

Is Maintenance Repetitive Transcranial Magnetic Stimulation for Patients With Depression a Valid Therapeutic Strategy?

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Repetitive transcranial magnetic stimulation (rTMS) is now a well-established intervention used in the management of acute episodes of major depressive disorder. However, a smaller body of research has explored the use of rTMS as a maintenance strategy to reduce depressive relapse. The research conducted to date does suggest that rTMS can be usefully applied as a maintenance antidepressant strategy but further research is required to define the optimal parameters to achieve the greatest clinical outcome.

Repetitive transcranial magnetic stimulation (rTMS) is now an established treatment for patients with major depressive disorder (MDD) who have failed to respond to one or more medication trials supported by multiple trials and meta-analysis.¹ Response rates seen in groups of patients with treatment-resistant symptoms have been reported between 30% and 50%, although remission rates are lower than this.² However, like all antidepressant strategies, it is recognized that patients may relapse in the 6–12 months following rTMS treatment.³ For this reason, there has been growing interest in the potential use of rTMS as a maintenance therapeutic strategy.

The first report of rTMS used for maintenance appeared in 2002, which described a patient who maintained a degree of wellness during 4 months of weekly or twice weekly rTMS sessions, and this was followed by several open label studies (see review in ref. 4). The majority of more maintenance studies have adopted an approach most closely analogous with the way in which maintenance electroconvulsive therapy (ECT) is used. Treatment is initially tapered from the acute application of treatment 5 days per week, usually reducing to 3 times per week, and then twice per week. Maintenance then progresses to 1 per week and then 1 every 2 weeks (and, in some cases, once per month).

A second form of maintenance has developed referred to as a “clustered maintenance” approach. In the first use of this, we applied 5 transcranial magnetic stimulation (TMS) sessions over a 2½-day period once per month: this was approximating slightly >1 treatment per week. We developed this approach based upon preclinical TMS studies (for example, ref. 5) that had suggested that rTMS effects may accumulate when applied over sessions provided closely together in time⁵ proposing that multiple sessions provided closely together may have greater benefits than the provision of an individual treatment at much greater interval (e.g., weekly). We initially demonstrated patient acceptability, tolerability, and clinical benefits in the majority of

37 patients treated. Importantly, cluster maintenance was not associated with serious adverse events, such as seizures. A number of recent studies have also described patients treated in this manner. Pridmore *et al.*⁶ found that patients returning for this form of intermittent treatment, on average, demonstrated some degree of early relapse of symptoms (which was generally successfully managed with the short burst of treatment sessions), although there was a degree of variability in the duration between treatment applications in this population.

Fortunately, a number of more recent studies have used randomized designs or larger samples to try and demonstrate the role of maintenance treatment. In the first of these, 49 patients who had improved with rTMS were randomized to either a single rTMS treatment once per month or no treatment at all.³ Notably, all patients remained off medication during the study, although a further course of rTMS was allowed if patients started to relapse. Patients receiving monthly rTMS sessions had a numeric, but not statistically significant, longer duration until the needed reintroduction of treatment and a numeric but nonsignificant lower rate of treatment reintroduction. It is possible that the failure of the differences in this study to reach significance arose from the limited sample size, although the overall “low dose” of treatment (sessions only once monthly) may well have contributed.

In a second study, 17 patients who had responded to an initial course of rTMS were randomized to receive either active (10) or sham (7) maintenance treatment for 11 months.⁷ The schedule reduced from 3 sessions per week to 1 session every 2 weeks. There was a greater improvement in depression in the active group in the first 3 months of follow-up, although not after this time when the frequency of TMS sessions was reduced from weekly to every second week. The low numbers and dropout rate make interpretation of this study challenging.

In a third study, 66 patients (medication-resistant but not having failed venlafaxine in the past) were randomized who were either in remission or had a partial response to an acute course of rTMS treatment.⁸ Twenty-five patients received maintenance rTMS, 22 received venlafaxine, and 19 received both. The 12-month maintenance schedule began twice-weekly and was progressively reduced to once every 2 weeks. The percentage of patients who did not meet relapse criteria was similar across 3 groups: 40% for the rTMS, 45% for the venlafaxine, and 37% for the combination groups.

By far, the largest published study investigated the efficacy of clustered maintenance.⁹ Two hundred eighty-one patients who

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had achieved full or partial remission with antidepressant medication were randomized to rTMS, medication, or combination treatment. Treatment involved 10 sessions over a 5-day period monthly for the first 3 months and then 5 sessions over a 3-day period monthly thereafter. Patients in this group withdrew from their antidepressant drugs over the initial 1–2 weeks of the study. There was a significant benefit in time to relapse and total relapse rate for rTMS (24.2%) or combination treatment (15.9%) over antidepressant medication alone (44.4%). The benefit of rTMS was significantly greater in patients having been treated for a first episode of depression. Five patients receiving medication, but none receiving rTMS, experienced a manic switch during the study.

The final study of note differed in its use of a deep TMS stimulation system.¹⁰ In this study, 212 depressed subjects received either active or sham stimulation over 4 weeks and then received two treatments per week for a further 12 weeks. There was a significant benefit of active over sham stimulation after the initial 4 weeks of treatment (38.4 vs. 21.3% response rate), and this difference remained stable during the 12 weeks of maintenance with a significantly greater number of patients in the active treatment group remaining well at study end (32.6% met response at end vs. 14.6%).

The major difficulty with interpreting this research is the marked heterogeneity between the maintenance schedules used across treatment. Clearly the most substantive randomized maintenance study conducted to date⁹ investigated the use of clustered maintenance rather than the more traditional schedules that have been adopted more widely in clinical practice. There is certainly a suggestion that protocols involving greater numbers of treatments are associated with better outcomes with the one study providing treatment in a single session once per month showing no benefits of active over sham therapy.³ However, it is not really possible from the studies conducted to date to understand whether there is a critical level of treatment that is required to successfully maintain

remission. Another factor that clouds interpretation of this literature is the frequent inclusion in studies of patients who are both in remission or have had a partial response to treatment. It is logical to assume that patients with a more dramatic initial response to treatment are more likely to remain well long term independently of the administration of maintenance therapy, and it may well be that the frequency and schedule of treatment administration needs to be adapted very specifically to the level of symptoms that patients experience when transitioning from acute to maintenance intervention. It is of note that recent consensus guidelines for the use of maintenance ECT suggested that treatment frequency of maintenance ECT sessions be slowly reduced to establish the maximum effective therapeutic window between treatments. It would seem sensible to utilize this same principle for maintenance rTMS, although the much lower rate of side effects with rTMS means that, at times, clinicians are likely to favor more rather than less intensive treatment protocols to “err on the side of caution.” The literature is also limited by the rarity of sham-controlled trials. There are substantive issues with the provision of a valid sham once a patient has had the experience of “true” rTMS during initial treatment. An interesting comparison is maintenance ECT, which is widely used despite the lack of similar sham controlled studies. Finally, we currently lack a comprehensive analysis of how the maintenance schedule offered to patients affects patient engagement.

In conclusion, there is emerging evidence that maintenance rTMS strategies can be used to prevent relapse but further research is required to define the most effective and efficient strategies. This may include the development of predictors of response (clinical or biomarkers or prediction algorithms), as has been tested with ECT to aid in appropriate treatment selection. The use of maintenance rTMS should be considered in the broader context of other relapse prevention strategies (Table 1). Given the limited evidence base currently, maintenance rTMS

Table 1 Maintenance strategies after a successful course of rTMS

Strategy	Detail	Evidence base	Comment
Continued or recommenced antidepressant medication	Medication is frequently continued during a course of rTMS and afterward	No systematic trials have evaluated the use of medication in preventing relapse following a successful course of rTMS	This is likely to remain a default strategy for many in the absence of clinical trial evidence
Addition of Lithium	Evidence supports the use of Lithium in addition to an antidepressant in reducing relapse following ECT	No trials	Patients frequently wish to reduce or stop medication after responding to rTMS so this is not likely to be commonly acceptable
MBCBT	MBCBT has been shown to reduce relapse rates following successful treatment with other antidepressant treatments	No trials following rTMS	This seems a sensible option to offer patients to enhance well-being and would seem likely to offer some relapse prevention benefit
Maintenance rTMS	This is most commonly provided on a slowly reducing schedule from 1–2 sessions per week to 1 session per 2–4 weeks	Modest number of small open or randomized trials	The optimal scheduling—frequency of treatment and rate of tapering—remain unclear
Clustered maintenance rTMS	The provision of 5–6 treatment sessions usually in 2–3 days every 4 weeks	Several open-label and one-large scale randomized study showing superiority over antidepressant medication alone	Maintenance rTMS + medication was the most effective option in the large comparative trial

ECT, electroconvulsive therapy; MBCBT, mindfulness-based cognitive behavioral therapy; rTMS, repetitive transcranial magnetic stimulation.

would seem to be most usefully applied in patients who have responded well to TMS but experienced a relatively early return of symptoms—patients would receive a second course of treatment to restore remission followed by maintenance to try and prolong clinical benefits. The duration of relapse seen with maintenance can then be compared with the clinical outcomes following treatment without maintenance on an individual patient basis to help determine whether maintenance is proving valuable or not.

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CONFLICT OF INTEREST

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