Repetitive Transcranial Magnetic Stimulation versus Electroconvulsive Therapy for Major Depression: Preliminary Results of a Randomized Trial

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Background: *Many severely depressed patients do not benefit from or tolerate existing treatments. Repetitive transcranial magnetic stimulation (rTMS) has been reported to benefit depression. We compared rTMS to electroconvulsive therapy (ECT) in severely ill, depressed patients.*

Methods: *Twenty-five patients with a major depression (unipolar or bipolar) deemed clinically appropriate for ECT were randomly assigned to rTMS (10–20 treatments, 10 Hz, 110% motor threshold applied to the left dorsolateral prefrontal cortex for a total of 10,000–20,000 stimulations) or a course of bitemporal ECT (4–12 treatments). The primary outcome measure was the 24-item Hamilton Depression Rating Scale (HDRS). The Brief Psychiatric Rating Scale (BPRS), Young Mania Rating Scale (YMS), and Clinical Global Impression scale (CGI) were secondary measures. Minimal rescue medications were utilized.*

Results: *Mean percent improvement on the baseline HDRS score did not significantly differ between the two treatments (i.e., 55% for the rTMS group vs. 64% for the ECT group [*p = *ns]). With response defined as a 50% reduction from baseline and a final score* ≤ *8 on the HDRS, there was also no significant difference between the two groups. We did not observe any differences between groups on the secondary measures.*

Conclusions: *A 2–4 week randomized, prospective trial comparing rTMS to ECT produced comparable therapeutic effects in severely depressed patients.* Biol Psychiatry 2002;51:659–667 © *2002 Society of Biological Psychiatry*

Key Words: rTMS, ECT, major depression, randomized trial

Introduction

Depression is a common and serious illness afflicting 10% of all patients seeking treatment at primary health care facilities worldwide (World Health Organization 2000). Major depressive disorder (MDD) is associated with substantial personal and societal costs, owing to issues such as suicide, lost productivity, and the high rates of health service utilization (Janicak et al 2001; Sturm and Wells 1995).

Since the 1950s, antidepressants have been the primary treatment approach for depressive disorders, and electroconvulsive therapy (ECT) has remained an option for patients refractory or intolerant to pharmacotherapy (Janicak et al 2001). Although there is strong support for antidepressant efficacy (Janicak et al 1985, 1989), a substantial number of depressed patients do not benefit from or cannot tolerate psychopharmacotherapy or ECT (Janicak and Martis 1999). Furthermore, ECT has well-documented side effects, including short-term anterograde, retrograde, and autobiographical memory deficits; is costly; often requires hospitalization; and is associated with substantial social stigma (Fink 1997; Janicak et al 1991). Given the pervasive nature of depression and the need for more effective, safer, and more socially acceptable therapeutic strategies, alternative approaches are being investigated, including repetitive transcranial magnetic stimulation (rTMS) (Martis and Janicak 2000; Gates et al 1992; Hufnagel et al 1993), vagal nerve stimulation (Rush et al 2000), and bright-light therapy (Terman et al 2001).

Repetitive TMS utilizes an electrical current that passes through a metal coil applied to the scalp to produce fluctuating magnetic pulses (George et al 1998a). Unlike electrical stimulation, these magnetic pulses enter the brain painlessly and unimpeded, causing neuronal depolarization in a localized area under the coil and possibly distal effects as well (Barker et al 1987; Lisanby et al 2000a). Early observations in which this technique was used as a neurophysiological probe indicated that some neurology patients experienced mood elevation (Lisanby et al 2000a). The subsequent therapeutic application of

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transcranial magnetic stimulation (TMS) for depression has produced encouraging preliminary results (Beedle et al 1998; Hallet and Cohen 1989). Furthermore, both human and animal studies have observed a number of similar effects induced by rTMS, ECT (or electroconvulsive shock), and antidepressants on the endocrine system, sleep parameters, and in certain behavioral and biochemical measures, all of which are associated with potential antidepressant properties (Keck et al 2001; Krystal et al 2000; Lisanby et al 2000b; Szuba et al 2000).

Concurrent with these observations, several studies have explored the potential antidepressant effects of rTMS in humans. To date, much of the literature has centered on comparisons of rTMS to sham rTMS. Although there are significant methodological questions to be resolved (Loo et al 2000; Lisanby et al 2001a), and not all reports have been positive (e.g., Loo et al 1999; Padberg et al 1999), most studies observed that patients treated with rTMS had a significantly better result than those receiving sham rTMS (George et al 1997, 2000; Kimbrell et al 1999; Klein et al 1999; Nahas et al 1998; Pascual-Leone et al 1996). Furthermore, although the literature reveals uncertainty as to what constitutes optimal rTMS parameters for the treatment of depression, we believe the existing data provide reasonable direction, and our choice of parameters for the present study reflects this literature (see Table 1 for a description of the parameters).

The relative efficacy of rTMS versus sham rTMS has also been studied in patients with drug treatment–resistant depression (TRD), albeit variably defined (Avery 1999; Berman et al 2000; Figiel et al 1998; Greer 1998; Hoflich et al 1993; Loo et al 1999; Nahas et al 1998; Padberg et al 1999; Pascual-Leone et al 1996). Overall, the majority of studies have reported a positive outcome with rTMS for TRD (see Martis and Janicak 2000 for review).

There have also been favorable preliminary results in comparisons of rTMS to ECT for a more severely ill, often drug-resistant, heterogeneous group of patients typically seen in clinical practice (Grunhaus et al 2000; Pridmore et al 2000). The aim of the present study was to extend these findings by comparing the efficacy of rTMS to ECT for patients with major depression for whom ECT would be considered appropriate in a general clinical setting. The issues that differentiated this study from earlier comparisons were the use of more aggressive rTMS parameters; administering ECT with bitemporal electrode placement; and minimizing the use of concurrent medication.

Methods and Materials

Subjects

Eligible subjects were between the ages of 18 to 75 years, met the Structured Clinical Interview for Diagnosis (SCID)-derived DSM-IV criteria (American Psychiatric Association 1994) for major depression (unipolar or bipolar) and were deemed clinically appropriate for a course of ECT by their treating psychiatrist. The severity of depression and/or lack of adequate response to or intolerance of pharmacotherapy were important factors in making this decision (American Psychiatric Association 1990). All subjects enrolled in the study had a chronic illness, scored greater than twenty on the Hamilton Rating Depression Scale (HDRS; Hamilton 1960), and had multiple medication trials. Twenty-five subjects (age range, 18–66) diagnosed with a depressive episode (unipolar or bipolar) were randomized to rTMS or ECT (see Table 2). One subject randomized to ECT withdrew from the study after receiving only three treatments and before any clinical effect or assessment. Only one patient crossed over from ECT to rTMS, achieving a 60% reduction on the HDRS with rTMS versus only a 36% reduction with ECT (Levy et al 2000). This patient, however, inadvertently received low-energy right unilateral RUL-ECT. One subject withdrew from rTMS treatment following four sessions and before any clinical effect or assessment. Therefore all analyses related to treatment response are based on 22 subjects.

Table 1. ECT and rTMS Administration Parameters

ECT administration:
- ECT treatment parameters
  - Monday, Wednesday, Friday treatment schedule
  - MECTA SR1 or Thymatron™ DGx device
  - Bitemporal stimulus electrode placement
  - 100% oxygenation
  - Methohexitol (1 mg/kg)
  - Succinylcholine (1 mg/kg)
  - Minimal rescue medications were used. Those medications included sedative–hypnotics (e.g., zolpidem 5–20 mg q.h.s., p.r.n.) and occasionally lorazepam (1–2 mg p.o. p.r.n.) for anxiety
- 3–12 bitemporal ECT treatments
- If subjects meet response criteria at treatment 3 through 12, study is completed
- If subjects do not meet response criteria by the 12th treatment they are offered the option to cross over to rTMS

rTMS administration:
- rTMS treatment parameters:
- Monday through Friday daily treatment schedule
- Magstim Super Rapid™ device with double 70mm coil (Magstim Company US, LLC: New York, NY)
- Left dorsolateral, prefrontal cortex; 110% MT; 10 Hz frequency
- Twenty trains of 50 stimulations per train, each 5 sec in duration (i.e., 1000 stimulations per session; total of 10,000–20,000 stimulations per course).
- 20, 30-sec, inter-train intervals
- Minimal rescue medications (e.g., anxiolytic, sedative–hypnotic) as described above
- To avoid any potential hearing impairment patients also wore earplugs during the procedure
- 10–20 rTMS treatment sessions
- If subjects meet response criteria at treatment 10 or 15, their study participation is completed
- If subjects do not meet criteria by session 20, they are offered the option to cross over to ECT

ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; MT, motor threshold.

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Table 2. Clinical Characteristics of the Sample

	Treatment	
	rTMS	ECT
Number of subjects	15	11
Gender (M/F)	11/4	6/5
Race:		
African American	2	1
Caucasian	13	9
Asian	0	1
Diagnosis		
Bipolar–psychotic	1	3
Bipolar–nonpsychotic	3	1
Unipolar–psychotic	2	3
Unipolar–nonpsychotic	8	4
Mean no. of treatments (SD)	14 (5)	7 (3)
	$n = 13$	$n = 9$
Mean no. of treatment weeks (SD)	3.2 (1.2)	2.5 (1.1)

rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy; M, male; F, female.

Following a description of all procedures, subjects provided informed consent as approved by the University of Illinois at Chicago, Alexian Brothers Hospital, and the University of Chicago's Institutional Review Boards. Patients were excluded if they had any serious medical conditions that would preclude a course of ECT or rTMS or a history of clinically significant substance or alcohol abuse/dependency within the previous 3 months. Females who were pregnant or of childbearing potential not on acceptable contraception were also excluded because of unknown risks to the fetus. Subjects were also excluded if they had intracranial metallic or magnetic implants or a pacemaker.

Methods

Subjects were randomly assigned to either the ECT or rTMS treatment arm. Following the initial randomized treatment trial, subjects who did not meet response criteria could crossover to the alternative arm. Using the Magstim Super Rapid™ device, rTMS was administered as a U.S. Food and Drug Administration–approved investigational procedure at the Psychiatric Clinical Research Center at the University of Illinois at Chicago. Electroconvulsive therapy was administered at three sites: the University of Illinois clinical psychiatric unit, Alexian Brothers Hospital, and the University of Chicago. Table 1 lists the schedules and treatment parameters for both ECT and rTMS administration.

There were no differences between the rTMS and ECT treatment groups in terms of age, number of previous hospitalizations, age at first episode, length of episode, length of medication washout, and baseline symptoms (see Table 3). There were also no differences in the history of ECT treatment (Fisher's Exact Test; p = ns) and the gender distribution (Fisher's Exact Test; p = ns) between the two groups.

In rTMS, motor threshold (MT) was determined by using the right first dorsal interosseous (FDI) as the target muscle (Wassermann et al 1996). Mapping studies have found that the greatest responses for FDI stimulation are derived from coil (center) placement in a lateral–sagittal orientation at a point 2 cm behind and 4 cm to the left of the nasion–inion line. Therefore, our point of stimulation began in approximately this region. The stimulator was set at 1 Hz, a low intensity, and methodically moved across the left frontal–parietal region of the cranium centered at the above-indicated point until the motor cortex for the FDI was located. Up to 10 single pulses were given at each level of intensity. Beginning at 60% intensity, it was increased by 2% and the procedure repeated until FDI MT was achieved, which was defined as the stimulus intensity that reliably produces visibly observable right FDI muscle contractions. The point of prefrontal cortex magnetic stimulation was determined by moving the coil 5 cm anteriorly from the point of MT determination. The site was then marked for reference with an indelible skin marker.

Stimulus parameters for ECT were determined by the use of preselected dosage methods when using the MECTA SR 1 device and the age-adjusted method when using the Thymatron™ DGx device as described in the manufacturers' instruction manuals. Dosing was adjusted during the treatment based on seizure duration, side effects, and response. Patients recently tapered from benzodiazepines or anticonvulsants were started at lower stimulus intensity, owing to the possibility of prolonged initial seizures. Motor and electroencephalogram (EEG) seizure durations were generally quite robust. The mean length of seizure duration as measured by EEG recording was 48.93 (13.26) sec with a minimum of 29 sec and a maximum of 74 sec.

Before treatment, 20 of the 22 subjects completed a brief medication washout (mean number of days = 4 ± 3). There were

Table 3. Mean Demographic Information for the Entire Sample

	rTMS	ECT	Total	p
Age (SD)	42.87 (12.9)	42.73 (14)	42.04 (13.9)	.979
Number previous hospitalizations	6.9 (8.9)	5.50 (7)	5.9 (8.1)	.697
Age at first episode	29.20 (9.9)	25.38 (9)	27.40 (8.8)	.373
Length of episode in weeks	22.20 (24.5)	12.67 (7)	16.33 (19.3)	.178
Length of medication washout in days	2.47 (2.4)	3.73 (4)	3.00 (3.5)	.348
Baseline HDRS	32.53 (6.4)	33.36 (9)	31.86 (7.4)	.782
Baseline YMS	30.7 (3.2)	5.09 (5)	3.45 (3.6)	.194
Baseline BPRS	35.1 (3.9)	39.00 (10)	36.3 (7.1)	.163
CGI baseline severity of illness	4.93 (0.8)	5.45 (0.9)	5.2 (0.9)	.139

rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; YMS, Young Mania Rating Scale; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale.

no differences between groups in medications received before washout. No patients were receiving depot neuroleptics, and those previously treated with fluoxetine had not received that medication for at least 1 month before starting the trial. Ratings were administered at baseline and weekly throughout the course of ECT/rTMS. Assessments included the 24-item HDRS, the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), the Young Mania Rating Scale (YMS; Young et al 1978), and the Clinical Global Impression scale (CGI; Guy 1976). Response was defined "*a priori*" as a 50% decrease in HDRS score from baseline and a total HDRS score of 8 or less. Raters were first trained during formal educational seminars, then co-rated with an experienced rater, and finally conducted supervised interviews. The intra-class coefficient among raters for the HDRS was 0.958. Given the experimental nature of the procedure, data were collected on all adverse events associated with the rTMS procedures (i.e., seizure activity, psychiatric side effects, and local skin irritation) through an open-ended questionnaire.

Every attempt was made to minimize the use of concomitant rescue medications. Total avoidance of adjunctive medications in severely depressed patients receiving ECT or rTMS is not always possible owing to significant sleeplessness, anxiety, apprehension, and psychosis. Anxiolytics (primarily lorazepam or zolpidem) were used sparingly, provided only on a p.r.n. basis, and an attempt was made to slowly taper their use. In all cases, those subjects who received anxiolytics did so from the outset of the trial. Three subjects received clonazepam during the study, because they had been receiving it before admission. Early in the study, three of the ECT subjects with psychosis also received rescue antipsychotic medication for at least part of the treatment course. This was stopped for all subsequent ECT subjects, and the rTMS subjects did not receive any antipsychotic medication.

Data Analysis

Clinical improvement was computed in several ways. A paired samples *t* test comparing baseline to end-of-treatment ratings was computed for each group. A continuous measure of improvement was obtained by computing percent change on the rating scale total scores ((pretreatment − posttreatment)/pretreatment). Additional nonparametric tests were also run to further explore the results. In addition, a categorization of responders or nonresponders was based on whether a subject achieved at least a 50% reduction from baseline and a total score of ≤8 on the final HDRS rating. All *p* values are two-tailed. Pearson correlations were used to examine the relationship between continuous measures.

Results

The data analyses of response to treatment included all subjects who completed the study ($n = 22$). We computed a paired samples *t* test comparing baseline and end-of-treatment HDRS total within each group. Both the rTMS and ECT groups evidenced significant improvement [$t(12) = 4.7$, $p = .000$, and $t(8) = 5.0$, $p = .001$, respectively]. Further, based on percent change scores comparing baseline to end-of-treatment, there were no significant differences between the ECT and rTMS groups [$t(20) = .587$, $p = .564$] (see Table 4). Thus, both groups evidenced a significant decrease in the baseline HDRS at the end of treatment and the decrease was not significantly different between the two groups. Given the present sample size, a difference of 1.3 SD between the two groups would be detected, if present with power 0.81 (2 sided test, alpha = 0.05).

Table 4. Mean HDRS Scores and Percent Change

	Baseline	End of treatment	Percent change
rTMS (SD) ($n = 13$)	32.2 (6.8)	13.9 (11.1)	55% (36)
ECT (SD) ($n = 9$)	31.4 (8.5)	10.9 (9.5)	64% (30)
TOTAL (SD) ($n = 22$)	31.9 (7.4)	12.8 (10.4)	59% (33)

HDRS, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy.

We also employed a rigorous *a priori* response criteria, defined as a ≥50% decrease from baseline HDRS and a total final score ≤ 8. Utilizing both of these response criteria, we found no significant difference in response rates between the treatment groups (Fisher's Exact Test; $p =$ ns) (see Table 5).

Within each group, a paired samples *t* test comparing baseline BPRS total score to end-of-treatment total score evidenced significant improvement in those subjects treated with rTMS [$t(12) = 3.47$, $p = .005$ and ECT $t(8) = 2.9$, $p = .019$]. A paired samples *t* test comparing baseline YMS to end-of-treatment scores found no significant change in the rTMS [$t(12) = .353$, $p = .730$] or in the ECT [$t(8) = -1.08$, $p = .310$] groups. The mean score on the CGI improvement item averaged a score of 2 (much improved) for both the rTMS and ECT groups.

Analyses of change scores on our secondary measures (i.e., BPRS, YMS, and CGI) found no significant differences between the treatment groups [BPRS $t(20) = -1.08$, $p = .292$; YMS $t(9.5) = -0.935$, $p = .373$; and CGI $t(19) = -0.051$; $p = .960$] (see Table 6). All of the

Table 5. Number of Subjects Who Achieved a ≥50% Reduction from Baseline and a Final HDRS Score of ≤8 by Treatment Group

	≥50; ≤8	<50%; >8	Response rate
rTMS ($n = 13$)	6	7	46%
ECT ($n = 9$)	5	4	56%

Fisher's Exact test; $p =$ ns.
HDRS, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; ECT, electro convulsive therapy.

Table 6. Mean Scores on Secondary Measures of Response

	BPRS	YMS	CGI
rTMS (n = 13)			
Baseline (SD)	35.2 (4.2)	2.7 (3.2)	
Final (SD)	27.6 (6.9)	2.5 (3.0)	2.1 (1.0)
ECT (n = 9)			
Baseline (SD)	38 (9.92)	5 (4.10)	
Final (SD)	26 (10.63)	3 (3.50)	2 (1.62)

t test; p = ns.
BPRS, Brief Psychiatric Rating Scale; YMS, Young Mania Rating Scale; CGI, Clinical Global Improvement Scale; rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy.

qualitative statements above hold when based on nonparametric techniques.

A post hoc examination of the subjects who responded to rTMS (n = 6) revealed a significant correlation between the number of treatments to achieve response (defined as a ≥50% improvement and a score of ≤8 on the HDRS) and age [$r(4) = .90$, $p < .05$]. By contrast, in the ECT responder's group (n = 5) there was no correlation between the number of treatments to achieve the same response criteria and age [$r(3) = .046$, p = ns].

Data comparing treatment response in psychotic patients were not analyzed owing to the small number (i.e., three in the rTMS group and five in the ECT group) and because three of the five subjects in the ECT group received antipsychotic medication during the study.

In general, the utilization of rescue medications during the study was minimal and did not differ between the two treatment groups (see Table 7).

There were no significant adverse events (e.g., seizures) and generally only mild side effects were reported in the rTMS group. Facial twitching was noted in six subjects during the stimulus train period. Six of the rTMS subjects evidenced erythema at the site of coil placement. Subjectively, various effects localized to the stimulation site were reported, including mild pain or discomfort (n = 6), feelings of warmth (n = 3), a tapping sensation ("like a hammer") (n = 2), and headache (n = 1). One subject

Table 7. Use of Rescue Medications by Group

	Anxiolytics	Sedative–hypnotics	Antipsychotics
rTMS group			
Week 1 (n = 13)	12	2	—
Week 2 (n = 11)	8	1	—
Week 3 (n = 9)	5	2	—
Week 4 (n = 6)	2	—	—
ECT group			
Week 1 (n = 9)	2	2	3
Week 2 (n = 7)	1	1	1
Week 3 (n = 2)	1	—	1
Week 4 (n = 1)	1	—	—

rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy.

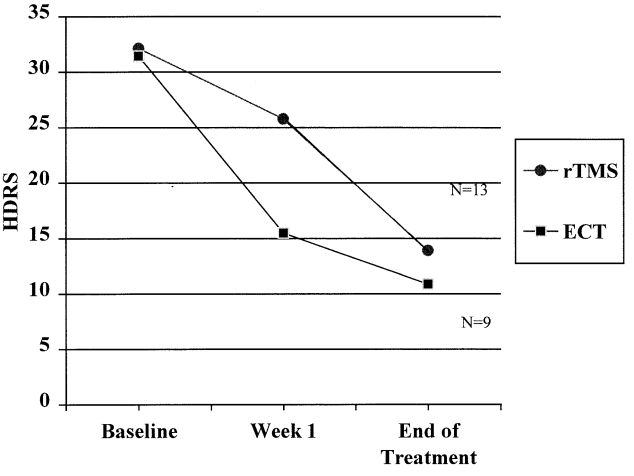

Figure 1. Hamilton Depression Rating Scale (HDRS) ratings at baseline, week 1, and at end of treatment. rTMS, repetitive transcranial magnetic stimulation; ECT, electroconvulsive therapy.

reported moderate pain at the site of the coil placement, and a topical anesthetic was applied for several treatments, but eventually this subject was able to continue treatments without the anesthetic. Four subjects described a sense of nervousness or anxiety before and during the treatments. Conversely, one subject described that rTMS was like "meditation" and was calming and relaxing. There were no serious or unexpected adverse events associated with ECT. Adverse effects with bitemporal ECT included short-term memory impairment, drowsiness shortly after treatment, and postictal and anesthesia-induced confusion.

Discussion

Our 2–4 week preliminary trial found that rTMS produced comparable antidepressant efficacy to bitemporal ECT in 22 patients with a major depressive episode (see Figure 1). Although there was a steeper initial drop in HDRS scores in the ECT group, an analysis of the mean change scores from baseline to week 1 showed no significant difference between the ECT and rTMS groups [$t(19) = -1.7$, p = .099]. Using a conservative *a priori* response criteria (i.e., ≥50% decrease from baseline HDRS and ≤8 score on the final HDRS), we failed to show a difference between the two groups. We also calculated percent improvement from baseline rating scores on the 24-item HDRS and found no significant group differences between rTMS and bitemporal ECT. Additionally, on our secondary measures of response (BPRS, YMS, and CGI scale), there were no significant differences between the two treatment groups, with both evidencing significant improvements (i.e., BPRS and CGI) or no change (i.e., YMS).

Of interest, an exploratory analysis on rTMS responders found a correlation between age and the number of treatments needed to achieve response. Although predic-

tive conclusions cannot be made from such a correlation, these findings may relate to the study by Figiel et al (1998) that reported that older age was associated with poorer rTMS outcome. Sixteen of 28 of the younger subjects responded, and only 5 out of the 22 subjects over the age of 65 responded (i.e., a 60% decrease and a score of 16 or less on the HDRS, and a moderate score on the CGI). In their study, however, only five rTMS sessions were given.

Overall, we observed a 55% improvement from the baseline HDRS score in the rTMS group. Our results are consistent with the two earlier reports comparing rTMS to ECT, albeit with varying designs.

In an open study design, Grunhaus et al (2000) randomly assigned 40 patients with MDD to either rTMS or right unilateral, nondominant ECT. Subjects with insufficient response could be switched to bilateral ECT administration. The authors concluded that ECT was more effective than rTMS for patients with MDD and psychosis. In the nonpsychotic group, however, the therapeutic effects of rTMS were similar to those of ECT. Of note, the psychotically depressed patients receiving ECT also received antidepressants and/or antipsychotics, whereas the rTMS patients did not. In addition, stimulus intensity with rTMS (i.e., 90% of MT) was lower than those reported to be most effective by George et al (1998a).

Pridmore et al (2000) randomly assigned 32 patients with MDD who failed to respond to at least one course of medication to rTMS or unilateral, nondominant ECT. Although the ECT group had a significantly greater percent improvement on the Beck Depression Inventory (BDI) (69% vs. 46%), blind raters found that on the HDRS the rate of remission (i.e., a total final score of $\leq$8) and percent improvement over the course of treatment were the same for subjects receiving either ECT or rTMS. Of note, an equal number of subjects in both groups received concurrent medication, but no other information was provided.

Thus, Grunhaus et al (2000) reported a 40% improvement, and Pridmore et al (2000) found a 56% improvement on the HDRS. Our findings approximate the upper end of this range and are comparable to sham-controlled studies in which the range in percent improvement has been reported to be 18% (George et al 1997) to 51% (Epstein et al 1998).

The absence of a placebo control or sham rTMS group is an important limitation to this study. Because this was a pilot study designed to involve subjects with more severe depression, we did not feel that a placebo arm was justified at this time. Given the severity and chronicity of illness and the prior exposure to multiple treatments without adequate resolution of symptoms in our sample, we also think it less likely to observe a placebo response in such a patient group. Thase (1999), in a review of the use of clinical trials reported that placebo response rates are likely to approach zero in severe depression (e.g., psychotic). Further, there remains considerable debate about what constitutes an appropriate sham TMS control. For example, Lisanby et al (2001a), comparing the effects of active rTMS to four types of sham TMS on motor evoked potentials (MEPs) in human subjects, reported cortical stimulation in the range of 48%–76% with the sham procedures.

In addition, although bias is inherent with the use of unblinded assessments, the raters in the study did undergo rigorous training and had a very high intraclass correlation on the HDRS reliability analysis. Again, the goal of this study was to collect preliminary data examining the potential benefits of rTMS relative to standard ECT treatments. Based on this experience, a larger study is planned to address these issues.

Grunhaus et al (2000) reported that ECT was more effective than rTMS in depressed patients with psychosis. In the sample of the present study, three out of five psychotic subjects treated with ECT received antipsychotic medication versus none of the three psychotic rTMS subjects (Table 7). The three rTMS psychotic subjects had a mean percent change from the baseline HDRS score of 78% versus the five psychotic subjects in the ECT group, who averaged a 70% improvement. In turn, the nine nonpsychotic subjects in the rTMS group averaged a 47% improvement on the HDRS versus the four nonpsychotic subjects in the ECT group, who averaged a 56% improvement.

In the present study, the subjects assigned to rTMS did not report any severe adverse events and none dropped out of the trial because of side effects. Unlike a recent report that described a switch to mania following rTMS treatment (Ornah et al 2001), none of our subjects, including the three bipolar depressed subjects, exhibited a change in manic symptoms as evidenced by ratings on the YMS. None of the mild to moderate side effects were persistent, and these generally responded to minimal intervention. This is consistent with other studies that found relatively mild adverse effects (Grunhaus et al 2000; Pridmore et al 2000). In turn, the ECT group did not experience any serious adverse events, and no subject dropped out because of side effects.

This pilot project also included an examination of select components of cognition designed to assess potential changes in functioning in the rTMS group. These data were collected primarily for safety purposes. Thus, we only obtained information on the cognitive effects of rTMS and do not have comparable information for the ECT group. Results of this preliminary investigation have been presented in abstract form (Martis et al 2000).

All attempts were made to reduce the risk for seizure by

using rTMS stimulus parameters promulgated in the guidelines published by the International Workshop on the Safety of rTMS (Wassermann 1998). Although the optimal parameters for rTMS have not yet been established, we chose parameters based on current research tempered by these safety guidelines. Thus, for coil placement, most studies with positive outcomes in depression have used stimulation over the left dorsolateral prefrontal cortex (DLPFC) (Figiel et al 1998; George et al 1997; Greer et al 1998; Nahas et al 1998; Pascual-Leone et al 1996;). Although the optimal frequency of stimulation continues to be studied, higher frequencies (e.g., ≥1–20 Hz) appear to be more efficacious over the left DLPFC. There is a smaller database, however, which indicates that right DLPFC coil placement and lower frequencies (e.g., ≤1Hz) may also be efficacious. Based on recent imaging studies, George et al (1998a, 2000), Nahas et al (2000) and Kozel et al (2000) have hypothesized that using higher intensities, as determined by MT, may have more robust effects (as the magnetic field declines logarithmically with distance from the coil); however, intensities greater than 120% of MT have generally been avoided because of the potential to increase seizure risk (Wassermann 1998). The number of stimulations delivered is determined by the frequency (Hz) plus stimulation train duration. In this context, one safety issue is the intertrain interval, which has typically been 20–50 sec in duration (George et al 2000; Grunhaus et al 2000; Janicak et al 2000; Pridmore et al 2000). Although the number of stimulations has varied across studies, most positive trials deliver between 8000 and 20,000 stimulations per treatment course.

Although our rTMS stimulus parameters were more aggressive than many of the previous studies, they did not produce a seizure or other serious adverse events. In a similar vein we attempted to maximize efficacy with bitemporal ECT (Sackeim et al 2000). This differs from the Grunhaus et al (2000) and Pridmore et al (2000) studies, wherein treatment was initiated with unilateral nondominant ECT; however, eight subjects in the Grunhaus study were subsequently switched to bitemporal ECT.

Repetitive transcranial magnetic stimulation may be a viable intermediate strategy between antidepressants and ECT or may augment medication or ECT treatment (Conca et al 1996; Grunhaus et al 2000; Lisanby et al 2001c; Martis and Janicak 2000; Pridmore et al 2000; Sackeim 2000). Magnetic stimulation with more aggressive treatment parameters is also being studied as a possible alternative to electrically induced seizures. The potential benefit may be less cognitive disruption (Lisanby et al 2001b, 2001d).

Our preliminary data indicate that rTMS may be an alternative to ECT for at least some patients with more severe depression. Even if only a proportion of subjects responds to this alternative intervention, there are distinct advantages to rTMS. Compared to ECT, rTMS appears to have a potentially lower adverse effect profile, including fewer cognitive adverse effects (Little et al 2000); is easier to administer; and more cost effective (e.g., no need for anesthesia induction or operating room recovery monitoring). An additional important social benefit is that rTMS may engender less stigma than ECT. We believe that the positive preliminary results in three reported comparison trials (i.e.; Grunhaus et al 2000; Pridmore 2000; and our data) warrant further investigation with advancing designs and larger subject sample size. To that end, as noted earlier, we plan to conduct a larger, more rigorously controlled study.

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