Long-Term Maintenance Therapy for Major Depressive Disorder With rTMS

John P. O'Reardon, M.D.; Kate H. Blumner, M.P.H.; Andrew D. Peshek, M.D.; Rocio Romero Pradilla, M.D.; and Pilar Cristancho Pimiento, M.D.

Objective: There is growing evidence to support the short-term antidepressant effects of repetitive transcranial magnetic stimulation (rTMS), but few published data pertain to the maintenance treatment of patients with DSM-IV–diagnosed major depressive disorder who have responded acutely to rTMS. We describe long-term maintenance therapy for major depressive disorder with rTMS.

Method: Repetitive transcranial magnetic stimulation was applied in 10 adults over the left prefrontal cortex at 100% of motor threshold, most often at a frequency of 10 Hz for sessions consisting of 40 trains at 5 seconds per train (2000 pulses per session), for periods ranging from 6 months to 6 years. Session frequency averaged 1 to 2 per week. The study was conducted in the TMS lab of an academic medical center.

Results: Seven of the 10 subjects experienced either marked or moderate benefit, which was sustained without the addition of concomitant antidepressant medication in 3 cases. There were no serious adverse events reported by any participant. The seizure rate for the 1831 reported rTMS sessions was zero.

Conclusions: These data, while open label, suggest that maintenance rTMS may be a safe and effective treatment modality in some patients with unipolar depression. Further research into the long-term safety and efficacy of rTMS is warranted.

(J Clin Psychiatry 2005;66:1524–1528)

Received March 21, 2005; accepted July 6, 2005. From the Department of Psychiatry, University of Pennsylvania, Philadelphia.

Some financial support for this research was provided by Magstim, Woburn, Mass., manufacturer of the TMS technology under investigation.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services) occurring at least 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: Drs. O'Reardon, Peshek, Pradilla, and Pimiento and Ms. Blumner report no financial or other affiliations relevant to the subject of this article.

Corresponding author and reprints: John P. O'Reardon, M.D., Laboratory for TMS, University of Pennsylvania, Suite 4005, 3535 Market St., Philadelphia, PA 19104 (e-mail: oreardon@mail.med.upenn.edu).

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technology that uses pulsed electromagnetic fields to modulate neuronal activity in the cortex of the brain.[1,2] Most clinical studies, including several meta-analyses, of high-frequency rTMS have shown that it is more effective than a sham control in the acute treatment of major depression.[3–9] Some studies have also reported efficacy similar to that of electroconvulsive therapy (ECT) for patients with nonpsychotic severe major depression.[10,11]

Only limited data have been published to date describing a possible role for rTMS in maintaining therapeutic effects beyond an acute course of treatment. A recent case series suggests some efficacy for rTMS in the long-term treatment of bipolar depression.[12] Three of 7 initial responders maintained a good response over a period of up to 1 year when rTMS was administered over the left prefrontal cortex at 5 Hz in combination with pharmacotherapy.

The first published case report to describe successful continuation treatment in unipolar depression with rTMS administered over a 4-month period was in a 45-year-old woman with medication-resistant depression.[13] More recently, a case series suggested beneficial effects in 8 of 11 patients with refractory depression who maintained responder status over a period of 3 months with rTMS administered at 10 Hz over the left prefrontal cortex.[14] Both of these reports are limited by their short-term nature (< 6 months) and therefore reflect continuation rather than maintenance phase treatment with rTMS. In addition, medication status during rTMS maintenance was not reported. Based on these reports, it is unclear what potential maintenance rTMS might have as monotherapy for responders to an acute course of rTMS. If rTMS has potential in this regard, it might serve a useful future role as an option for maintenance treatment for responders to acute courses of either rTMS or ECT, as its benign adverse event profile will likely make it an attractive option for patients who need long-term treatment.

METHOD

Case Series

We report here a case series of 10 patients (6 female, 4 male, mean age = 50 years, standard deviation [SD] = 16

© Copyright 2005 Physicians Postgraduate Press, Inc.

years) with DSM-IV–diagnosed major depressive disorder treated with maintenance rTMS for periods ranging from 6 months to 6 years in a TMS lab of an academic medical center (see Table 1). These patients had responded to an acute course of rTMS administered either on an open-label basis or following participation in a randomized acute treatment trial,[15] with response defined as a 50% or greater reduction in the baseline score on the 17-item Hamilton Rating Scale for Depression (HAM-D).[16] All participants signed a written informed consent form approved by the Institutional Review Board of the University of Pennsylvania prior to receiving rTMS and subsequently were offered maintenance rTMS on a humanitarian basis.

While the assessment of medication resistance was not operationalized by means of the Antidepressant Treatment History Form from New York State Psychiatric Institute,[17] the patients evaluated by a clinician experienced in treatment-resistant depression were all clearly medication nonresponsive. All had a minimum of 1 failed adequate antidepressant trial (6 weeks of an adequate dose of a standard antidepressant), and most had multiple failed adequate trials. No patient was merely intolerant to antidepressant medications. Two patients in this series had been prior responders to ECT, but both had problems tolerating the adverse effects of ECT. No patients in this case series were known to have received a prior failed ECT trial.

Patients who responded to the acute phase treatment of rTMS who requested maintenance rTMS were started on maintenance rTMS immediately following the acute treatment course and thus had not relapsed prior to the initiation of maintenance rTMS.

rTMS Session Parameters

Repetitive transcranial magnetic stimulation sessions were administered using a Magstim Rapid 200 stimulator (Magstim, Woburn, Mass.) with a figure-of-8 coil. Initially, all participants received rTMS at 10 Hz over the left prefrontal cortex at 100% of motor threshold (MT) in sessions consisting of a series of 40 trains of 5 seconds duration each, with a 25-second intertrain interval of no stimulation, administered over 20 minutes (2000 pulses per session). The number of trains was increased in some participants (N = 4) to 60 trains over 30 minutes (3000 pulses) to optimize clinical response. The frequency of maintenance sessions was determined by the clinical course of the patient. One participant (case 9) was unable to tolerate high-frequency TMS and so received low-frequency TMS at 1 Hz over the left prefrontal cortex. Her first 3 weeks of rTMS were at 10 Hz, and the remaining 59 weeks were at 1 Hz, with each session administered over the left prefrontal cortex. Another participant (case 8) had a suboptimal response to rTMS at 10 Hz over the left prefrontal cortex but subsequently responded to rTMS at 20 Hz administered at 100% of the determined MT, and these settings were then used as the appropriate parameters during maintenance treatment.

RESULTS

Outcomes

Two of the earliest participants did not have their rTMS sessions logged on an individual basis initially for a period of 1 to 2 years (for cases 1 and 2, during that period, their clinical course of rTMS was documented, but each individual session was not specifically recorded; therefore the rTMS sessions that were delivered during that period were not included in Table 1). Thus, the total number of rTMS sessions administered across all participants is somewhat greater than the 1831 sessions documented in Table 1. The clinical benefit of rTMS maintenance was assessed using the physician-rated Clinical Global Impressions-Improvement scale (CGI-I) measure.[18] These physician ratings were cross-checked with the patients' self-rated global impression of improvement, and any discrepancies if identified were resolved. Formal HAM-D scores were not included in this report as they were not uniformly available across the treatment periods for all patients.

Overall, 5 of the 10 participants were classified as having received marked benefit from rTMS maintenance therapy during their treatment course, defined as a CGI-I rating of 1 or very much improved, as compared to baseline (cases 1–5). This group underwent a mean (SD) of 257 (± 86) sessions of rTMS at a session frequency of 2.1 per week. Three of the 5 participants were maintained successfully with rTMS alone and did not require any concurrent antidepressant medication.

A further 2 patients experienced moderate benefit from rTMS maintenance, defined as a CGI-I score of 2 or much improved compared to baseline (cases 6 and 7). Both experienced a recurrence of major depressive disorder during maintenance therapy over a 12- to 18-month timeframe. This moderate response group received a mean (SD) of 125 (± 26) sessions of rTMS at a session frequency of 1.8 per week.

Three patients experienced only minimal benefit from rTMS and received a mean (SD) of 98 (± 40) sessions (1.7 per week) each. Two of the 3 patients experienced recurrences of depression, and none maintained a sustained improvement during maintenance therapy despite the addition of antidepressant medication (cases 8–10). In these patients, rTMS was ultimately discontinued due to inadequate results.

Although some patients in this series had had previous psychiatric hospitalizations, no patients required psychiatric hospitalization during the course of maintenance rTMS. No patients had ECT treatment (acute, continuation, or maintenance) during the course of maintenance rTMS.

Two patients (cases 1 and 2) remain on maintenance rTMS as of the writing of this report and continue to display marked benefit from treatment. The remaining 8 patients have exited from maintenance rTMS over the years for a variety of reasons, including insufficient benefit (N = 3), moved away from the area (N = 2), patient decision (N = 2), and lost to follow-up (N = 1).

Safety

The most significant potential adverse risk with rTMS is the induction of a seizure. Several seizures have been reported in conjunction with the use of rTMS in the treatment of major depression.[19] In order to minimize the risk of seizures, subjects were excluded at baseline if they had a personal or family history of epilepsy, a history of medication-induced seizures, or a preexisting neurologic disorder that might increase the risk of seizures. The rTMS parameters utilized for the acute and maintenance phases of treatment were in accord with the published safety guidelines.[20] No seizures occurred out of a total of 1831 sessions. Observed side effects included occasional headache that required simple analgesics in 2 cases. One subject experienced dizziness and jaw tremor during 1 session that resolved spontaneously at the end of the session and did not recur subsequently. Another subject complained of ear and sinus pain during rTMS stimulation in the setting of a coexisting sinus infection. Finally, 1 subject experienced a nosebleed during a session that was felt to be unrelated to the stimulation.

There were no complaints of memory loss or other cognitive impairment in any of the participants, although cognitive functioning was not formally assessed. No participant complained of any hearing changes, although no audiometry assessments were conducted. Subjects were counseled on the need to wear earplugs during the sessions to mitigate the potential risk of hearing loss.

This diverse group of patients, who received rTMS with a range of treatment settings, over an extended period of time (for a total of 1831 sessions), in certain cases in combination with psychopharmacologic regimens, displayed no serious adverse events during the rTMS maintenance phase. Although the number of patients in this sample is small, we feel that this is an important naturalistic representation of the general safety of maintenance rTMS treatment in patients with treatment-resistant depression.

Case Examples

Three participants are described in greater detail below, illustrating a possible range of uses of rTMS in the maintenance treatment of major depressive disorder. These cases include use in the setting of resistance to antidepressant medications (cases 1 and 2). We also report on the safety of rTMS observed when it was used in combination with medication (case 2 had inadequate responses to medication and case 8 was medication resistant).

Case 1. This 63-year-old widowed white man had a 20-year history of recurrent major depressive disorder. He was resistant to multiple antidepressant medications including fluoxetine, paroxetine, venlafaxine, mirtazapine, bupropion, amitriptyline, and phenelzine and augmentation with lithium. He experienced marked benefit from long-term rTMS therapy by both clinical assessment and self-report. To date, he has remained medication free without experiencing any significant recurrence of depressive symptoms over a period of 6 years. Repetitive transcranial

Table 1. Characteristics of 10 Subjects With Major Depression Treated With Maintenance rTMS Grouped by Treatment Response

	Case Number													
	Marked Benefit						Moderate Benefit			Minimal Benefit				Total
Characteristic	1	2	3	4	5	Mean (SD)	6	7	Mean (SD)	8	9	10	Mean (SD)	Mean (SD)
Gender	Male	Male	Female	Female	Female		Male	Female		Male	Female	Female		
Age, y	63	65	27	23	64	50 (9)	53	50	52 (2)	35	44	72	40 (5)	50 (16)
Total weeks of rTMS recorded	201*	201*	116	37	46	120 (36)	80	62	71 (9)	117	34	21	57 (30)	92 (66)
Total sessions of rTMS	437	441	296	73	39	257 (86)	151	99	125 (26)	178	71	46	98 (40)	183 (155)
Total no. of pulses administered (in thousands)	942	882	592	201	78	539 (175)	397	198	297 (99)	356	186	92	211 (77)	392 (314)
Relapse/recurrence	No	Yes	No	No	No		Yes	Yes		Yes	Yes	No		
Antidepressant medication added	None	VLF, FLU	NFZ, OLZ	None	None		S-CIT	MTZ, NFZ		NTP, TCP, LIT	SLG	None		

*This subject received significantly more sessions of rTMS than those documented, as sessions were not logged individually during the first 2 years of maintenance and so were not included in the above calculations.

Abbreviations: FLU = fluoxetine, LIT = lithium carbonate, MTZ = mirtazapine, NFZ = nefazodone, NTP = nortryptiline, OLZ = olanzapine, rTMS = repetitive transcranial magnetic stimulation, S-CIT = escitalopram, SLG = selegiline, TCP = tranylcypromine, VLF = venlafaxine.

© Copyright 2005 Physicians Postgraduate Press, Inc.

magnetic stimulation session frequency has averaged 2.2 per week. To maintain a good clinical response, his session parameters were increased incrementally from 40 5-second trains at 10 Hz at baseline (2000 pulses) to his current regimen of 60 5-second trains per session (3000 pulses). Over a period of 6 years, he has received a total of 942,000 pulses of rTMS at 10 Hz at 100% MT. His course of rTMS has been well tolerated with no adverse events reported.

Case 2. This 65-year-old married white man had a history of recurrent major depressive episodes since the age of 20 years. He had only partial responses to trials of fluoxetine, venlafaxine, and bupropion as well as augmentations with lithium carbonate and L-thyroxine. He ultimately responded to a course of ECT but was unable to tolerate maintenance ECT due to adverse cognitive effects. He responded well acutely to rTMS and has been maintained subsequently at an average session frequency of 2.2 per week over a period of 6 years (10 Hz, 2000 pulses per session).

He has had 2 recurrences of major depressive disorder during that time, each precipitated by a major bereavement and each of relatively short duration, lasting 3 months on average. Each recurrence was managed by temporarily increasing the frequency of rTMS to 5 sessions per week for several weeks and by the addition of antidepressant medication. On the first occasion, venlafaxine was added and titrated to 300 mg per day. He subsequently tapered his venlafaxine after 6 months, and his depression then recurred 10 months later. His depression failed to respond to the reintroduction of venlafaxine and a temporary increase in rTMS session frequency. His medication was changed to fluoxetine with good effect, and he has maintained a stable remission for the past 2 years on a combination of fluoxetine 40 mg daily and twice-weekly rTMS sessions (10 Hz, 2000 pulses). In total, this patient received 842,000 rTMS pulses at 10 Hz at 100% of MT over a period of 6 years. No adverse events were noted with either monotherapy rTMS or rTMS in combination with pharmacotherapy.

Case 8. This 35-year-old single white man had a 16-year history of unipolar major depressive disorder. He was resistant to treatment with antidepressant medications from multiple classes. Past failed medication trials included fluoxetine, sertraline, nefazodone, venlafaxine, bupropion, mirtazapine, desipramine, amoxapine, phenelzine, moclobemide, and lamotrigine. He had only partial responses to courses of unilateral and bilateral ECT. Due to the extreme severity of his illness, rTMS was added to his preexisting pharmacotherapy regimen of nortriptyline, tranylcypromine, lithium carbonate, and mixed amphetamine salts, which he was not able to taper without becoming acutely suicidal and requiring hospitalization.

During the maintenance period with rTMS, he received a total of 178 sessions over 117 weeks, averaging 1.5 rTMS sessions per week. Despite the addition of rTMS to a preexisting combination of monoamine oxidase inhibitor, tricyclic antidepressant, lithium, and mixed amphetamine salts, the combination was well tolerated. The only adverse events noted were jaw tremor and dizziness, each occurring on 1 occasion during an rTMS session and resolving by the end of the session. In particular, no symptoms occurred at any point that might suggest development of a serotonin syndrome such as fever, myoclonic jerks, or mental status change. Benefit from the combination was noted over an initial period of 1 year but ultimately was not sustained, and rTMS was terminated due to recurrence of major depressive disorder. The lack of adverse events in this case suggests that the addition of rTMS to preexisting medication regimens might be appropriate in some situations after a careful weighing of the risks and benefits on a case-by-case basis.

DISCUSSION

To our knowledge, this is the first report to describe the use of rTMS as a maintenance therapy for periods longer than 6 months in major depressive disorder. In 5 of the 10 participants, a marked benefit based on clinical assessment was observed for periods ranging from 9 months to 5 years, without the need for adjunctive pharmacotherapy in 3 of these cases. These data suggest that rTMS may have a role both as an adjunctive agent and as a monotherapy intervention in the maintenance treatment of major depressive disorder. The absence of serious adverse events, even with some participants receiving close to 1 million electromagnetic pulses over a period of several years, suggests that long-term rTMS may be safe and well tolerated.

Clinically, we observed that patients who responded robustly to the acute treatment phase also tended to benefit most from maintenance rTMS. However, more studies are needed to better delineate which patients are most likely to benefit from maintenance rTMS and to determine where maintenance rTMS would fall in the spectrum of maintenance treatments for major depressive disorder ranging from pharmacotherapy to maintenance ECT.

This case series is limited by its descriptive nature, open-label design, lack of fixed treatment parameters, outcome measures limited to use of the CGI-I, and adjunctive use of pharmacotherapy in some participants. However, it does suggest the need for double-blind maintenance trials of rTMS therapy in major depressive disorder. Any future studies would benefit from inclusion of a standard measurement of depression such as the HAM-D or the Montgomery-Asberg Depression Rating Scale.

Drug names: bupropion (Wellbutrin and others), desipramine (Norpramin and others), escitalopram (Lexapro), fluoxetine (Prozac

and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), levothyroxine (Synthroid, Levo-T, and others), mirtazapine (Remeron and others), mixed amphetamine salts (Adderall and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), selegiline (Eldepryl and others), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, lamotrigine, lithium, levothyroxine, mixed amphetamine salts, and selegiline are not approved by the U.S. Food and Drug Administration for the treatment of major depressive disorder.

REFERENCES

1. Barker AT, Jalinous R, Freeston IL. Noninvasive magnetic stimulation of human motor cortex. Lancet 1985;1:1106–1107
2. Lisanby SH, Kinnunen LH, Crupain MJ. Applications of TMS to therapy in psychiatry. J Clin Neurophysiol 2002;19:344–360
3. 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
4. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am J Psychiatry 1997;154:1752–1756
5. McNamara B, Ray JL, Arthurs OJ, et al. Transcranial magnetic stimulation for depression and other psychiatric disorders. Psychol Med 2001; 31:1141–1146
6. Holtzheimer PE, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacol Bull 2001;35:149–169
7. Martin JL, Barbanoj MJ, Schlaepfer TE, et al. Transcranial magnetic stimulation for treating depression. Cochrane Database Syst Rev 2002; CD003493
8. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta-analysis. Int J Neuropsychopharmacol 2002;5:73–103
9. Kozel AF, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. J Psychiatr Pract 2002;8:270–275
10. Grunhaus L, Dannon P, Schreiber S. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biol Psychiatry 2000;47:314–324
11. Grunhaus L, Schreiber S, Dolberg OT, et al. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. Biol Psychiatry 2003;53:324–331
12. Li X, Nahas Z, Anderson B, et al. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? Depress Anxiety 2004; 20:98–100
13. Abraham G, O'Brian S. Repetitive transcranial magnetic stimulation is useful for maintenance treatment [letter]. Can J Psychiatry 2002; 47:386
14. Benadhira R, Saba G, Samaan A, et al. Transcranial magnetic stimulation for refractory depression [letter]. Am J Psychiatry 2005;162:193
15. Szuba MP, O'Reardon JP, Rai AS, et al. Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. Biol Psychiatry 2001;50:22–27
16. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
17. Sackeim HA. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 16):10–17
18. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
19. Rosa MA, Odebrecht M, Rigonatti SP, et al. Transcranial magnetic stimulation: review of accidental seizures. Rev Bras Psiquiatr 2004;26: 131–134
20. Wasserman EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop in the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998; 108:1–16

For the CME Posttest for this article, see pages 1649–1651.

© Copyright 2005 Physicians Postgraduate Press, Inc.