENCES

1. George, MS, Taylor JJ, and Short EB: The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry 2013; 26:13-18
2. Leuchter AF, Cook IA, Jin Y, Phillips B: The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Front Hum Neurosci 2013; 26;7:37
3. Fuggetta G, Noh NA: A neurophysiological insight into the potential link between transcranial magnetic stimulation, thalamocortical dysrhythmia, and neuropsychiatric disorders. Exp Neurol 2013; 245:87-95
4. Jin Y, Phillips B: A pilot study of the use of EEG-based synchronized Transcranial Magnetic Stimulation (sTMS) for treatment of Major Depression. BMC Psychiatry 2014; 14(1):13. doi: 10.1186/1471-244X-14-13
5. Martiny K, Lunde M, Bech P: Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. Biol Psychiatry 2010; 68:163–169

FINANCIAL DISCLOSURES

This study was sponsored by NeoSync, Inc. Several authors have received compensation from, or have equity interest in, NeoSync or manufacturers of other devices or medications for the treatment of MDD. Details are available upon request.