Transcranial Magnetic Stimulation Accelerates the Antidepressant Effect of Amitriptyline in Severe Depression: A Double-Blind Placebo-Controlled Study

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Background: *Transcranial magnetic stimulation (TMS) is a noninvasive method to stimulate the cortex, and the treatment of depression is one of its potential therapeutic applications. Three recent meta analyses strongly suggest its benefits in the treatment of depression. The present study investigates whether repetitive TMS (rTMS) accelerates the onset of action and increases the therapeutic effects of amitriptyline.*

Methods: *Forty-six outpatients meeting DSM-IV criteria for nonpsychotic depressive episode were randomly assigned to receive rTMS (n = 22) or sham repetitive TMS (sham) (n = 24) during 4 weeks over dorsolateral prefrontal cortex (DLPFC) in this double-blind controlled trial. All patients were concomitantly taking amitriptyline (mean dose 110 mg/d). The rTMS group received 20 sessions (5 sections per week) of 5 Hz rTMS (120% of motor threshold and 1250 pulses per session). Sham stimulation followed the same schedule, however, using a sham coil. The efficacy variables were the Hamilton Depression Rating Scale-17 items (HAM-D/17), the Montgomery-Åsberg Depression Rating Scale (MADRS), a Visual Analogue Scale (VAS), and the Clinical Global Impression (CGI). Tolerability was assessed by clinical examination and a safety screening of TMS side effects.*

Results: *Repetitive TMS had a significantly faster response to amitriptyline. There was a significant decrease in HAM-D/17 scores, already after the first week of treatment ($p < .001$ compared with baseline and $p < .001$ compared with sham). The decrease in HAM-D/17 scores in the rTMS group was significantly superior compared with the sham group throughout the study ($p < .001$ at fourth week).*

Conclusions: *Repetitive TMS at 5 Hz accelerated the onset of action and augmented the response to amitriptyline.*

Key Words: Transcranial magnetic stimulation, tricyclic antidepressant, (amitriptyline) augmentation, severe depression

During the last 5 years, an increasing number of studies have investigated the potential role of active repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. Transcranial magnetic stimulation (TMS) is based on the placement of a coil on the scalp. The coil produces magnetic field pulses, which, in turn, induce an electric field in the underlying region of the cortex. This electric field might cause several changes in the target cortex, including changes in metabolism, neurotransmitters release, and induction of gene expression (Barker et al 1985; Hausmann et al 2000).

Recent reviews about the antidepressant efficacy of rTMS have reached different conclusions, from supporting an antidepressant effect (Gershon et al 2003) to concluding that there is insufficient data to make definite determinations (Martin et al 2003). Four recent meta-analyses of the efficacy of rTMS in depression have indicated a positive benefit with an effect size that varied from moderate to large effect (Holtzheimer et al 2001; McNamara et al 2001; Burt et al 2002; Martin et al 2003).

The relationship between clinical effects and stimulation parameters has not yet been established. It has been suggested that slow TMS (≤1 Hz) has inhibitory effect and fast (>1 Hz) TMS facilitates neuronal activity (Pascual-Leone et al 1994; Sackeim 2000).

A frequency between 3 Hz and 5 Hz was reported to have a greater antidepressant effect in depressed patients when compared with faster rTMS (≥10 Hz) (George et al 2000); although the findings of such studies were not statistically significant, evidence suggests differences between 3 Hz to 5 Hz and 10 Hz to 20 Hz frequency ranges..

To date, add-on studies are insufficient to demonstrate if rTMS has any additional advantage if combined with antidepressant drugs (George et al 2003). The aim of the present study was to investigate whether the addition of rTMS would enhance the antidepressant efficacy of the tricyclic antidepressant amitriptyline in severely depressed patients.

Methods and Materials

Subjects

The sample comprised 46 outpatients with the diagnosis of nonpsychotic major depressive disorder (DSM-IV) (American Psychiatric Association 1994). Diagnosis was made using the *Structured Clinical Interview for DSM-IV (SCID-P) version 2.0* (First et al 1996). The eligibility criteria included a baseline score of at least 22 points in the Hamilton Depression Rating Scale-17 items version (HAM-D/17) (Hamilton 1960). Randomization to one of these groups was done using an automated interactive voice response system (http://www.icti-usa.com/index2.html).

The study protocol and informed consent were approved by local Ethics Committee, and all patients signed it before their enrollment in the trial. The clinical and demographic characteristics were similar in the two treatment groups (Table 1). Exclusion criteria were neurological conditions, personality disorders, suicide risk, severe uncontrolled organic disease, alcohol

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Table 1. Demographic and Clinical Characteristics of the Sample

Characteristic	Study Group		p
	TMS	Sham	
Gender			
Male	3 (13.6)	4 (16.7)	.77[a]
Female	19 (86.4)	20 (83.3)	
Age (years)	39.3 (12.8)	38.9 (±8.8)	.89[a]
Mean Duration of Current Episode (months)	24.9 (±29.6)	27.6 (±34.7)	.78[b]
Number of Previous Episodes	2.5 (±1.8)	2.0 (±1.5)	.32[b]
Family History of Depression[c]	12 (66.7%)	11 (57.9%)	.58[a]
Baseline HAM-D Score	29.71 (±6.38)	30.92 (±5.45)	.99
History of Previous Hospitalizations	13 (59.1%)	13 (54.2%)	.74[a]

TMS, transcranial magnetic stimulation; HAM-D, Hamilton Depression Rating Scale.

[a]Chi-square or Fisher exact test (when at least one frequency <5).

[b]Mann–Whitney Test.

[c]Nine patients (four from TMS and five from Sham) could not provide reliable information on this item.

or drug abuse, abnormal laboratory tests, use of pacemaker, history of seizures, and major head trauma. Patients with risk factors for TMS procedure were excluded, such as severe and repetitive headache episodes, previous neurosurgery with implants of metal or clips, and pregnancy.

During 4 weeks, all patients received 20 sessions of rTMS or sham rTMS (5 sessions/week; see below). Clinical assessments during treatment were done with the HAM-D/17 scale, the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979), a Visual Analogue Scale (VAS), and the Clinical Global Impression (CGI).

Drug Treatment

Seven days prior to the start of rTMS, all patients received amitriptyline 50 mg at evening, and the dose was increased by 50 mg every second day. The initial purpose was to evaluate a fixed dose of 150 mg daily. However, due to tolerability issues, we had to adjust the dosage of amitiptyline accordingly. The mean daily dose of amitriptyline at the end of this titration period was 110.2 ± 26.3 mg for the rTMS group and 109.4 ± 27.4 mg for the sham rTMS group (p = .991). These doses were maintained during the 4-week trial. Most of them were taking other antidepressants drugs prior to starting amitriptyline.

Clonazepam was the only allowed drug in case of need for sedative purposes, and the needed amount of clonazepam during the trial was used as a covariate of the therapeutic response.

Repetitive TMS Procedures

Transcranial magnetic stimulation was performed using a high-speed magnetic stimulator (Magpro, Medtronic, Minneapolis, Minnesota). At each session, motor threshold of the right abductor of pollicis brevis muscle (the thumb) was determined, as described elsewhere (Pascual-Leone et al 1994).

We used this visual method to determine motor threshold instead of eletroneuromyography, since the effectiveness of both methods are reported to be equivalent (Pridmore et al 1998).

Subjects assigned to the TMS group then received repetitive stimulations of 120% of motor threshold during 4 weeks. Each weekday, subjects received 5 Hz stimulations in the following scheme: 25 trains per day (1250 pulses/d), each train lasting 10 seconds, with 20-second interval. Total days of treatment were 20 for each patient.

Stimulation occurred over the left dorsolateral prefrontal cortex, which was defined as the region 5 cm rostral to the point of optimal stimulation for the right abductor pollicis brevis muscle at a parasagittal plane in the left hemisphere. We used an 8-shaped coil, perpendicular to an imaginary line extending from the point of stimulation to the subject's nose.

Sham stimulation followed the same schedule, using a placebo coil. It was not MU-metal coil. The construction was done with normal spalted iron and ferrit. The magnetic field was reduced with 95%.

The study was conducted in compliance with the Declaration of Helsinki and its amendments and was approved by the local Institutional Review Board (IRB).

Efficacy Variables

The efficacy variables were the HAM-D/17 and MADRS scores, the CGI changes, and VAS.

Assessments were conducted at baseline and at weekly

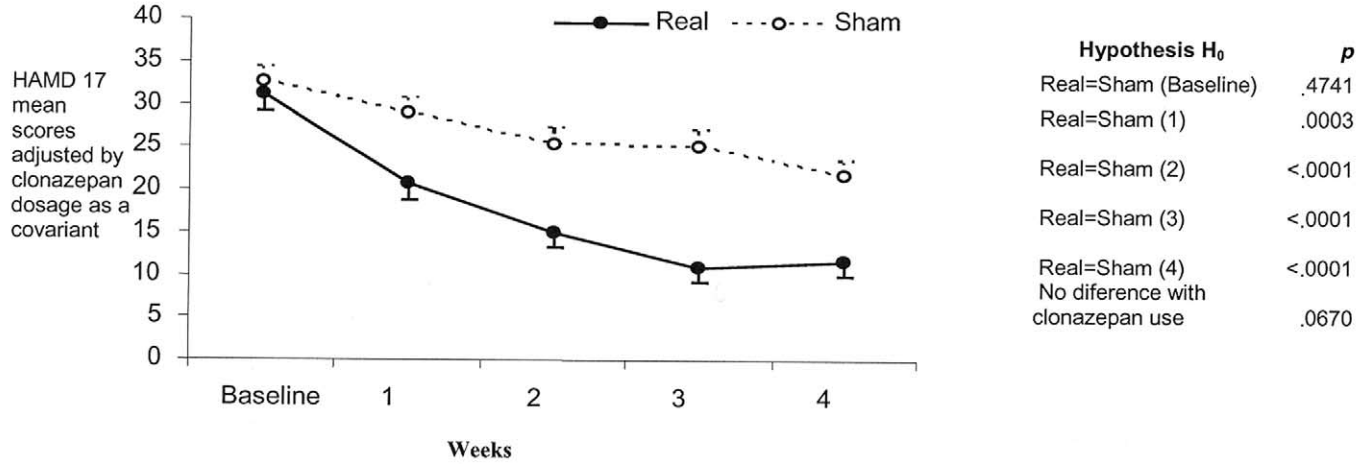

Figure 1. Mean scores on Hamilton Depression Rating Scale (HAM-D) with clonazepan as a covariant in amitriptyline-treated patients receiving repeated transcranial magnetic stimulation (rTMS) (n = 22) or sham rTMS (n = 24).

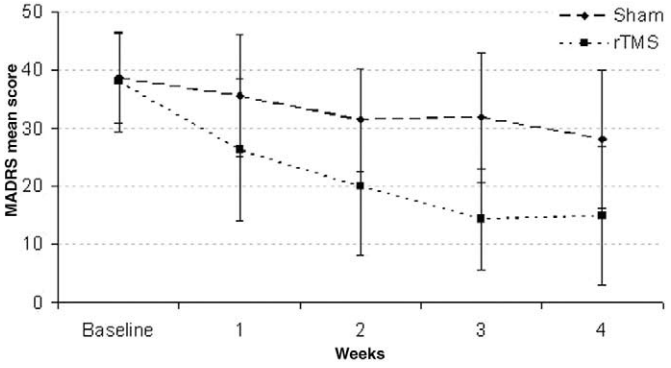

Figure 2. Mean scores on Montgomery Asberg Depressive Rating Scale (MADRS) in amitriptyline-treated patients receiving repeated transcranial magnetic stimulation (rTMS) ($n = 22$) or sham rTMS ($n = 24$).

intervals. Both patients and rater were blinded to patients' treatment.

We considered a clinical response a decrease of 50% or more in the HAM-D/17 baseline scores. Remission was defined as a HAM-D/17 score ≤7 at the end of the fourth week of treatment. Subjective assessment was performed with a VAS, which consisted of a 100-mm horizontal line oriented with anchors placed at both poles, indicating from no depression to severe depression. Patients were asked to mark somewhere along this line that best indicated the magnitude of their state.

Side effects and tolerability were assessed through clinical interview and also a specific questionnaire focused on the most reported side effects of TMS (International Society for Transcranial Stimulation 2003). Measures of safety, assessed at baseline and last visit, included physical examination and measurement of vital signs.

Statistical Analysis

Chi-square test was used to verify the association among categorical variables, and the Fisher test was used when at least one of the expected frequencies was <5. Student *t* test was used to compare the mean quantitative variables of independent samples in both groups. The Mann–Whitney test was used in cases where the variables did not show a normal distribution. Repeated measures of analyses of variance (ANOVA) were used to compare measures of quantitative variables: HAM-D/17, MADRS, CGI, and VAS score. In case of nonhomogeneous variances, Friedman test was used. When there was a significant

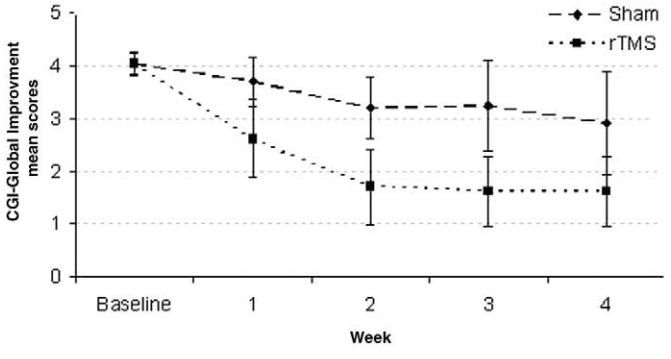

Figure 3. Mean scores on Clinical Global Impression Scale (improvement) (CGI) in amitriptyline-treated patients receiving repeated transcranial magnetic stimulation (rTMS) ($n = 22$) or sham rTMS ($n = 24$).

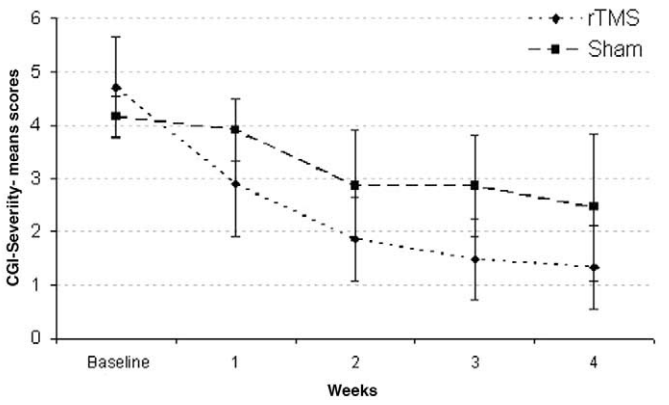

Figure 4. Mean scores on Clinical Global Impression Scale (severity) in amitriptyline-treated patients receiving repeated transcranial magnetic stimulation (rTMS) ($n = 22$) or sham rTMS ($n = 24$).

overall effect, post hoc analyses were made between groups using Tukey Honestly Significant Difference (HSD) method. For all tests, it was established an error with $\alpha = 5\%$. It was also performed as an analysis of covariance (ANCOVA) with clonazepan as a covariate.

Results

Efficacy

Twenty-two patients were included in the rTMS group (3 male patients, 19 female patients; age 39.3 ± 12.8 years) and 24 patients were included in the sham repetitive TMS (sham) group (4 male patients, 20 female patients; age 38.9 ± 8.8 years). The overall response ratio (reduction ≥50% of HAM-D/17 scores) was significantly higher in the rTMS group than in the sham rTMS group (95% and 46% respectively, $p < .001$). Remission was observed in 54% of the rTMS group and in 12% of the sham rTMS group ($p < .002$). Patients receiving rTMS showed a faster reduction of HAM-D/17 scores than the sham rTMS group, and this difference was already significant at the end of the first treatment week ($p < .001$) and remained significant thought the 4 weeks. Figure 1 shows these data with clonazepan as a covariate.

Similar findings were observed for the MADRS and CGI scales, as well as for the subjective assessments through the VAS (Figures 2, 3, 4, and 5).

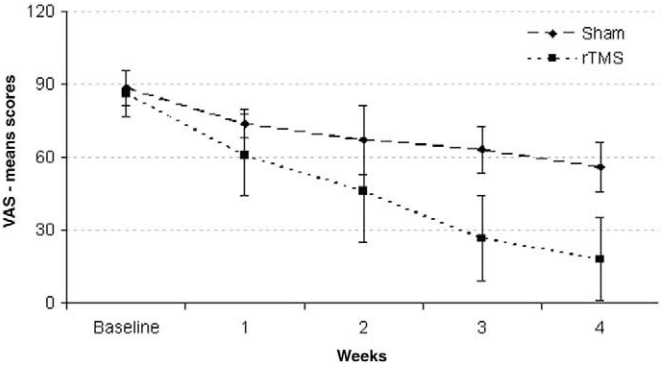

Figure 5. Mean scores on Visual Analogue Scale (VAS) in amitriptyline-treated patients receiving repeated transcranial magnetic stimulation (rTMS) ($n = 22$) or sham rTMS ($n = 24$).

Table 2. Needed Clonazepam Doses

	Basal Week	Week 1	Week 2	Week 3	Week 4
rTMS	.86 (.69)	.91 (.65)	.63 (.54)	.55 (.41)	.41 (.35)
Sham	.83 (.76)	.89 (.48)	.91 (.45)	.91 (.45)	.85 (.47)
p^a	(.38)	(.91)	(.05)	[a]	[a]

Mean ± SD in mg per group/weekly. rTMS, repetitive transcranial magnetic stimulation.
[a] $p < .001$.

The need for clonazepam in the rTMS group was significantly smaller than in the sham rTMS group (Table 2).

Tolerability and Safety

The adverse events are listed on Table 3. Neck pain and burning and pain in the scalp were significantly predominant in the rTMS group.

After 4 weeks of treatment, there was no incidence of seizures. Incidence of symptoms is listed in Table 3. There was a significant decrease in the incidence of headache, concentration difficulty, and pain on the scalp in the TMS group at the fourth week when compared with baseline.

Discussion

This study provides evidence that rTMS at 5 Hz is effective in accelerating the onset and augmenting the therapeutic response to amitriptyline. The rTMS group had faster and larger improvements in all efficacy measures compared with the sham group, and the response was observed already at the first week of treatment. Clinical response and remission rates were also significantly higher in the rTMS group than in the sham group at the fourth week. The achieved HAM-D/17 and MADRS improvements were parallel to the subjective ratings through the VAS.

Transcranial magnetic stimulation in our sample was a safe and well-tolerated procedure. Side effects were usually mild and transient and decreased during the treatment. It should be noted that the use of clonazepam as a co-medication was higher in the sham rTMS group for complaints such as anxiety and insomnia. It is likely that this fact reduced the magnitude of the differences in favor of rTMS as compared with the placebo applications. There was no significant difference in improvement between the groups with and without clonazepam, showing that in our sample, clonazepam did not block the efficacy of rTMS as observed in Figure 1.

The studied population had severe depression, with HAM-D/17 scores higher than 22 (Blacker 2000) and a mean duration of the disease of more than 2 years. Our intention was to study the add-on effect of rTMS to one antidepressant only, and our choice was amitriptyline because of its unquestionable efficacy and its double mechanism of action in the noradrenergic and serotonergic systems. Amitriptyline is available at the Public Health System in Brazil and thus widely used in the community from where our sample came.

It might be possible that the psychological effect of the application of a modern technology, unusual to most of the patients' daily experiences, had a considerable placebo effect. However, the sham stimulation with placebo coil was used to minimize this bias; an appropriate sham is still one of the most troublesome issues in TMS research. The main limitation of the placebo stimulation used in our study was the absence of scalp contraction, which could eventually be noticed by a more attentive patient. All patients were naïve to TMS and since this study was not a crossover design, the previously cited limitation (e.g., lack of muscle twitches during the procedure) was not a serious problem.

Twenty-three patients from our sample were assessed again in a routine ambulatory consultation 3 weeks after receiving the last rTMS ($n = 11$) or sham rTMS ($n = 12$) application. These patients were comparable to the whole sample regarding demographic and clinical variables. In patients who received rTMS, the degrees of clinical response and remission remained similar to those at the end of the 4-week trial. Conversely, patients who received sham rTMS worsened during these 3 weeks, suggesting that sham rTMS had only a transient placebo effect (Table 4).

The technical parameters in our study are widely in line with those recommended in an excellent review by Gershon et al (2003), which showed an antidepressant effect of high-frequency rTMS administered to the left prefrontal cortex.

To our knowledge, there are three add-on studies similar to ours in which the combination of rTMS with antidepressants was investigated. These trials showed a greater improvement in patients receiving additional rTMS, and this effect could be observed already after the third rTMS session. Although these results are in line with ours, caution is needed in comparison of studies. As in the Conca et al (1996) trial, there was no sham group, and five different antidepressants were used with a heterogeneous distribution between the groups. In addition, rTMS parameters differed from ours (stimulation at eight different sites, use of a circular coil, frequency of 0, 17 Hz, 10 days of treatment, and 400 total pulses).

García-Toro et al (2001) found no effect of high-frequency TMS compared with sham rTMS in depressed patients treated during 10 days with sertraline. Again, differences in technical

Table 3. Side Effects During the Applications

	rTMS Baseline	Sham Baseline	rTMS 4th Week	Sham 4th Week
Headache[a]	21 (95.5%)	22 (91.0%)	0 (0%)	11 (45.8%)
Cervical Pain[a]	21 (95.5%)	18 (75.0%)	1 (4.5%)	3 (12.5%)
Pain in the Scalp[a]	19 (86.4%)	17 (70.8%)	1 (4.5%)	14 (58.3%)
Burning in the Scalp[a]	21 (95.5%)	15 (62.5%)	7 (31.8%)	3 (54.2%)

rTMS, repetitive transcranial magnetic stimulation.
[a] Tukey Honestly Significant Difference test $p < .001$.

Table 4. Percentages of Response and Remission During the Weeks 4 and 7

	% Response at Week 4 ($p < .001$)	% Response at Week 7 ($p < .001$)	% Remission at Week 4 ($p = .002$)	% Remission at Week 7 ($p = .009$)
rTMS	95.5[b] ($n = 22$)	100[b] ($n = 11$)	54.5[a] ($n = 22$)	63.6[a] ($n = 11$)
Sham rTMS	45.8 ($n = 24$)	16.7 ($n = 12$)	12.5 ($n = 24$)	8.3 ($n = 12$)

rTMS, repetitive transcranial magnetic stimulation.
[a] $p < .01$ compared with sham rTMS.
[b] $p < .001$ compared with sham rTMS.

parameters with our study preclude direct comparisons (shorter treatment with lower total number of pulses, lower pulse intensity, and use as a sham rTMS of an active coil angulated in 90°, which has been shown to have active properties [Lisanby et al 2001]).

Hausmann et al (2004) compared the effects of rTMS with sham rTMS in 38 patients with major depression. Twelve patients received unilateral rTMS over the left dorsolateral prefrontal cortex and sham rTMS over the right side. Thirteen patients received rTMS over the right side and sham over the left side. Thirteen patients received bilateral sham rTMS.

All patients received treatment with different nontricyclic antidepressants.

No significant differences were found in the outcome among the three groups, although the improvement in the rTMS groups was quantitatively superior to placebo in all assessments. Besides technical differences between Hausmann et al (2004) and our study, such as the use of lower number of pulses and a shorter treatment period, the use of four different antidepressants makes comparisons with our study problematic.

These contradictory findings stress the need for standardization of rTMS parameters before definitive conclusions about its efficacy can be drawn. It is important to note the absence of seizures during rTMS treatment concomitant with tricyclic antidepressants and the use of a 120% motor threshold intensity that is one of the highest intensities used in known TMS studies. This may be relevant to the positive outcomes found in this study. Regarding add-on studies, the question has been raised as to which antidepressant drugs may work well with rTMS (George et al 2003). The present findings indicate that addition of rTMS to amitriptyline may be potentially useful in the treatment of severely depressed patients.

Conclusion

This randomized controlled trial provides evidence that rTMS at 5 Hz frequency is effective in accelerating and augmenting the therapeutic response to amitriptyline and it is a safe and well-tolerated procedure. The effect was sustained with maintenance treatment with amitriptyline only where a residual effect of rTMS was observable after the applications had finished.

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