Does rTMS Hasten the Response to Escitalopram, Sertraline, or Venlafaxine in Patients With Major Depressive Disorder? A Double-Blind, Randomized, Sham-Controlled Trial

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Background/Objective: Repetitive transcranial magnetic stimulation (rTMS) has been mainly studied as adjunctive treatment for drug-resistant patients. We assessed the effectiveness of rTMS started concomitantly with antidepressant medications in non–drug-resistant major depressive disorder patients. We also evaluated if, among the 3 antidepressants administered, one had a better synergy with rTMS.

Method: In this 5-week, double-blind, randomized, sham-controlled study, we recruited 99 inpatients suffering from a major depressive episode (DSM-IV criteria). They were randomly assigned to receive venlafaxine, sertraline, or escitalopram in combination with a 2-week period of sham or active 15-Hz rTMS on the left dorsolateral prefrontal cortex. Data were gathered from February 2004 to June 2005.

Results: The active rTMS group showed a significantly faster reduction in Hamilton Rating Scale for Depression (HAM-D) scores compared with the sham group ($p = .0029$). The response and remission rates were significantly greater in the active rTMS group after the stimulation period ($p = .002$ and $p = .003$, respectively), but not at the endpoint. We found no significant difference in HAM-D score reduction among the 3 drugs administered, either in the active or in the sham group.

Conclusion: These findings support the efficacy of rTMS in hastening the response to antidepressant drugs in patients with major depressive disorder. The effect of rTMS seems to be unaffected by the specific concomitantly administered drug.

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Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method used to stimulate human brain cortex through the induction of a current that can cause action potentials and excitatory or inhibitory postsynaptic potentials.[1] This mechanism can modify the activity in the targeted cortical area and, trans-synaptically, in functionally connected brain structures.[2] In particular, rTMS may exert an antidepressive effect because of its ability to influence frontocingulate mood-regulating circuits[3–5] and to produce neurobiological effects resembling those of some antidepressant drugs.[6–8]

In recent years, several studies have evaluated the use of rTMS in the treatment of major depressive disorder, but a considerable variability in the stimulation parameters and the small sample sizes used in most studies have prevented the drawing of definitive conclusions about its clinical efficacy.[9–11]

Most of the published studies have tested the efficacy of rTMS in the treatment of drug-resistant and severe depression,[12–16] while fewer trials have investigated the effectiveness of rTMS in combination with antidepressant drugs in non–drug-resistant major depressive disorder patients, particularly in those who concomitantly started taking a new medication.[17–21] Moreover, to our knowledge, no published data are available regarding comparison of the ability of rTMS to hasten the effectiveness of different antidepressant drugs in the same double-blind, randomized, sham-controlled trial.

The aim of this study was 2-fold. The first was to prospectively assess the effectiveness of rTMS started concomitantly with antidepressant medications in non–drug-resistant major depressive disorder patients. The second was to evaluate if, among the 3 prescribed antidepressants, one may work better in combination with rTMS.

METHOD AND MATERIALS

Patients

We screened 124 right-handed inpatients consecutively admitted to our Research Center for Mood Disorders (San Raffaele Hospital, Milan, Italy) for a major depressive

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Table 1. Clinical and Demographic Characteristics at Baseline of Major Depressive Disorder Patients Treated With Active or Sham rTMS and Escitalopram, Sertraline, or Venlafaxine[a]

	Active			Sham					
Characteristic	Escitalopram (N = 17)	Sertraline (N = 16)	Venlafaxine (N = 17)	Escitalopram (N = 17)	Sertraline (N = 16)	Venlafaxine (N = 16)	Active (N = 50)	Sham (N = 49)	Total (N = 99)
Age, y	48.2 (12.4)	48.6 (13.9)	48.6 (15.6)	42.2 (11.5)	48.3 (10.0)	49.1 (14.0)	48.4 (13.7)	46.4 (12.1)	47.4 (12.9)
Education, y	10.2 (4.8)	9.7 (4.4)	8.2 (3.5)	10.1 (4.9)	9.9 (3.0)	9.5 (3.9)	9.3 (4.2)	9.8 (4.0)	9.5 (4.1)
Age at onset, y	36.2 (17.1)	37.3 (14.3)	36.9 (13.7)	33.1 (13.0)	37.8 (12.8)	35.2 (14.6)	36.8 (14.8)	35.3 (13.3)	36.1 (14.1)
No. of episodes	3.2 (2.4)	2.5 (1.4)	3.5 (3.6)	2.4 (2.3)	3.8 (2.4)	3.0 (2.8)	3.1 (2.6)	3.1 (2.5)	3.1 (2.6)
Episode duration, wk	12.8 (7.5)	7.3 (4.1)	10.9 (5.9)	10.0 (4.5)	8.8 (5.5)	13.3 (7.8)	10.4 (6.3)	10.7 (6.2)	10.5 (6.3)
Gender, N, male/female	6/11	2/14	3/14	4/13	3/13	2/14	11/39	9/40	20/79
Menopause, N, yes/no	5/6	6/8	9/5	3/10	7/6	6/8	20/19	16/24	36/43
HAM-D score	25.3 (3.6)	25.7 (3.5)	24.2 (3.4)	25.1 (2.7)	24.9 (3.2)	25.3 (3.5)	25.1 (3.5)	25.1 (3.1)	25.1 (3.3)
CGI-S score	5.0 (0.7)	5.1 (0.6)	4.7 (0.7)	5.0 (0.5)	4.9 (0.6)	5.0 (0.6)	4.9 (0.7)	5.0 (0.6)	4.9 (0.6)

[a]Data shown as mean (SD) unless otherwise noted.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

episode (due to major depressive disorder and not induced by a substance or a medical condition) using DSM-IV criteria.

Lifetime diagnoses were assigned by a trained psychiatrist on the basis of unstructured clinical interviews and medical records according to DSM-IV criteria and following a best estimate procedure.[22] The exclusion criteria were presence of any concomitant Axis I diagnosis, manic or hypomanic episodes, or psychotic features; somatic or neurologic illnesses impairing psychiatric evaluation; age younger than 18 years or older than 75 years; left-handedness evaluated with the Edinburgh Handedness Inventory[23]; and a 21-item Hamilton Rating Scale for Depression (HAM-D)[24] score less than 21. In accordance with the safety criteria for rTMS,[25] patients with a history of seizures or bearing pacemakers, mobile metal implants, implanted medical pumps, or metal clips placed inside the skull were also excluded.

After the procedure had been completely explained to the subjects, informed written consent was obtained. The study was approved by the Ethical Committee of San Raffaele Hospital and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. Data were gathered from February 2004 to June 2005.

Study Design

Twenty-five of 124 patients were excluded according to the above-mentioned criteria. Ninety-nine patients were randomly assigned to 6 different groups derived from the combination of 2 independent variables: rTMS (active or sham) and antidepressant medication (escitalopram, sertraline, or venlafaxine). Consequently, 50 patients were in the active rTMS group and 49 were in the sham group. The subgroup composition and the demographic and clinical characteristics of the sample are reported in Table 1. Randomization was performed by a computer-originated schedule, using nonprofit software freely available on the Internet.[26] Repetitive transcranial magnetic stimulation in combination with antidepressants was administered for the first 2 weeks. During the following 3 weeks, patients continued only the pharmacologic treatment.

Drug Treatment

No patient had failed to respond to more than 1 antidepressant treatment, at adequate dosage and for an adequate period of time, for the current episode. Subjects had not taken nonreversible monoamine oxidase inhibitors, fluoxetine, or slow-release neuroleptics for at least 1 month before entering the study.

A 7-day washout period preceded the 5-week period of active treatment. During this period, physical examination, laboratory tests, and electrocardiograms were performed and evidenced no clinically relevant abnormalities in any patient.

The dosage schedule of antidepressant drugs was as follows: on days 1 through 3, escitalopram 5 mg, sertraline 50 mg, or venlafaxine 75 mg, all once per day; on days 4 through 7, escitalopram 10 mg (5 mg twice per day), sertraline 100 mg (50 mg twice per day), or venlafaxine 150 mg (75 mg twice per day); and on days 8 through 14, escitalopram 15 mg (5 mg 3 times per day), sertraline 150 mg (50 mg 3 times per day), or venlafaxine 225 mg (75 mg 3 times per day). Selective serotonin reuptake inhibitors (SSRIs) were administered more than 1 time per day in order to maintain the blind in comparison with venlafaxine. Dosage was maintained unchanged in the following weeks. No other psychotropic medication was allowed, with the exception of lormetazepam up to 2.5 mg at bedtime.

rTMS Procedure

Stimulation was performed for 10 consecutive working days (Monday to Friday for 2 weeks) over the left dorsolateral prefrontal cortex (DLPFC) with the following

parameters: 100% of motor threshold (MT), 15 Hz, 30 trains of 30 pulses (2 seconds each, with a 28-second inter-train interval), for a total of 900 pulses per day. We used a Magstim Rapid Stimulator for biphasic pulses (Magstim Company Ltd; Whitland, U.K.) with a focal 70-mm 8-shaped coil. Prior to the first treatment, the resting MT was determined as the lowest intensity able to induce, 5 out of 10 times, an involuntary movement of the right abductor pollicis brevis muscle. The MT was rechecked for each patient at the beginning of the second week. The site of stimulation was defined as 5 cm anterior to the scalp position for the determination of the MT, on the parasagittal plane,[27,28] and was marked.

Real stimulation was applied with the coil held flat on the scalp (tangentially) and the handle making a 45° angle with the midline, in the left posterior direction. The patients in the sham group received the same number of stimuli, with parameters identical to those used in the active group except for intensity, but the coil was placed at a 90° angle (perpendicularly), with only 1 wing in contact with the scalp and forming a 45° angle with the midline in the left posterior direction. The intensity of the sham stimulation was 90% of the MT. In this way, the sham intervention gave the patient a similar sound effect but no relevant stimulation of the cortical structures underneath the area of coil placement.[29,30]

No patient had previously undergone electroconvulsive or rTMS therapy.

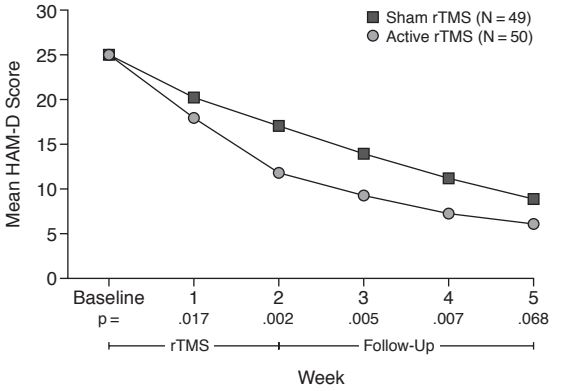
Clinical Assessment

Assessment was performed using the 21-item HAM-D[24] and the Clinical Global Impressions-Severity of Illness scale (CGI-S),[31] administered at baseline and weekly thereafter for 5 weeks. Response was defined as a ≥ 50% decrease in the HAM-D total score from baseline, and remission was defined as a HAM-D total score ≤ 8. The assessment was performed by 2 trained psychiatrists with a good interrater reliability (intraclass correlation coefficient on HAM-D = 0.95) who were blind to the stimulation parameters. Patients were asked to report side effects daily in a diary.

Statistical Analysis

One-way analyses of variance (ANOVAs) and Pearson χ^2 tests were used to investigate the differences among the 6 groups for demographic and baseline clinical variables. Changes in HAM-D scores over time were analyzed with a repeated-measures ANOVA, with rTMS condition and drug therapy as the between-subject factors. An intent-to-treat (ITT) analysis was carried out for all patients who had a baseline assessment after randomization, with the last observation carried forward on the HAM-D. The same analysis was repeated considering only the patients who completed the whole period of the trial and follow-up. The differences in improvement from baseline at each week between the active and sham groups were analyzed with linear contrasts for the time × rTMS interaction, and 95% confidence intervals were calculated for each difference. We achieved a good power (0.80) to detect a medium effect size (Cohen d = 0.50), corresponding to a difference of about 3.5 points on the HAM-D at the end of the rTMS period. Analysis of covariance was used when including clinical and demographic features in the model. All p values were 2-tailed, and statistical significance was set at the 5% level ($p < .05$). Pearson χ^2 tests were used to investigate the differences between groups in the rates of responders and remitters at weeks 2 and 5. Computerized analyses were performed with a commercially available statistical package.[32]

Figure 1. HAM-D Score Reduction Over Time in Active Versus Sham rTMS Groups



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

RESULTS

Patients

Baseline demographic and clinical characteristics of patients who entered the double-blind phase of the study are summarized in Table 1. There were no statistically significant baseline differences between active and sham rTMS groups. When patients were compared according to their pharmacologic treatment, no statistically significant differences were found (Table 1).

Treatment Efficacy

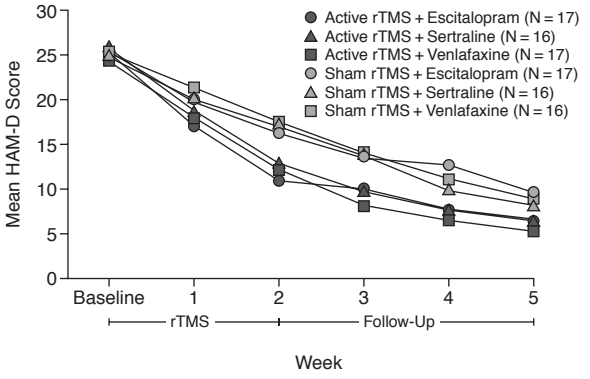
Figure 1 shows HAM-D score reduction over time in active versus sham rTMS groups. The overall repeated-measures ANOVA showed that both the rTMS main effect (ITT: $F = 7.8$, $df = 1,93$; $p = .0064$; completers: $F = 7.6$, $df = 1,83$; $p = .0073$) and the time × rTMS interaction (ITT: $F = 3.66$, $df = 5,465$; $p = .0029$; completers: $F = 4.00$, $df = 5,415$; $p = .0015$) were significant. The difference in improvement between the groups showed a significant advantage in favor of the active group starting at

Table 2. Changes From Baseline in HAM-D Scores in Active Versus Sham rTMS Groups

Week	N (active/sham)	Change From Baseline, Mean (SE)		Difference Between Groups		
		Active rTMS	Sham rTMS	Estimate[a]	95% CI	p Value
1	50/49	7.0 (0.70)	4.6 (0.71)	–2.4	–4.4 to –0.5	.017
2	49/47	12.9 (1.03)	8.3 (1.06)	–4.6	–7.6 to –1.7	.002
3	49/47	15.5 (1.07)	11.1 (1.09)	–4.4	–7.4 to –1.3	.005
4	46/47	17.9 (1.02)	14.0 (1.01)	–3.9	–6.8 to –1.1	.007
5	45/44	19.1 (1.12)	16.2 (1.14)	–2.9	–6.1 to 0.2	.068

[a]Least squares mean differences between sham and active groups in improvement from baseline (sham – active).
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

Figure 2. HAM-D Score Reduction Over Time Among the 3 Pharmacologic Groups Receiving Active or Sham rTMS



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, rTMS = repetitive transcranial magnetic stimulation.

the end of the first week of rTMS treatment. Analyzing the mean HAM-D score improvement for each week, we observed an increased significance until the second week (end of rTMS stimulation) and then a reduction of the difference that remained statistically significant until the fourth week of treatment (data shown as ITT [completers]: week 1, p = .017 [p = .017]; week 2, p = .002 [p = .002]; week 3, p = .004 [p = .005]; week 4, p = .013 [p = .007]; week 5, p = .097 [p = .068]) (Table 2).

The CGI-S scores showed an improvement over time similar to that observed on the HAM-D (repeated-measures ANOVA; ITT: $F = 3.89$, df = 5,465; $p = .002$; completers: $F = 4.84$, df = 5,415; $p = .002$) in the time × treatment interaction.

Figure 2 shows HAM-D score reduction over time among the 3 pharmacologic groups receiving active rTMS treatment as well as those receiving sham rTMS treatment. The rTMS × drug interactions (ITT: $F = 0.39$, df =2,93; $p = .67$; completers: $F = 0.22$, df = 2,83; $p = .80$) and rTMS × drug × time (ITT: $F = 0.14$, df = 10,465; $p = .99$; completers: $F = 0.15$, df = 10,415; $p = .99$) were not significant. We also conducted 2 additional analyses, 1 for the active and 1 for the sham group; the drug × time interaction was not significant in any group. Response rates were calculated at the end of rTMS treatment (week 2) and after the end of the follow-up pharmacologic treatment phase (week 5). At the end of the second week, the response rates were 25/49 (51%) in the active rTMS group and 10/47 (21.3%) in the sham group ($\chi^2 = 9.16$, df = 1, $p = .002$), and the remission rates were 18/49 (36.7%) and 5/47 (10.6%) for the active and sham rTMS groups, respectively ($\chi^2 = 8.96$, df = 1, $p = .003$). At the end of the fifth week of treatment, the response rates were 36/45 (80.0%) in the active rTMS group and 32/44 (72.7%) in the sham group ($\chi^2 = 0.65$, df = 1, $p = .419$), and the remission rates were 33/45 (73.3%) and 24/44 (54.5%) for the active and sham rTMS groups, respectively ($\chi^2 = 3.41$, df = 1, $p = .064$).

Table 3 shows the response and remission rates at the end of the second week and at the end of the fifth week of therapy, subdivided according to the 3 pharmacologic treatments and the presence of active or sham rTMS.

Tolerability

Three patients (1 in the active rTMS group [venlafaxine] and 2 in the sham group [1 venlafaxine and 1 escitalopram]) dropped out within 12 days of treatment because of unpleasant side effects. More specifically, the patients in the sham group discontinued the therapy because of intolerable agitation (the patient receiving escitalopram) and gastric symptoms not resolved using pantoprazole (the patient receiving venlafaxine), and the patient receiving active rTMS and venlafaxine reported headache and cervical pain. During the 3 weeks that followed the rTMS, 7 patients dropped out for the following reasons: 2 for lack of improvement of depressive symptoms, 2 because they went on holiday, 2 because they did not come to the planned visit, and 1 for consent withdrawal. Our patients were all unipolar at the time of inclusion in the study, and we did not record any switch into mania. No patient developed psychotic symptoms during the trial.

DISCUSSION

Our data support the conclusion that rTMS may hasten the effectiveness of antidepressant medications. This effect was statistically significant from the first week of treatment to the fourth week, while at the end of the follow-up it showed a trend toward significance both in

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Table 3. Response and Remission Rates Subdivided According to the Pharmacologic and rTMS Treatments, N/N (%)

	Active rTMS				Sham rTMS			
Week	Escitalopram	Sertraline	Venlafaxine	p	Escitalopram	Sertraline	Venlafaxine	p
Responders								
2	9/17 (52.9)	7/16 (43.7)	9/16 (56.2)	.764	3/16 (18.7)	4/16 (25.0)	3/15 (20.0)	.901
5	12/16 (75.0)	10/14 (71.4)	14/15 (93.3)	.278	10/15 (66.7)	12/15 (80.0)	10/14 (71.4)	.708
Remitters								
2	7/17 (41.2)	6/16 (37.5)	5/16 (31.2)	.837	2/16 (12.5)	1/16 (6.2)	2/15 (13.3)	.501
5	11/16 (68.7)	10/14 (71.4)	12/15 (80.0)	.764	7/15 (46.7)	10/15 (66.7)	7/14 (50.0)	.780

Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

average improvement on the HAM-D and in remission rates.

The use of the same randomly assigned antidepressants for both of the groups together with restrictions on taking other medications represents a valuable condition of homogeneity between the groups. Residual effects of previous medications are unlikely to account for the observed group differences, because the patients were free from psychotropic medications other than lormetazepam from the run-in period to the end of the study. Moreover, lormetazepam use was equally distributed among the 6 study groups.

Since we studied patients who were not medication resistant, we decided to use the antidepressants most commonly prescribed in our center. In this regard, we never use tricyclics as first-line treatment in major depressive disorder patients. However, data on tricyclic drugs (amitriptyline) and rTMS are already available and encouraging.[21] It is currently recognized that each SSRI has a peculiar clinical and pharmacologic profile[33–36]; we used the widely prescribed SSRI sertraline and the newer and more selective escitalopram. We also included venlafaxine as a widespread exponent of the serotonin-norepinephrine reuptake inhibitor class.

It has been shown that psychoactive medications can affect various parameters of cortical excitability.[37] As an example, different antidepressants can differently modulate cortical excitability as measured with rTMS,[38–41] even if they have similar pharmacodynamic properties (e.g., sertraline[42] and citalopram[43]). These effects can change from acute to chronic administration of the same antidepressant,[44] and a similar difference has been observed for acute and chronic intake of benzodiazepines.[45] These differences in cortical excitability are measured on the motor cortex, and it is not completely predictable whether the effect on the DLPFC would be the same. Even if that were the case, it is not known if a change in the excitability of the DLPFC could in any way affect the antidepressant properties of rTMS. It has been proposed that antidepressants and rTMS may share some common mechanisms of action[6–8] and target some common regions in the brain,[5] but little is known about their possible interactions. It is also possible that the physiologic effects of medications and rTMS do not interact in a relevant way with regard to the antidepressant response. In our sample, we were not able to reveal significant differences between the different drug-rTMS combinations. However, it must be considered that the size of each drug subgroup may have been too small to underline these differences.

Until now, few studies[17–21] have tested the efficacy of rTMS started concomitantly with antidepressant medications. The first study[17] was encouraging, obtaining appreciable results from the third day of stimulation. The rTMS group was compared with a group of patients taking only antidepressant medications, but there was not a sham rTMS group. Garcia-Toro et al.[18] compared the effects of 2 weeks of active or sham rTMS (at 90% of MT) started together with 50 mg/day of sertraline in 28 depressed patients. Although the mean improvement of the active group was greater than that of the sham group, results did not reach the significance level. A similar study was conducted by Poulet et al.[20] on 19 patients taking 20 mg/day of paroxetine, without finding significant differences between the groups. The mild rTMS parameters used (400 stimuli/day, 80% of MT), the small sample size, and the 45° sham condition may at least in part account for this result. Hausmann and colleagues[19] found only a trend toward significance in the Beck Depression Inventory score improvements between active and sham conditions. However, it should be taken into account that the antidepressant assignment was not randomized and that lorazepam up to 5 mg/day was used. In a recent study, Rumi et al.[21] treated 46 severely depressed outpatients with real or sham rTMS and amitriptyline, with results that were largely in favor of the active group from the first week to the end of the 4 weeks of treatment.

A difference between our study and the previous ones[18–21] was in the higher dosage of antidepressant medications that we used. The only study that reached a dose of antidepressant higher than the lowest recommended for the treatment of depression was that of Rumi and colleagues[21] (about 110 mg of amitriptyline). It could be argued that a higher antidepressant dosage may improve the action of rTMS, even if it should be considered that in this last study the highest stimulation intensity (120% of MT) was used. On the other hand, Garcia-Toro and colleagues[18] proposed that the good efficacy of sertraline in their trial could have obscured the effect of rTMS. The

evidence so far is too scarce to draw clear conclusions on this matter.

Considering the question of maintenance of response, rTMS seems more appropriate as add-on treatment than as monotherapy. In this regard, a worsening of mood after the end of the stimulation period that was reversed by the initiation of antidepressant medication has been shown in drug-free rTMS responders.[46] In our sample, antidepressant treatment was administered during the whole period of follow-up, and patients who achieved response after the active rTMS treatment maintained their improvement except in 1 case.

An important question about rTMS treatment of depression is that of possible predictors of response. There is now a certain agreement that psychotic features are negative predictors of response, partly due to the prodopaminergic activity of rTMS[47]; accordingly, we did not include this kind of patient in our study. In some trials,[15,48,49] elderly patients have shown a poor response, perhaps due to a tendency of the scalp-cortex distance to augment with age in the DLPFC.[50] In this regard, we found a slight tendency for lower and slower response in our elder patients, but this was observed both in the active and in the sham groups, without significant differences. A negative predictive role for a longer depressive episode duration was found in a previous trial.[51] We obtained a marginal trend toward fewer responders among individuals with longer episodes, but no differences between groups. The role of these potential predictors merits further study.

Some limitations of our study should be taken into account. The intensity and number of pulses chosen were quite conservative. However, they seemed appropriate for patients who were not medication resistant and were also starting a new antidepressant medication. The 90° sham condition is largely used in rTMS trials for depression; it can evoke only negligible physiologic effects,[29,30] but compared with the real condition, it does not elicit a comparable sensation on the patient scalp. This may have created different expectations about its therapeutic effect. The method used to target the DLPFC, although widespread, is not always accurate,[52] even if the clinical benefits provided by the use of neuronavigation techniques have yet to be demonstrated.

Many of our patients achieved a fast response and were remitters at the end of the trial. However, it is reasonable to hypothesize that a longer period of rTMS treatment for those who did not respond may have yielded an even higher response rate.[5,14–53] Moreover, it has been shown that beneficial effects of rTMS may also appear after the end of our follow-up period.[54]

In conclusion, the results of this study provide evidence that 2 weeks of rTMS treatment may accelerate the antidepressant response to escitalopram, sertraline, and venlafaxine.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro), fluoxetine (Prozac and others), lorazepam (Ativan and others), pantoprazole (Protonix), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), venlafaxine (Effexor).

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