



## An Open Label Trial of Clustered Maintenance rTMS for Patients with Refractory Depression

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### ARTICLE INFO

#### Article history:

Received 2 April 2012

Received in revised form

9 May 2012

Accepted 9 May 2012

Available online 8 June 2012

#### Keywords:

Repetitive transcranial magnetic stimulation

Depression

Prefrontal cortex

Response

Maintenance treatment

### ABSTRACT

Whilst the antidepressant properties of repetitive transcranial magnetic stimulation treatment (rTMS) have been repeatedly demonstrated, minimal research has investigated the use of rTMS to prevent relapse in patients who have responded to treatment. To address this issue, a large open label trial of a new form of clustered maintenance rTMS was conducted. Thirty-five patients with treatment resistant depression were included. All patients had responded to two courses of rTMS treatment for depression. Following their second course of rTMS, they received clustered maintenance rTMS which involved monthly maintenance sessions of five rTMS treatments over a two day period. The time to relapse and clinical characteristics are described. Twenty-five patients experienced a relapse within the study period, with a mean treatment duration of  $10.5 \pm 10.3$  months. This was substantially longer than their period of wellness following their initial acute treatment without maintenance (<3 months). Ten additional patients continued maintenance until withdrawal from the study without having experienced relapse (4 at a mean of  $6.2 \pm 4.3$  months) or until study end (6 patients with mean duration of  $12.0 \pm 9.7$  months). Although preliminary, this study suggests that clustered maintenance rTMS has the potential to substantially delay the occurrence of relapse following a successful course of rTMS treatment.

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### Introduction

Over recent years repetitive transcranial magnetic stimulation (rTMS) has been extensively investigated in regard to its potential antidepressant effects and it is progressively transitioning into

clinical practice in many countries. Numerous open label and double blind studies have been conducted and their results have been summarized in a number of meta-analyses (for example [1–3]). Generally, these studies have supported the antidepressant effects of rTMS, with greater and potentially more clinically relevant effect sizes reported in recent studies that have employed higher doses and longer treatment periods [4].

Depression is a disorder typified by remission and relapse and this aspect of the illness contributes considerably to its long-term morbidity. The vast majority of research investigating rTMS has focused on the acute short-term efficacy of the treatment and little attention has been paid to its impact on the long-term course of the illness. Past studies suggest that there is a considerable risk of relapse post rTMS although the rates of this in published studies are quite variable. For example, Dannon et al. found a 20% six month relapse rate, the same as that seen in a patient group post ECT [5]. In contrast, only 22.6% of patients remained well at six months in a larger follow-up study [6]. The mean duration of rTMS benefit was five months in a small study of the reintroduction of rTMS treatment [7]. In the most uniform study to date, 10 (of 99) patients relapsed in a 24 week follow-up period following treatment in the

This research was supported by a National Health and Medical Research Council (NHMRC) project grant (546105). PBF is supported by an NHMRC Practitioner Fellowship. Author ZJD is supported by a CIHR Clinician Scientist Award. In the last two years PBF has received equipment for research from Brainsway Ltd., Medtronic Ltd. and MagVenture A/S, and funding and equipment for research from Cervel Neurotech. He has no other affiliations or financial involvement with organisations related to the subject matter of the manuscript including employment, consultancies, honoraria, stock ownership or options, grants, patents or royalties. In the last two years, author ZJD has received equipment and operational expenses for research from Brainsway Ltd. He has no other affiliations or financial involvement with organisations related to the subject matter of the manuscript including employment, consultancies, honoraria, stock ownership or options, grants, patents or royalties. No writing assistance was utilised in the production of this manuscript.

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Neuronetics Ltd. sponsored device registration trial and a total of 38.4% experienced significant symptom worsening [8]. Research following successful acute treatment of depression with electroconvulsive therapy (ECT) suggests that up to 50% of patients will relapse in the six months following acute treatment, even when standard medication treatment or maintenance ECT is administered [9,10].

These observations have led to an interest in the potential of maintenance rTMS to prevent depressive relapse following acute treatment. To date, few studies have explored this possibility. An initial report was a single case study of a woman who maintained a degree of wellness (not quantified) during four months of weekly or twice weekly rTMS sessions (type of rTMS unspecified) [11]. The most substantive sample subsequently reported was of ten patients treated once or twice per week over a period ranging from six months to six years [12]. Marked or moderate benefit was described for seven of the ten patients. Treatment involved high frequency left prefrontal stimulation, used in the majority of the controlled trials to date. Benefits of maintenance rTMS (weekly high frequency prefrontal stimulation) were also described in a group of seven patients with bipolar disorder treated over a 12 month period [13]. In addition to these studies of maintenance treatment, a number of reports (for example [7,14]) have also demonstrated the potential value of the reintroduction of rTMS treatment in response to symptom deterioration.

In all of the studies of maintenance rTMS, treatment was provided in a single session at biweekly, weekly or twice weekly frequency. However, the current study provided treatment less frequently but in a more intensive manner. We administered five treatments 'at a time' over a 2 ½ day period every four weeks in a sample of 37 patients. From a practical perspective, this involved a brief hospital admission with a single treatment on a Friday evening and two treatments on both Saturday and Sunday. This schedule was developed partially due to the lack of access to our treatment machine on weekdays (due to the intensity of its use) but also with the intent that weekend treatment would minimally disrupt the capacity for patients to continue work or study. The decision to use a 'clustered' approach was based on the presumption that greater effects with rTMS would be induced by the repeated application of stimulation within a short time interval and that effects induced within this acute treatment

session would last for a substantive period of time between the monthly sessions. Some support for the suggestion that multiple sessions may have greater effects than a single session came from a neurophysiological study that found a greater effect of rTMS on cortical excitability during a second rTMS session provided within 24 h than the first session [15].

## Methods

### Subjects

Thirty-five patients who received treatment in the rTMS program of The Alfred Hospital or the Victoria Clinic in Melbourne, Australia were included in this study. The study was approved by The Melbourne Clinic Ethics Committee. All patients provided informed consent. All patients had previously received a minimum of two courses of rTMS. In all instances, the first course of rTMS was provided during one of a series of clinical trials. The second course was provided as open label treatment following a subsequent relapse of depression. Patients were considered eligible for the maintenance study following their second acute treatment if their relapse following the first course of rTMS occurred between one and three months following the end of the first acute treatment (Fig. 1). A minimum period of one month between relapses was required to increase the likelihood that the patients would not relapse subsequently prior to the first maintenance treatment session. Previous relapse within three months was chosen as a length of time which seemed reasonable to justify inclusion in what was a relatively intensive maintenance schedule.

The types of rTMS provided varied according to the type of rTMS received in the initial clinical rTMS trial and always remained the same across time for each participant (Table 1). Fourteen patients received treatment with high frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC; 10 Hz), 12 received low frequency rTMS applied to right DLPFC (five of these with preceding 'priming' 6 Hz stimulation) and nine received sequential bilateral rTMS (six of these with bilateral 1 Hz and three with 10 Hz on the left DLPFC and 1 Hz on the right DLPFC).

Patients had a mean age of  $44.8 \pm 13.3$  years and included 8 males and 27 females. Of the 35 patients, 26 (74%) had major

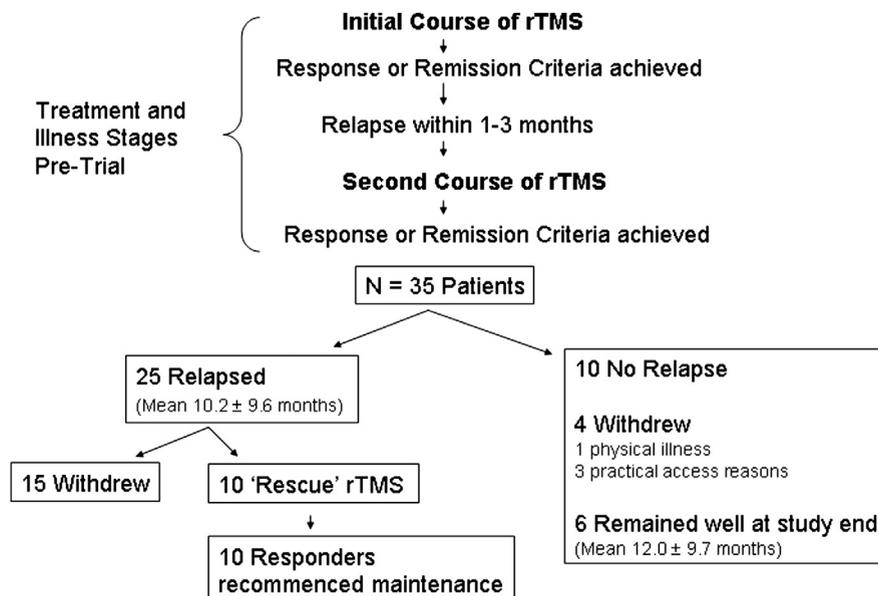


Figure 1. Progression of patients through the study.

**Table 1**  
Stimulation parameters for each type of rTMS.

	Hemisphere	Frequency (Hz)	Intensity <sup>a</sup>	Number of trains	Train duration (sec)	Inter-train interval (sec)
Unilateral	Left	10	110%	30	5	25
Unilateral	Left	5	110%	30	10	20
Unilateral	Right	1	110%	1	900	–
Priming	Right	6	90%	10	5	25
	Right	1	110%	1	900	–
Bilateral 1	Right	1	110%	1	900	–
	Left	1	110%	1	900	–
Bilateral 2	Right	1	110%	1	900	–
	Left	10	110%	30	5	25

<sup>a</sup> Intensity is the percentage of resting motor threshold (RMT).

depressive disorder (unipolar) and 9 (26%) had bipolar disorder, depressive episode (DSM IV criteria as of the time of the commencement of maintenance episode). Only one patient experienced psychotic symptoms whilst depressed. In regard to comorbidity, 12 patients had a comorbid anxiety disorder (10 Generalized Anxiety Disorder, one Panic Disorder and one Obsessive Compulsive Disorder) and one patient had a Borderline Personality Disorder. At the time of initial treatment, the sample had a mean number of past failed antidepressant medication trials of  $6.2 \pm 4.0$ . All but one patient were on a current antidepressant, 14 were receiving a mood stabilizer (Lithium, Na Valproate or Carbamazepine) and 14 were receiving an atypical antipsychotic. The medication treatment patients were receiving during their initial treatment was mostly continued until they relapsed and subsequently during the second period of acute treatment and maintenance rTMS, although changes were not prevented if required for reasons of treatment tolerability: patients were allowed to reduce medication doses or stop medications causing side effects or believed to be ineffective but not increase doses or commence new medication treatment.

During active treatment in the period of rTMS prior to maintenance therapy, patients experienced a decrease in Hamilton Depression Rating Scale (17 item) (HAMD) scores from  $22.9 \pm 7.6$  to  $6.8 \pm 3.9$  ( $P < 0.001$ ) and Beck Depression Inventory (BDI) scores from  $36.2 \pm 12.5$  to  $12.8 \pm 9.5$  ( $P < 0.001$ ). On entry to maintenance, 20 patients were in remission (HAMD score  $< 8$ ), 10 had mild depressive symptoms (HAMD score between 8 and 13) and 5 had moderate, persistent depressive symptoms. The patients with mild or moderate persistent symptoms had experienced a substantive improvement from baseline with rTMS (all meeting response criteria ( $>50\%$  reduction in HAMD score)) but did not meet remission criteria prior to entering maintenance.

#### Maintenance rTMS

The rTMS maintenance schedule involved the provision of five individual rTMS treatments over the course of two and a half days, every four weeks. Patients were admitted to hospital on Friday afternoon and received one treatment late on Friday, two treatments on Saturday and two treatments on Sunday prior to discharge. On days when two treatments were provided, treatments were administered at least two hours apart. The individual stimulation parameters used were the same as those provided during acute treatment. The resting motor threshold (RMT) was assessed each month prior to the first treatment. All treatment was provided with a Medtronic Magpro 30 (MagVenture A/S, Denmark). Stimulation was always provided using a stand-held 70 mm figure-of-8 coil. At all times the coil was held tangential to the scalp with the handle pointing back and away from the midline at  $45^\circ$ . The site

of stimulation during the rTMS treatment sessions was defined by a point 6 cm anterior to that required for maximum stimulation of the abductor pollicis brevis muscle.

#### Statistical analysis

The mean duration until relapse or withdrawal from treatment was calculated for each subject as the primary variable of interest. Relapse was defined clinically, not by a specific change on rating scale scores. Relapse was considered to have occurred when there was an increase/return of depressive symptoms of sufficient severity to warrant re-institution of acute rTMS treatment (treatment for more than the standard 5 sessions), addition or change of antidepressant medication treatment or withdrawal from maintenance treatment to pursue other treatment options. This decision was made by the patients' treating psychiatrist and a study psychiatrist (PF).

Group comparisons were made using chi square tests for equal proportion or student *t*-tests with results presented as numbers (percentages) or means (standard deviations) respectively. The time to relapse was analysed using a Cox-proportional hazard regression model with results presented as Hazard Ratios (95% CI) and displayed using a Kaplan Meier curve. Variables investigated for their relationship to relapse included the concurrent use of medications (antidepressant, antipsychotic and mood stabilizer), the HAMD and BDI scores at the start of the maintenance period, whether patients achieved remission in their acute course of rTMS preceding maintenance treatment, whether patients met responder criteria in their acute course of rTMS preceding maintenance treatment, type of rTMS, age and sex.

All procedures were two-tailed and significance was set at an alpha level of 0.05. Statistical analysis was conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and SPSS 18 (SPSS for Windows. Chicago: SPSS; 2010).

## Results

#### Outcomes of maintenance treatment

Of the 35 patients who entered the study, twenty-five patients experienced a relapse of depression after a mean of  $10.2 \pm 9.6$  months (range 2–48 months) (Fig. 1). The pattern of relapse over time for these twenty-five patients is presented in Fig. 2.

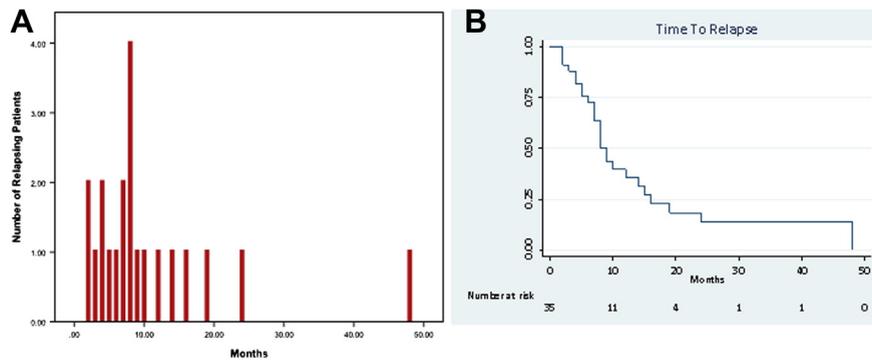
The other ten patients either withdrew whilst still in remission (one due to physical illness, three for practical treatment access reasons) or remained well and in maintenance treatment at study end ( $n = 6$ , mean  $12.0 \pm 9.7$  months, range 1–24 months). Of the total sample, five ended maintenance treatment within the first three months: two of these experienced relapse and three withdrew. Therefore, thirty patients receiving maintenance remained well for a period of time numerically longer than after their initial rTMS treatment when they did not have maintenance rTMS.

#### Prediction of time to relapse

There was no effect of any of the analysed clinical or demographic variables on duration of time (months) until relapse (Table 2). The lack of relationship was seen with initial correlations and *t*-tests as well as in the regression model. There was also no difference in time to relapse for uni or bipolar patients ( $P = 0.50$ ).

#### Prediction of likelihood of relapse

Comparing the patients who experienced relapse to those who did not, there was no difference in any of the relevant clinical or



**Figure 2.** (A) Duration of time until relapse and (B) Survival curve for patients experiencing relapse during maintenance treatment.

demographic variables, as shown in Table 3. A greater proportion of patients with bipolar disorder experienced a relapse (89% compared to 65%) but this was not significant (Fischer’s exact test = 0.23).

*‘Rescue’ treatment following failure of maintenance rTMS treatment*

Of the 25 patients who relapsed, ten (40%) were provided a ‘rescue’ course of acute/intensive rTMS treatment provided in the same manner of their initial rTMS acute treatment with one treatment session five days per week, mostly for a total of 20 treatment sessions. All of these 10 patients achieved a similar level of benefit as experienced with prior acute courses of rTMS. They all elected to recommence maintenance treatment outside of this research study.

*Second courses of maintenance treatment*

Ten patients who received rescue acute rTMS following failure of maintenance treatment recommenced maintenance outside of the formal research study. For these 10 patients, five received treatment until a second relapse (mean 11.8 ± 3.9 months). In two of these five patients, sessions were rescheduled from every four to every two weeks due to a pattern of very early return of symptoms. Both patients subsequently sustained remission with this schedule for more than 12 months. Of the rest of the ten patients who recommenced maintenance, four continued until eventually withdrawing whilst still well after a mean number of 20.5 ± 6.8 monthly sessions. One patient was still in treatment after four months at the end of data collection.

*Tolerability*

For all patients across all phases of maintenance treatment described, the mean total number of treatment episodes (groups of 5 treatments) was 17.3 ± 21.5 (median 9, range 1–106) and mean

total number of rTMS sessions 96.7 ± 132.2 (median 45, range 5–699). rTMS was tolerated very well throughout with no serious adverse events, including an absence of seizures.

**Discussion**

This paper is the first description of the use of repeated brief clusters of rTMS treatment sessions as a form of maintenance treatment following successful response to acute rTMS treatment. It is also by far the most substantive description of any form of maintenance rTMS treatment to date. This study found that despite the considerable degree of variability in the duration of effects, the vast majority of patients experienced continued periods of absence of depression far longer than the period of time they remained well after their first period of treatment (i.e. less than 3 months). Only two patients relapsed within the first three months of maintenance treatment. Overall the mean duration until relapse was over 10 months. However, for those who remained in treatment at the end of data collection, the mean duration in the study was 12 months.

The provision of maintenance treatment in this study was considerably different than has been described previously [12,13] using an intensive clustered application of treatment periodically. Although this approach was initially speculative, our results suggest that for a considerable number of patients, this type of regimen has value in delaying depressive relapse. However, a substantial body of research is required to try to define optimal treatment parameters for maintenance rTMS. An immediate comparison that may prove of value would be to compare a protocol like the one employed in this study to a more traditional approach where single sessions are applied at weekly or fortnightly intervals. One substantial consideration in understanding these results is the confounding impact of repeated hospital admissions. Little additional treatment was provided within the hospital milieu due to the absence of a substantial group or other therapy program over the weekends. However, some patients may still have found regular periods of admission containing or therapeutic. Counter to this, the

**Table 2**  
Relationship of potential predictors of time to relapse.

Variable	Hazard ratio (95% CI)	P-value
Age	0.99 (0.96–1.03)	0.64
Sex	1.49 (0.56–3.99)	0.42
Total HAMD at start of maintenance	1.06 (0.94–1.19)	0.36
Total BDI at start of maintenance	1.01 (0.97–1.05)	0.69
rTMS (left/right/bilateral)	0.99 (0.89–1.10)	0.83
Initial remission (start maintenance)	0.72 (0.31–1.66)	0.42
Antipsychotic current	1.55 (0.69–3.48)	0.27
Mood stabilizer current	0.93 (0.41–2.09)	0.86

HAMD = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory.

**Table 3**  
Comparison of patients who relapsed and did not relapse.

Variable	Non relapsed (n = 10)	Relapsed (n = 25)	P-value
Age	46.5 (15.2)	44.1 (12.7)	0.64
Male	2 (22%)	6 (23%)	0.80
Total HAMD at start of maintenance	6.6 (3.8)	7.0 (4.0)	0.81
Total BDI at start of maintenance	13.2 (11.5)	12.6 (8.9)	0.88
rTMS (left/right/bilateral)	5/3/2	9/9/7	0.74
Initial remission (start maintenance)	7 (78%)	16 (62%)	0.26
Antipsychotic current	2 (22%)	12 (46%)	0.13
Mood stabilizer current	2 (22%)	12 (46%)	0.13

HAMD = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory.

inconvenience of readmission was considerable for some patients with many finding this process difficult to tolerate, possibly negatively impacting on the success of maintenance treatment and certainly leading to dropout in a number of cases.

Because of the unique form of maintenance treatment applied, but also due to characteristics of the patient sample, it is difficult to compare our results with those of other rTMS follow-up or maintenance studies. Our overall relapse rate was fairly high (71% at a mean of ~10 months) and certainly higher than that seen in some follow-up reports, for example the study of Janicak et al. (38% rTMS reintroduction rate) [8] although not greater than the results reported by Cohen et al. (77% six month relapse rate) [6]. Our sample had a considerably higher degree of treatment resistance compared to the study described by Janicak et al. [8]. In addition and critically, our subjects were explicitly selected as patients who had already demonstrated a vulnerability to post rTMS depression relapse: they had already experienced a relapse of depression within 3 months of a successful course of rTMS. These patients, by selection, are much more likely to relapse than patients who have just responded to rTMS treatment for the first time, regardless of their prior level of treatment resistance. As there are no equivalent groups described in the literature, the outcome of these patients (duration of successful maintenance treatment) is best evaluated in comparison to this initial period of only brief persistence of wellness, rather than some other comparator.

In the analysis we did not identify any clinical or demographic variables that were related to the likelihood of relapse. Previous research has suggested that there are factors related to the likelihood of relapse after a single episode of rTMS treatment (not during maintenance rTMS): for example, age and possibly factors such as depression severity or specific medication use [6]. Our capacity to establish relationships of this sort is clearly limited by the sample size of our study. Although our study sample is substantially greater than any previous reports of maintenance treatment, the sample size remains much smaller than that which is required to get reliable results from regression analyses, especially with multiple potential predictors. There was a suggestion that patients who achieved initial remission from treatment were slightly less likely to relapse (78% versus 62%) and that current mood stabilizer or antipsychotic treatment and bipolar diagnosis were associated with a higher risk of relapse but none of these relationships were significant in simple or multivariate analysis.

One interesting observation derived from this data is that the experience of relapse on one occasion during maintenance treatment should not necessarily indicate that maintenance therapy should permanently cease. In a number of patients, maintenance treatment failed and they received acute 'rescue' treatment. However, after responding to rescue therapy, a group of these patients elected to recommence a 'second course' of maintenance rTMS and for several patients, this second period of maintenance resulted in a very long periods of remission. The average duration of successful maintenance treatment on the second occasion for these patients was almost 12 months. This is in substantial contrast to the brief period of remission sustained originally following their first rTMS treatment which was followed by no maintenance schedule. Two of these patients undergoing a second maintenance treatment course required treatment at a more intensive rate, with fortnightly sessions provided over a significant period of time for both. This treatment has been resource intensive to supply but has been the only mechanism to otherwise prevent relapse in these patients.

Despite treating patients with this intensive cluster approach and in some instances for extremely long periods of time, maintenance treatment sessions were universally tolerated and no substantive adverse events or complications were recorded. There was a moderately high dropout rate which was predominately

related to the practical issues involved in patients accessing the intensive monthly sessions which were provided during a brief inpatient stay.

There are a number of obvious limitations to this data. First, and most significantly, there is no form of placebo control. It is a considerable challenge to conduct substantive clinical trials of maintenance rTMS given that patients having received acute rTMS are likely to be unblinded if randomised to a sham control, unless the sham control can extremely accurately reproduce the somatic sensation produced with rTMS treatment. A second limitation is that changes in medication treatment across the duration of maintenance therapy were not accurately documented. However, anecdotally very few medication changes occurred with the vast majority of patients not wishing to make any changes to medication that would have undermined their successful continuation of remission. In addition, there was variability in the type of rTMS used in both the initial and maintenance treatment periods. This resulted from maintenance treatment being provided to patients as they graduated from a series of differing clinical protocols over time. Although this confounds interpretation of the results somewhat, as no consistent pattern of differential efficacy between unilateral and bilateral forms of rTMS or between left and right sided rTMS (see review in [16]) has emerged, this mitigates the issue to some degree. Finally, as previously noted, the employed format of maintenance therapy was not compared with a more standard approach, such as the regular provision of a single treatment session on a weekly or two weekly basis.

In conclusion, rTMS treatment is increasingly becoming part of the therapeutic armamentarium of psychiatry. Extremely limited information is currently available about the therapeutic value of maintenance rTMS and the most appropriate ways to apply this. This study has demonstrated that a cluster of rTMS treatment, provided intensively once per month, appears to substantially delay the relapse of depression in a considerable proportion of patients who were previous rTMS responders. Long-term maintenance rTMS treatment also appears to be safe and well tolerated by patients who have previously responded to rTMS.

## Acknowledgements

The authors would like to thank the support of Julie Lindsey-Halls, Lorraine Gardner and the other nursing staff of the Victoria Clinic involved in the provision of rTMS treatment to these patients.

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