

Adjunctive fast repetitive transcranial magnetic stimulation in depression

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Summary The place of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression remains unclear. In this sham-controlled study we determined the efficacy and acceptability of fast, left frontal rTMS given three times a week over 4–6 weeks to 29 patients with depression (79% treatment-resistant). The procedure was generally well tolerated and more effective than sham treatment (55 v. 7% responding, $P < 0.05$), with improvement maintained to 12 weeks. This therapy could be a useful addition to available treatments but further research is needed to determine the optimum treatment parameters.

Declaration of interest None.

Approximately a third of people treated for depression fail to respond to initial treatment and in 10–15% of cases the disorder is refractory to multiple treatments (Anderson *et al*, 2000). The usefulness of repetitive transcranial magnetic stimulation (rTMS) is not clear because optimal treatment parameters are unknown and studies have been small, of short duration and have used different methods (Loo & Mitchell, 2005). We investigated the antidepressant efficacy of rTMS in a clinically practical protocol in patients with depression.

METHOD

We recruited out-patients aged over 17 years with a DSM-IV major depressive episode (American Psychiatric Association, 1994), diagnosed using the Mini International Neuropsychiatric Interview (Lecrubier *et al*, 1997), who were poorly responsive to – or choosing not to take – antidepressant drugs. Exclusion criteria were safety considerations (e.g. suicidality, contraindications to TMS), organic brain disorder, non-affective

psychosis or current alcohol/drug misuse or dependence (by DSM-IV criteria). The study was approved by the local research ethics committee and all participants gave written informed consent.

After determination of motor threshold, patients were randomised (sealed envelope) to active or sham treatment stratified by degree of treatment resistance (fewer than two *v.* two or more antidepressant trials equivalent to imipramine 150 mg). Treatment was thrice weekly for 4 weeks, extended for 2 more weeks in partial responders. Medication at entry continued unchanged through the trial. Assessments were made before and 2, 4, 6 and 12 weeks after the start of treatment with patients and assessors unaware of treatment allocation. Assessments were the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), the Clinical Global Impression Severity and Improvement scales (CGI-S, CGI-I; Guy, 1976), the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994), and the self-rated Hospital Anxiety and Depression scale (HAD; Zigmond & Snaith, 1983). Adverse effects were determined by open questions and a checklist.

Treatment using a Magstim Super Rapid (Magstim, Whitland, UK) was given using a figure-of-eight and matching sham coil. After determination of the motor threshold (the minimum setting to stimulate the right first abductor pollicis brevis muscle), treatment sessions consisted of 1000 stimulations at 10 Hz in 20 trains each separated by 30 s at 110% of motor threshold over the left dorso-lateral prefrontal cortex (5 cm anterior to the motor threshold point).

The primary outcome measures were MADRS score and HAD depression scores at treatment end-point given at least one post-baseline assessment (last observation carried forward; LOCF). Secondary outcome measures were other rating scale scores and responder status at treatment end-point (LOCF), scores at 12 weeks

(LOCF and completers) and treatment withdrawal. Response was defined as a reduction of at least 50% in MADRS score plus a CGI-I rating of much or very much improved. Partial response at 4 weeks was defined as 25–49% reduction in MADRS score from baseline. Statistical analysis using SPSS for Windows, release 11.5, was by univariate analysis of variance covaried for baseline values. Fisher's exact test was used for categorical data and the exact proportion test for treatment allocation guesses.

RESULTS

Thirteen patients (7 women; mean age 48 years, s.d.=8) received active treatment and 16 (9 women; mean age 46 years, s.d.=12) received sham treatment. There was no significant difference between groups in median duration of episode (active 14 months, range 3–60; sham 12 months, range 2–144); median number of treatment trials (active 3, range 0–7; sham 3, range 0–12); treatment resistance (active 85%; sham 75%); electroconvulsive treatment in episode (active 31%; sham 38%); and chronic (≥ 2 years) episode (active 46%; sham 38%). All but 3 patients were taking antidepressants (active 92%; sham 88%); venlafaxine 34%; selective serotonin reuptake inhibitors 24%; tricyclic antidepressants 14%; combinations were most often with lithium (31%), an atypical antipsychotic (34%) or two antidepressants (17%). More patients in the active group were receiving venlafaxine (62 *v.* 13%; $P < 0.05$), with a trend for the opposite for selective serotonin reuptake inhibitors (8 *v.* 38%, $P < 0.1$).

Three patients in the active group partially responded at 4 weeks and received a further 2 weeks' treatment. Twenty-five cases were evaluable for efficacy; at treatment end-point the active group improved more than the sham group on primary outcomes (MADRS effect size 0.86, HAD depression effect size 0.92), GAF and in number of responders (Table 1). At 12 weeks significant benefit to the active treatment group on self-rated HAD depression remained.

Two patients per group withdrew before completing 2 weeks of treatment (active: scalp pain, unrelated finger infection; sham: self-harm, treatment too stressful). Two patients in the active group received 100% (reduced from 110%) motor threshold stimulation owing to initial scalp discomfort, but overall the treatment was well tolerated. Three participants did not return for assessment at 12

weeks. One patient in the active group was mildly hypomanic at 4 weeks. Four days after his last treatment he had a series of epileptic seizures leading to hospitalisation, but a primary cause was not identified.

Of 25 participants, 19 (76%, $P < 0.05$) guessed their correct treatment allocation; 3 gave a reason related to the treatment itself and 18 of 25 cited degree of improvement.

DISCUSSION

In this small study, fast left frontal rTMS given three times a week for 4–6 weeks was effective in mainly treatment-resistant depression and tolerability was generally good. Hypomania following rTMS has been reported before (Dolberg *et al*, 2001), is consistent with rTMS having antidepressant properties and indicates the need to screen for bipolarity. Seizures have occasionally occurred during fast rTMS stimulation (Wassermann, 1998); however, delayed seizure provocation has not been described, is mechanistically implausible and rTMS causation in this case was thought very unlikely.

Meta-analyses of the clinical efficacy of rTMS for depression have been conflicting (e.g. Holtzheimer *et al*, 2001; Couturier, 2005). Variations in treatment methodology and patient factors make interpretation of the literature problematic (Loo & Mitchell, 2005). However, a number of recent studies of fast left frontal rTMS support the efficacy of higher dosages and a greater number of treatments (e.g. Fitzgerald *et al*, 2006).

Our study is limited by its small number of participants, relatively brief follow-up and uncontrolled concomitant medication. Nevertheless, taken together with other

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recent studies, our findings suggest that fast left frontal rTMS warrants further evaluation as a clinically available treatment. A clinically feasible protocol of three treatments per week appears effective, provided that sufficient stimulation strength and numbers of treatments are used.

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Table 1 Effect of repetitive transcranial magnetic stimulation on efficacy outcome measures

	Sham treatment				Active treatment			
	Baseline (n=14)	Treatment end-point, LOCF (n=14)	12 weeks		Baseline (n=11)	Treatment end-point, LOCF (n=11)	12 weeks	
			LOCF (n=14)	Completers (n=13)			LOCF (n=11)	Completers (n=9)
Scores: mean (s.d.)								
MADRS	27.7 (7.1)	23.4 (9.8)	21.9 (9.7)	21.5 (9.7)	26.7 (3.6)	15 (9.7)*	14.0 (11.5)	16.0 (11.9)
CGI-S	4.1 (0.7)	4.0 (0.8)	3.7 (1.2)	3.7 (1.2)	3.7 (0.6)	3.0 (1.0)	3.0 (1.3)	3.0 (1.3)
HAD Depression	15.1 (3.0)	14.2 (4.2)	13.6 (3.7)	13.2 (3.6)	14.6 (3.3)	9.7 (5.5)*	8.3 (5.6)**	9.4 (5.4)*
HAD Anxiety	14.1 (5.1)	11.9 (5.2)	10.1 (4.9)	10.1 (5.1)	13.8 (4.0)	9.9 (4.9)	9.1 (5.1)	9.2 (4.9)
GAF	53.1 (9.3)	55.8 (8.0)	58.1 (13.0)	58.8 (13.3)	54.1 (10.6)	67.2 (11.2)**	65.6 (13.8)	65.8 (14.6)
Responders: n (%)		1 (7)	1 (7)	1 (8)		6 (55)*	5 (45)	3 (33)

CGI-S, Clinical Global Impression-Severity; GAF, Global Assessment of Functioning; HAD, Hospital Anxiety and Depression; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale.

* $P < 0.05$, ** $P < 0.01$ compared with sham treatment.