Add-On rTMS for Medication-Resistant Depression: A Randomized, Double-Blind, Sham-Controlled Trial in Chinese Patients

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Background: Repetitive transcranial magnetic stimulation (rTMS) has been developed as a novel tool for improving depression by delivering magnetic stimulation to the brain. However, the apparent effects of rTMS on depression have been varied in different studies. The aims of this study were to determine whether left dorsolateral prefrontal cortex rTMS can alleviate medication-resistant depression in Chinese patients and to investigate what demographic variables or clinical features may predict better response.

Method: We designed a 2-week randomized, double-blind, sham-controlled study of add-on rTMS. A total of 30 medication-resistant patients with DSM-IV major depressive disorder or bipolar disorder, depressed episode completed 10 sessions of active or sham rTMS—10 patients at each of 2 frequencies, faster (20 Hz) or slower (5 Hz) at 100% motor threshold, and 10 patients at sham stimulation.

Results: Patients at both stimulation frequencies demonstrated a superior reduction of depression severity compared to sham stimulation (active = 55.7% vs. sham = 16.3%). The response rate for active rTMS was 60%, in contrast to 10% for the sham treatment. No difference in clinical response was observed between 5 Hz and 20 Hz active rTMS. Clinical variables showed that younger age and less severe depression at entry may predict the clinical response to rTMS. Except for 1 patient in which rTMS appeared to induce mania, this procedure posed no safety problem.

Conclusions: To our knowledge, this is the first study to demonstrate the clinical efficacy and safety of rTMS in Chinese patients. Since not all the rTMS trials in previous reports had positive results, further larger trials are still warranted.

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Major depression is a common disorder, with a lifetime prevalence from about 15% to as high as 50% when bipolar and chronic minor depression are included.[1,2] While most depressive symptoms are eliminated by the current pharmacologic treatments, as many as 50% to 60% of patients have incomplete recovery or significant side effects.[3] Recently, repetitive transcranial magnetic stimulation (rTMS) has been developed as a novel tool for delivering antidepressant treatment for refractory patients.[4,5] rTMS is a noninvasive method for manipulation of neuronal activities in the human brain. In a substantial number of studies, but not all, depressive symptoms could be relieved through rTMS delivered over the brain cortex.[6]

In addition to this evidence of the effectiveness of rTMS, there is growing interest in what factors might affect the antidepressant response to rTMS. Knowledge of these influencing factors might help us not only to explain the disparity of results for rTMS in improving depression, but also to elucidate the possible mechanism of rTMS and to understand more about the nature of depression. As far as we know, no other rTMS study has been conducted in Taiwan, and the efficacy and clinical application of this novel treatment in the Chinese population need to be explored. Thus, our aims were (1) to investigate whether 2 weeks of rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) can alleviate medication-resistant depression and (2) to examine some demographic variables and clinical characteristics that might predict the antidepressant effects of rTMS.

METHOD

Subjects

Patients who met the DSM-IV[2] criteria for major depressive episode or for bipolar disorder, depressive episode based on the Mini-International Neuropsychiatric Interview[7] were recruited for this 2-week, randomized, double-blind, sham-controlled trial of rTMS. In addition, all subjects selected were medication-resistant depressed patients, that is, patients who had failed to respond to at least 2 adequate trials of antidepressant medications prior to rTMS treatment. An adequate medication trial was defined as a minimum of 6 weeks of treatment with a

dosage adequate for treatment of depression in the majority of patients. Severity of depression was determined to be above the moderate level (i.e., Hamilton Rating Scale for Depression [21-item HAM-D][8] scores greater than 18) at entry. Patients were excluded if they had a history of epilepsy, had a history of any physical and neurologic abnormalities, had an implanted pacemaker, showed any signs of substantial risk of suicide during the trial, or previously had major head trauma or displayed any psychotic symptoms. No patient had a previous history of rTMS or electroconvulsive therapy.

For ethical reasons, all patients continued their current antidepressant medications during the 2-week course of rTMS administration. Patients were using the following medications: a serotonin-norepinephrine reuptake inhibitor (venlafaxine [N = 9], mirtazapine [N = 3]) or a purely serotonin reuptake inhibitor (paroxetine [N = 5], fluoxetine [N = 2], citalopram [N = 1], sertraline [N = 1], fluvoxamine [N = 1]), and these were used in combination treatments either with antipsychotics (N = 4: 2 with olanzapine and venlafaxine; 1 with risperidone and sertraline; and 1 with quetiapine, valproic acid, and fluoxetine); with the mood stabilizer valproic acid (N = 3: 2 with venlafaxine and 1 with citalopram); or with the stimulant methylphenidate (N = 1: with venlafaxine). Moreover, no medication changes were allowed for at least 4 weeks preceding rTMS and throughout the period of rTMS treatment. After receiving a full explanation of the procedure, all subjects signed a consent form approved by the Institutional Review Board of Veterans General Hospital-Taipei and by the National Health Department of Taiwan.

Thirty-three patients enrolled in this study and were randomly assigned to either sham treatment (N = 11) or active treatment (N = 22) with 1 of 2 different active treatment frequencies, faster (20 Hz, N = 10) or slower (5 Hz, N = 12) at 100% motor threshold. Thirty patients completed the study, and 3 dropped out. In the active lower frequency rTMS group, 2 patients had to stop the trial during the first 3 treatment sessions because of pain induced by rTMS. One patient in the sham group withdrew from the study due to worsening of clinical depression. At the end of the 2-week treatment, the blind label was broken. The patients who were initially randomly assigned to the sham treatment group were offered the option of a course of active 20 Hz rTMS treatment. Seven of 10 patients completed this open-label active trial, but the results were not used in the analysis of primary outcome data.

Menopause is the permanent cessation of menstruation resulting from loss of ovarian follicular activity.[9] By convention, we defined perimenopausal status as having irregular menstrual cycles (fewer than 6 menstrual cycles per year) and postmenopausal status as having amenorrhea for 12 months or more.[10–12]

rTMS Protocol

A trained psychiatrist (C.-C.H.) performed rTMS using a Magstim super rapid magnetic stimulator (Magstim Company, Ltd., Wales, United Kingdom) with 4 booster modules equipped with a 70-mm air-cooled figure-eight–shaped coil. The coil was held with the handle posterior and oriented sagittally. Subjects were seated upright in a comfortable chair, and foam earplugs were used during rTMS to diminish the noise from the discharging coil.

On the initial treatment visit, we determined the motor threshold (MT) at rest for the contralateral (right) *abductor pollicus brevis* muscle, as described previously.[13] The DLPFC stimulation site was defined as the region 5 cm rostral and in a parasagittal plane from the site of maximal *abductor pollicus brevis* stimulation. This method of locating the rTMS stimulation site at the DLPFC has been used in previous rTMS studies of depression.[5,14] Each day the subjects were asked about events that could have changed the MT (medications, sleep deprivation, etc.), the MT was rechecked, and the intensity of stimulation was adjusted accordingly.

Subjects received 5 Hz stimulation in 40 8-second trains over 20 minutes for 10 weekdays (total = 16,000 pulses) at 100% of MT for the active lower frequency treatment and 20 Hz stimulation in 40 2-second trains over 20 minutes for 10 weekdays (total = 16,000 pulses) at 100% of MT for the active higher frequency treatment. Sham stimulation occurred in exactly the same manner as the faster rTMS, except that the angle of the coil, rather than being tangential to the skull, was at 90 degrees off the skull. In the open-label active follow-up treatment of the sham group, the parameters were also the same as for the active faster rTMS.

Patient Assessments

Severity of depression at baseline and at the end of each week was assessed by a psychiatrist (T.-P.S.), blinded to treatment arm, using the HAM-D-21,[8] the Hamilton Rating Scale for Anxiety (HAM-A),[15] and the Clinical Global Impressions-Severity of Illness (CGI-S)[16] scale. The Beck Depression Inventory (BDI)[17] was used to assess the patient's subjective feelings. Clinical response to rTMS was evaluated by calculating percent improvement in HAM-D-21 scores from the baseline to the end of treatment. *Response* was defined as a more than 50% reduction of HAM-D-21 scores, and *remission* was defined as HAM-D-21 scores less than 8 at the end of the trial.

Statistical Analyses

Demographic variables and clinical features at entry were compared for the 3 groups (5 Hz, 20 Hz, and sham) using 1-way analysis of variance (ANOVA) or the χ^2 test. ANOVA with repeated measures (ANOVA-R) was performed using treatment group (sham, 5 Hz, and 20 Hz) as the between-subjects factor and time point (baseline,

Table 1. Demographic Data, Clinical Features, and Mood Symptom Ratings at Entry to Trial[a]

Variable	All Subjects (N = 30)	20 Hz rTMS (N = 10)	5 Hz rTMS (N = 10)	Sham (N = 10)	p
Age, y	43.1 (10.8)	43.6 (12.0)	43.2 (10.6)	42.6 (11.0)	NS
Gender, N					NS
Male	8	3	2	3	
Female	22	7	8	7	
Menopausal status, N					NS
Premenopausal	13	5	4	4	
Perimenopausal	2	0	1	1	
Postmenopausal	7	2	3	2	
Education, grade	12.2 (4.3)	13.4 (5.2)	11.1 (5.0)	12.2 (2.4)	NS
Duration of current episode of depression, mo	11.0 (10.3)	10.2 (13.1)	7.0 (3.7)	15.8 (10.7)	NS
No. of total depression episodes	5.2 (5.1)	5.2 (3.7)	4.5 (1.1)	5.9 (8.2)	NS
Diagnosis, N					NS
Major depressive episode	25	9	8	8	
Bipolar I disorder, depressed episode	2	0	1	1	
Bipolar II disorder, depressed episode	3	1	1	1	
Motor threshold[b]	67.2 (9.2)	68.2 (8.0)	68.6 (13.1)	64.8 (5.0)	NS
HAM-D score	24.1 (6.0)	23.2 (7.5)	26.5 (5.2)	22.7 (4.7)	NS
CGI-S score	4.6 (0.7)	4.5 (0.7)	4.7 (0.8)	4.7 (0.5)	NS
BDI score	31.8 (9.0)	28.0 (9.1)	33.9 (7.6)	33.4 (9.6)	NS
HAM-A score	18.6 (5.2)	16.5 (7.1)	20.6 (3.5)	18.8 (3.9)	NS

[a]Data are given as mean (SD) unless otherwise indicated.
[b]Motor threshold indicates minimal amount of machine power that induces movement of abductor pollicus brevis muscle.
Abbreviations: BDI = Beck Depression Inventory, CGI-S = Clinical Global Impressions-Severity of Illness, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, NS = nonsignificant, rTMS = repetitive transcranial magnetic stimulation.

week 1, week 2) as the within-subjects factor to compare the rTMS efficacy in the 3 different groups. If the F value was significant for any of the aforementioned mood rating scales, 2-way ANOVA-R was then used to assess differences between each pair of groups, i.e., sham versus 5 Hz, sham versus 20 Hz, and 5 Hz versus 20 Hz. Final outcome ratings were calculated by subtracting mood ratings at the end of the trial from the baseline values. One-way ANOVA with Bonferroni correction was then performed to elicit differences of the final delta ratings between treatment groups.

In seeking predictors of clinical responsiveness to rTMS, characteristics of the active rTMS treatment groups (5 Hz and 20 Hz), such as demographic variables and clinical features at entry, were compared between responders and nonresponders using the nonparametric Wilcoxon test or the χ^2 with Fisher exact test. All statistical tests were 2-sided and at the 5% significance level.

RESULTS

Patients

Thirty patients who had completed 2-week trials were included in the final analysis. There were no significant differences of age, gender ratio, or education levels among these 3 treatment groups (Table 1). The mean age was 43.1 (SD = 10.8) years, and there were 3 times as many female patients as males. The data in Table 1 also demonstrated no significant group differences in the clinical features of major depression, in terms of duration of illness, number of depressive episodes, and mood symptom ratings at entry. The motor thresholds used for locating the rTMS site were also comparable. Among the 15 female subjects receiving active treatment, 5 were postmenopausal, 1 was perimenopausal, and 9 were premenopausal.

Efficacy

Table 2 illustrates the scores on the clinical mood rating scales over time in the 3 treatment groups.

Hamilton Rating Scale for Depression. ANOVA-R revealed a significant interaction of treatment group (sham, 5 Hz, and 20 Hz) with time (baseline, week 1, week 2) on changes in HAM-D ratings ($F = 4.8$, $df = 4,54$; $p < .01$) (Table 2). ANOVA-R also disclosed a significant time-by-group effect on changes in HAM-D ratings when comparing sham versus 5 Hz ($F = 6.6$, $df = 2,36$; $p < .005$) or sham versus 20 Hz ($F = 6.5$, $df = 2,36$; $p < .005$) but not 5 Hz versus 20 Hz ($F = 0.1$, $df = 2,36$; p = NS). These data suggest that the active rTMS treatments for reducing depression are significantly better than sham treatment but are not different from each other.

The mean baseline HAM-D-21 scores ranged from 22.7 (SD = 4.7) to 26.5 (SD = 5.2) but were not different (1-way ANOVA, p=NS) between groups (sham, 5 Hz, and 20 Hz) (Table 2). However, in Table 3, changes in HAM-D-21 scores from baseline to week 1 were signifi-

Table 2. Scores on the Clinical Rating Scales of 3 rTMS Groups Over Time[a]

	Baseline			Week 1			End of Treatment			ANOVA-R Group × Time	
	Active			Active			Active				
Rating Scale	20 Hz (N = 10)	5 Hz (N = 10)	Sham (N = 10)	20 Hz (N = 10)	5 Hz (N = 10)	Sham (N = 10)	20 Hz (N = 10)	5 Hz (N = 10)	Sham (N = 10)	F[b]	p
HAM-D	23.2 (7.5)	26.5 (5.2)	22.7 (4.7)	13.2 (5.6)	15.5 (6.4)	18.3 (6.7)	9.8 (7.1)	12.3 (7.7)	19.0 (7.7)	4.8	< .01
BDI	28.0 (9.1)	33.9 (7.6)	33.4 (9.6)	22.1 (8.7)	24.0 (10.5)	27.9 (13.7)	12.8 (6.7)	19.7 (12.3)	28.7 (15.1)	3.5	.01
CGI-S	4.5 (0.7)	4.7 (0.8)	4.7 (0.48)	3.2 (0.8)	3.5 (0.7)	4.0 (0.9)	2.8 (1.1)	2.7 (1.2)	3.6 (1.1)	1.2	NS
HAM-A	16.5 (7.1)	20.6 (3.5)	18.8 (3.9)	12.0 (5.2)	12.6 (6.3)	14.6 (5.5)	11.1 (10.8)	10.7 (7.1)	12.8 (4.6)	1.2	NS

[a]Only subjects who completed the entire study are included. Data are given as mean (SD).
[b]df = 4,54.
Abbreviations: ANOVA-R = repeated measures analysis of variance, BDI = Beck Depression Inventory, CGI-S = Clinical Global Impressions-Severity of Illness, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, NS = not significant, rTMS = repetitive transcranial magnetic stimulation.

cant (1-way ANOVA, F = 4.4, df = 2,27; p < .05) as were those from baseline to week 2 (1-way ANOVA, F = 7.0, df = 2,27; p < .005). Post hoc tests showed that a significant reduction in HAM-D-21 scores in the 5 Hz group (p < .05) and a trend toward reduction in the 20 Hz group (p < .1), compared with sham treatment, was found at week 1. At the week-2 endpoint, the reductions in HAM-D-21 score by 5 Hz and 20 Hz treatments were both significantly greater than for the sham treatment (p < .01) (Table 3). The improvement rates in HAM-D scores for the sham, 5 Hz, and 20 Hz treatment groups were found to be 19.1%, 41.5%, and 43.1% after the 1-week treatment and 16.3%, 53.5%, and 57.8% at the end of the trial, respectively.

Beck Depression Inventory. Table 2 shows a similar significant interaction of treatment group (sham, 5 Hz, and 20 Hz) with time (baseline, week 1, week 2) on changes in the BDI scores (F = 3.5, df = 4,54; p = .01). When the sham versus active treatments were compared, the 5 Hz and 20 Hz trials exerted significant time-by-group effects on changes in BDI ratings (F = 3.7, df = 2,36; p < .05 and F = 5.8, df = 2,36; p < .01, respectively), suggesting that both slower and faster rTMS may reduce subjective symptoms of depression.

There were no significant differences in baseline BDI ratings or changes in BDI scores from baseline to week 1 among these 3 groups (F = 1.4, df = 2,27; p = NS and F = 1.3, df = 2,27; p = NS, respectively). However, significantly different reductions in BDI scores from baseline to week 2 were demonstrated among the 3 treatment groups (1-way ANOVA, F = 4.1, df = 2,27; p < .05). Post hoc tests showed a trend to decrease in the 5 Hz group and a significant reduction in the 20 Hz group, compared with sham treatment (p < .1 and p < .05, respectively) (Table 3). The improvement rates for subjective feelings of decreased mood symptoms for the sham, 5 Hz, and 20 Hz groups were 16.4%, 29.2%, and 21.1% after the 1-week treatment and 14.1%, 41.9%, and 54.3% at the end of the trial, respectively.

Clinical Global Improvement. Analysis by ANOVA-R revealed a significant time (baseline, week 1, and week 2) effect for reduction of CGI-S scores (F = 39.7, df = 2,54; p < .001), but no group (sham, 5 Hz, and 20 Hz) effect (F = 2.1, df = 2,27; p = NS) or group-by-time interaction (F = 1.2, df = 4,54; p = NS) (Table 2) was observed. This finding indicates a significant global improvement of CGI-S rating (23.4%–42.6%) at the end of treatment for the 3 groups, but the differences among groups did not reach significance.

Hamilton Rating Scale for Anxiety. Results similar to those for the CGI-S were found for anxiety ratings. There was a significant time (baseline, week 1, and week 2) effect for reducing HAM-A scores (F = 27.1, df = 2,54; p < .001), but no group (sham, 5 Hz, and 20 Hz) effect (F = 0.42, df = 2,27; p = NS) and no group-by-time interaction (F = 1.2, df = 4,54; p = NS) (Table 2). The improvement in anxiety symptoms by rTMS varied from 32.7% to 48.1%, but the differences between the 3 treatments were not significant.

Two-Week Extended Active rTMS for the Sham Treatment Patients

Among 10 patients who received the sham treatment, 3 discontinued further active rTMS (1 achieved remission, 1 developed mania,[18] another patient refused). The remaining 7 patients received a 2-week course of 20 Hz active rTMS, and 3 of them (43%) became responders at the end of the trial, further supporting the outcome of the original active rTMS trial groups.

Comparison of Characteristics Between rTMS Responders and Nonresponders

With active rTMS treatment, response rate was 60% and remission rate was 50% for each 5 Hz and 20 Hz treatment group, while response was only 10% (1 of 10 patients) for the sham treatment group. Fisher exact test revealed that the responder rates for active rTMS patients were significantly higher than for the sham treatment group ($\chi^2 = 6.8$, df = 1, p = .01).

In the search for predictors of clinical outcome, Table 4 illustrates significant differences in age, age at disease onset, menopausal status, and scores of depression and

Table 3. Changes in Mean HAM-D and BDI Scores From Baseline to End of Trial

Treatment Group	Change in HAM-D Score, Mean (SD)	vs Sham			vs 5 Hz rTMS		
		t Test	df	p Value	t Test	df	p Value
Week 1							
Sham	4.4 (6.3)						
5 Hz rTMS	11.0 (4.9)	–2.6	18	< .05			
20 Hz rTMS	10.0 (4.8)	–2.2	18	< .1	0.46	18	NS
Week 2							
Sham	3.7 (9.3)						
5 Hz rTMS	14.2 (6.0)	–3.0	18	< .01			
20 Hz rTMS	13.4 (4.9)	–2.9	18	< .01	0.33	18	NS
Treatment Group	Change in BDI Score, Mean (SD)	vs Sham			vs 5 Hz rTMS		
		t Test	df	p Value	t Test	df	p Value
Week 1							
Sham	5.5 (6.4)						
5 Hz rTMS	9.9 (6.0)	–1.6	18	NS			
20 Hz rTMS	5.9 (7.5)	–0.13	18	NS	1.3	18	NS
Week 2							
Sham	4.7 (9.1)						
5 Hz rTMS	14.2 (10.4)	–2.2	18	< .1			
20 Hz rTMS	15.2 (7.5)	–2.8	18	< .05	–0.25	18	NS

Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression, NS = nonsignificant, rTMS = repetitive transcranial magnetic stimulation.

anxiety ratings at entry between responders and nonresponders. Most of the responders were younger than 50 years, with onset of disease before 35 years, and were of premenopausal status, suggesting a relationship between the age and hormonal status of females and their clinical treatment response. All 5 postmenopausal patients and only 1 of 9 premenopausal patients did not respond to rTMS, suggesting that menopausal status may play an important role in the prediction of clinical response. In addition, less severe baseline ratings on the HAM-D, the BDI, and the HAM-A were associated with better clinical outcome. Factors that showed no ability to predict clinical response were gender, type of depression (major depressive episode vs. bipolar disorder, depressed episode), number of previous depressive episodes, and duration of current episode.

Safety and Tolerability

In general, there was no safety problem, and patients withstood the procedure well. The rate of completing the study was high. As noted earlier, 3 subjects dropped out of the study because of pain and worsening of clinical symptoms. In addition, among the 30 subjects who completed the study, 4 in the active rTMS group (2 for faster, 2 for slower) and 1 in the sham group reported headaches. Most of them were relieved by taking rest, and 1 patient needed acetylsalicylic acid to diminish his headaches. In the open-label active treatment group, 1 patient suffered from a panic episode, which had happened before during her long course of major depression. One of the bipolar I depression patients developed hypomania after 3 sessions of rTMS treatment.[18]

DISCUSSION

This randomized, double-blind, sham-controlled study assessed the effect of rTMS applied to the left DLPFC as an add-on treatment in medication-resistant depressed patients. Patients demonstrated a significant reduction in the severity of depression following 10 continuous daily treatments with 5 Hz or 20 Hz active rTMS relative to sham rTMS. Improvement in the symptoms of depression was detected primarily in HAM-D and BDI ratings, with mean score decreases of 55.5% and 39%, respectively. In addition, 60% of the patients receiving active rTMS treatment were responders, and among them, 83% were remitters (HAM-D score < 8). In contrast, in the sham treatment group, the symptoms of depression improved only 16% to 20%, and only 1 of 10 patients was a responder.

In the published studies of rTMS on major depression in which a double-blind sham-controlled design was used, the range of effectiveness varied. Some studies demonstrated significant antidepressant effects, while others showed only modest effects or no effect at all. This disparity of results was suggested to be due to patient characteristics or rTMS technical parameters that might affect treatment success.[19] For example, George et al.[14] reported that active rTMS reduced depressive symptoms significantly more than did the sham control (35.6% vs. 21%, respectively). The responder rate for active rTMS was 45%, while it was 0% for the sham treatment. In medication-resistant depression, Garcia-Toro et al.[20]found a 30% decrement of depression score in real rTMS versus 10% in the sham group, and 29% of the patients responded to rTMS (more than a 50% reduction in symp-

Table 4. Characteristics of Responders and Nonresponders Among Patients Receiving Double-Blind Active rTMS[a]

Variable	Responders (N = 12)	Nonresponders (N = 8)	z/χ^2	p
Gender, N			1	NS
Female	9	6		
Male	3	2		
Age, y	38.8 (9.3)	50.3 (10.1)	–2.6	< .05
Age at disease onset, y	29.8 (9.3)	43.6 (9.7)	–2.5	< .05
Menopausal status, N			9.4	< .05
Premenopausal	8	1		
Perimenopausal	1	0		
Postmenopausal	0	5		
Duration of current episode, mo	6.2 (3.8)	12.3 (14.1)	–0.51	NS
No. of previous episodes	4.9 (2.6)	4.8 (3.0)	–0.08	NS
Motor threshold, %[b]	67.7 (8.6)	69.4 (13.6)	–0.04	NS
HAM-D score at entry	22.2 (4.0)	28.9 (7.6)	–2.2	< .05
CGI-S score at entry	4.4 (0.51)	4.9 (0.99)	–0.99	NS
BDI score at entry	27.6 (9.5)	36.0 (3.9)	–2.1	< .05
HAM-A score at entry	16.2 (4.3)	22.1 (6.2)	–2.3	< .05
Type of depression, N			0.8	NS
Major depressive episode	10	7		
Bipolar disorder, depressed episode	2	1		

[a]Data are given as mean (SD) unless otherwise indicated.
[b]Motor threshold indicates minimal amount of machine power that induces movement of abductor pollicus brevis muscle.
Abbreviations: BDI = Beck Depression Inventory, CGI-S = Clinical Global Impressions-Severity of Illness, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, NS = not significant, rTMS = repetitive transcranial magnetic stimulation.

toms) compared to 6% for the sham treatment. Fitzgerald et al.[21] demonstrated a 15% improvement in the HAM-D rating score and a 40% responder rate with high-frequency rTMS. Using parameters comparable to those used in the study of George et al.[14] (patients' age, gender, medication-resistant status, depression severity at entry, and the same location [left prefrontal cortex] where rTMS was applied), our data showed a greater decrease in symptoms of depression (55%) and a higher responder rate (60%) than the George et al.[14] study (36% and 45%, respectively). Neither study found significant differences in antidepressant efficacy between the 2 frequencies of rTMS used (5 Hz vs. 20 Hz). However, the only difference was the concurrent use of antidepressants in our study compared with medication-free status in the George et al.[14] study. Whether use of medications along with rTMS might account for more efficacy requires further study. In addition, it may be suggested that the lower efficacy of rTMS that Garcia-Toro et al.[20] obtained compared with our study might be attributed to their use of older patients (51 years vs. 43 years, respectively) and their use of a lower rTMS dose (total daily = 1200 pulses vs. 1600 pulses). Similarly, the key difference between our study and the Fitzgerald et al.[21] study was that their patients had a more severe depression rating at entry than ours (HAM-D score 32–35 vs. 24–26, respectively), and they used a lower rTMS dose (total daily = 1000 pulses). These speculations that might account for different levels of efficacy with almost identical parameters in the above studies merit further investigation.

Results have been conflicting when using rTMS as a stand-alone treatment (without concomitant pharmacotherapy) for medication-resistant depression. Two studies found that improvement in depression after active rTMS is better than after sham rTMS,[14,22] while 3 other studies did not find any benefit from active rTMS versus sham rTMS.[23–25] Given these results, whether use of antidepressants with rTMS may augment the underlying antidepressant effect or is a confounding factor for clinical efficacy still remains unclear. To resolve this issue, Garcia-Toro et al.[26] conducted a study using a single medication (sertraline) to test if high-frequency rTMS may speed up and strengthen the therapeutic response to sertraline in major depression. They found that high-frequency rTMS did not increase the effectiveness of this standard antidepressant.

It is noteworthy that the concurrent use of medications, especially valproic acid, could be a potential confounding factor. As indicated in an earlier study by Hoffmann et al.,[27] anticonvulsant drugs were associated with reduction in cortical excitability and poorer response to rTMS in patients with schizophrenia. On the contrary, Ziemann et al.[28] and Ziemann[29] found no motor excitability changes under anticonvulsants. Consistent with the latter report, our study elicited no significant difference in MT between patients' concomitant use of valproic acid (N = 4) and nonuse (N = 26) ($t = 0.24$, $df = 28$, $p > .05$). Additionally, there was also no difference in MT among varied antidepressants and between rTMS responders and nonresponders. Further, as shown in the method section, the relatively small number of subjects, combined with the concurrently large number of antidepressants, made the power of analysis very small.

For ethical reasons, our patients could not be asked to discontinue their medications while they received rTMS. Furthermore, the heterogeneity of concomitant antidepressant medications might have interacted differently with rTMS.[29] Therefore, whether the combination of drug with rTMS treatments, using the same dosages and medications as the patient used previously, is more beneficial than the stand-alone rTMS or may interfere with clinical response is in need of further research.

Although no significant differences in CGI-S rating with 2-week rTMS treatment among these 3 subject groups were observed, there seemed to be a greater percentage decrease in CGI-S score from baseline in the 20 Hz (38%) and 5 Hz (43%) treatment groups than in the sham group (23%). However, when comparing the difference between the active group (combined 20 Hz and 5 Hz) versus the sham group, it became a trend significant for active rTMS than sham (time and group interaction:

$F = 3.2$, $df = 1,28$; $p < .1$), indicating that CGI-S assessment is still in line with the results of the HAM-D and BDI. Part of the reason for CGI-S not being sensitive to changes with rTMS treatment may be that the range of the CGI-S scale is relatively smaller than the ranges of the HAM-D and BDI.

Despite the widely differing technical parameters used in a variety of rTMS studies, rTMS treatment success may be predicted by some of the patients' parameters, such as absence of psychosis, younger age, previous response to rTMS, and less depression at baseline.[19,30] In the present study, no subjects were psychotic, and the responders in comparison to nonresponders were younger, had onset of depression at an earlier age, had experienced a shorter duration of this depression episode, had less severe depression at entry, and were mostly premenopausal women.

Previous studies addressed age as a predictor of treatment success.[31–33] They observed that older patients responded less well to rTMS than younger patients. Kozel et al.[32] found that no depressed patients older than 55 years or with a scalp-to–prefrontal cortex distance greater than 17 mm responded to rTMS. This scalp-to–prefrontal cortex distance was also increased with age, suggesting that an age-related variable, such as brain atrophy, may confer a resistance to antidepressant response, whether with medications or with rTMS. Given that observation, basing the rTMS power only on the motor threshold of the motor cortex may result in an inadequate dose of rTMS.[34] Our study has confirmed that the age factor may distinguish responders from nonresponders, and all responders were under age 55 years. Larger studies in elderly depressed subjects are needed to directly test this hypothesis.

Our data found that none (0%) of the 5 postmenopausal females were responders, whereas 8 (88.9%) of 9 premenopausal women were, suggesting that menopausal status may play an important role in the antidepressant effect of rTMS. However, since menopausal status was highly associated with age, and age was found to be a predictor for rTMS response, no definite conclusion of the menopausal factor relating to the efficacy of rTMS could be drawn. To see if age is a more important factor than menopausal status for the efficacy of rTMS, study of male subjects is one of the solutions. Nevertheless, the sample size of our male patients is too small to be tested. The menopausal status may therefore be a potential item to explore in the future.

Consistent with a previous Grunhaus et al. report,[30] our data showed that patients with the more severe subjective and objective depression ratings at baseline tended to show a lower clinical response to rTMS. Severity of depression as a predictor of response to rTMS treatment was also supported by the report of Gershon et al.,[19] which indicated that psychotic depressed patients responded well to electroconvulsive therapy (ECT) but not to rTMS. However, for nonpsychotic depressed patients, ECT and rTMS were equally effective. This result, along with our data, suggest that rTMS may be more beneficial for a subset of less severely depressed and nonpsychotic patients and may replace ECT to provide a safer and more tolerable alternative.

Limitations of this study require consideration. First, the small sample size in our study might have prevented the detection of real differences between treatment arms, and therefore the finding of no differences between the 2 active treatments may be a type II error. Second, although the sham rTMS treatment was inferior to the active ones in our study, the sham treatment still showed a minimal clinical effect. The response to sham stimulation may be due to a placebo effect. The sham condition involved considerable clinical contact and attention to potentially therapeutic activities. However, there may also be a meaningfully active stimulation effect of sham treatment.[19] Third, all of our patients received only a 2-week trial of rTMS. The clinical response of reduction in both the subjective (BDI) and the objective (HAM-D) ratings seemed not to appear in the first week, unlike the acute effect within 5 days demonstrated by Figiel et al.[31] and Pascual-Leone et al.[5] In our study, the significant clinical response was seen by the second week, reflecting that the lag time for significant effect to occur is shorter than for most antidepressant medications. Does this mean that the optimal duration for rTMS treatment is 2 weeks, or do the treatment sessions need to be extended to increase the potential for clinical effect? Fourth, our study also could not assess how long the clinical effects of rTMS might persist in responders. Long-term outcome and safety follow-up studies on this cohort are needed. Fifth, to assess the ovarian function concomitantly with taking the patient's history might be more reliable in determining menopausal status.

To our knowledge, this is the first study using rTMS to treat depression in Chinese patients. The results of our study support some previous reports that high-frequency rTMS over the left dorsal prefrontal cortex may exert a significant antidepressant effect in medication-refractory patients and identify a number of potential predictors of better outcome with rTMS treatment. Nevertheless, not all of the rTMS trials were positive; there were still many negative studies.[23–25,35–37] Additionally, even with the positive results, the antidepressant effect of rTMS was not so robust, suggesting being cautious on the efficacy of rTMS. Further systematic study of the effect of rTMS on depression should consider using larger samples, extending treatment sessions, and conducting longer-term follow-up and should focus on investigating the influence of age and menopausal status. Through these efforts, the underlying mechanisms of rTMS and the guidelines for future management of depression using rTMS will be elucidated.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone

(Risperdal), methylphenidate (Ritalin and others), sertraline (Zoloft), valproic acid (Depakene and others), venlafaxine (Effexor).

REFERENCES

1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
3. Keller MB, Lavori PW, Muller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: a 5-year prospective follow-up of 431 subjects. Arch Gen Psychiatry 1992;49:809–816
4. George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 1995;6:1853–1856
5. Pascual-Leone A, Rubio B, Pallardo F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233–237
6. George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. Arch Gen Psychiatry 1999;56: 300–311
7. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
8. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
9. World Health Organization Scientific Group. Research on the Menopause. Geneva, Switzerland: World Health Organization. WHO Technical Services Report Series; 1981:670
10. Sowers MR, La Pietra MT. Menopause: its epidemiology and potential association with chronic diseases. Epidemiol Rev 1995;17:287–302
11. Harlow BL, Wise LA, Otto MW, et al. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry 2003;60:29–36
12. Cohen LS, Soares CN, Poitras JR, et al. Short-term use of estradiol for depression in perimenopausal and postmenopausal women: a preliminary report. Am J Psychiatry 2003;160:1519–1522
13. Pridmore S, Fernandes J, Nahas Z, et al. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. J ECT 1998;14:25–27
14. George MS, Nahas Z, Molloy M, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiatry 2000;48: 962–970
15. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
16. Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
17. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
18. Huang CC, Su TP, Shan IK. A case report of repetitive transcranial magnetic stimulation-induced mania [letter]. Bipolar Disord 2004;6:444–445
19. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. Am J Psychiatry 2003;160:835–845
20. Garcia-Toro M, Mayol A, Arnillas H, et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. J Affect Disord 2001;64:271–275
21. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 2003;60:1002–1008
22. Jorge RE, Robinson RG, Tateno A, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol Psychiatry 2004;55:398–405
23. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol Psychiatry 2000;47:332–337
24. Manes F, Jorge R, Morcuende M, et al. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. Int Psychogeriatr 2001;13:225–231
25. Holtzheimer PE, Avery D, Schlaepfer TE. Antidepressant effects of repetitive transcranial magnetic stimulation [letter]. Br J Psychiatry 2004; 184:541–542
26. Garcia-Toro M, Pascual-Leone A, Romera M, et al. Prefrontal repetitive transcranial magnetic stimulation as add-on treatment in depression. J Neurol Neurosurg Psychiatry 2001;71:546–548
27. Hoffman RE, Boutros NN, Hu S, et al. Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. Lancet 2000;355:1073–1075
28. Ziemann U, Lonnecker S, Steinhoff BJ, et al. Motor excitability changes under antiepileptic drugs. In: Stefan H, Andermann F, Chauvel P, et al, eds. Plasticity in Epilepsy: Dynamic Aspects of Brain Function, vol. 81. Philadelphia, Pa: Lippincott, Williams and Wilkins; 1999:291–298
29. Ziemann U. TMS and drugs. Clin Neurophysiol 2004;115:1717–1729
30. Grunhaus L, Dolberg OT, Polak D, et al. Monitoring the response to rTMS in depression with visual analog scales. Hum Psychopharmacol 2002;17:349–352
31. Figiel GS, Epstein C, McDonald WM, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. J Neuropsychiatry Clin Neurosci 1998;10:20–25
32. Kozel FA, Nahas Z, deBrux C, et al. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci 2000;12: 376–384
33. Janicak PG, Dowd SM, Martis B, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. Biol Psychiatry 2002;51:659–667
34. McConnell KA, Nahas Z, Shastri A, et al. The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. Biol Psychiatry 2001;49:454–459
35. Loo CK, Mitchell PB, Croker VM, et al. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. Psychol Med 2003;33:33–40
36. Loo C, Mitchell P, Sachdev P, et al. rTMS: a sham-controlled trial in medication-resistant depression [abstract]. Biol Psychiatry 1998;43:95
37. Boutros NN, Gueorguieva R, Hoffman RE, et al. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. Psychiatry Res 2002;113:245–254