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EDITORIAL

Is maintenance needed for patients who respond to acute TMS therapy?

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Major depressive disorder (MDD) is a prevalent mental health condition that poses a significant burden on individuals worldwide. Unfortunately, the risk of relapse in MDD is high, especially after each subsequent depressive episode.[1] Traditional pharmacologic antidepressant treatments often yield relatively low response rates[2] and carry a risk of adverse effects. As a result, neuromodulation, particularly transcranial magnetic stimulation (TMS), has emerged as a potential alternative for patients with treatment-resistant depression (TRD).

Although acute TMS therapy has shown strong evidence of efficacy, with response rates of 40-50% and remission rates of 25-30% in patients with MDD,[2] it is acknowledged that this approach alone is inadequate for chronic care due to the high likelihood of relapse experienced by the majority of MDD patients.[3,4] Consequently, there is a growing consideration for maintenance TMS treatments in acute responders as a means to sustain the antidepressant effect and prevent relapse.

Several studies have highlighted the potential benefits of maintenance TMS. For instance, Richieri et al. reported significantly lower relapse rates in TRD patients among responders receiving maintenance rTMS compared to no additional rTMS treatment.[5] Similarly, a prospective trial by Janicak et al. found that repeat TMS sessions triggered by symptom relapse resulted in symptomatic relief for a majority of participants.[6] These studies, and others, suggest that maintenance TMS may have a crucial role in improving long-term outcomes for patients with major depressive disorder (MDD). However, further research is needed to fully understand and establish the effectiveness of maintenance TMS in the treatment of MDD.

The current body of literature on maintenance TMS for MDD and TRD is limited, primarily consisting of open-label studies, case reports, and case series. However, valuable insights into the efficacy of maintenance TMS have been provided by two comprehensive systematic reviews conducted by Wilson et al.[3] and D'Andrea et al.[2]

Despite these reviews, important questions remain unanswered. Therefore we propose an optimal clinical trial design to enhance our understanding of maintenance TMS, described as follows.

Target population

Based on the available literature, the most appropriate target population that may show efficacy are patients with MDD who responded to acute TMS treatments.[7]

Stimulation frequency and target brain area

In the current literature on maintenance TMS, the most commonly targeted brain region was the left dorsolateral prefrontal cortex (DLPFC), using high-frequency (HF) activating protocols (i.e., 10-20 Hz).[2] However, there is insufficient evidence to suggest that HF left DLPFC is superior to low-frequency (LF) right DLPFC or bilateral stimulation.[8] Nonetheless, it is reasonable to consider targeting the same area during both acute and maintenance stimulation. This approach takes into consideration that TMS induces specific structural and functional changes in the cortical region, directly influencing the clinical manifestations of depression.[9] Sustaining stimulation in the same area may contribute to perpetuating the acute effects observed in the treatment of depression.

Frequency of maintenance sessions

Studies have shown that administering two or fewer stimulations per month may be ineffective in sustaining an antidepressant effect or reducing the risk of relapse in responder patients.[2] In the D'Andrea et al. review,[2] all nine studies that included protocols with more than two

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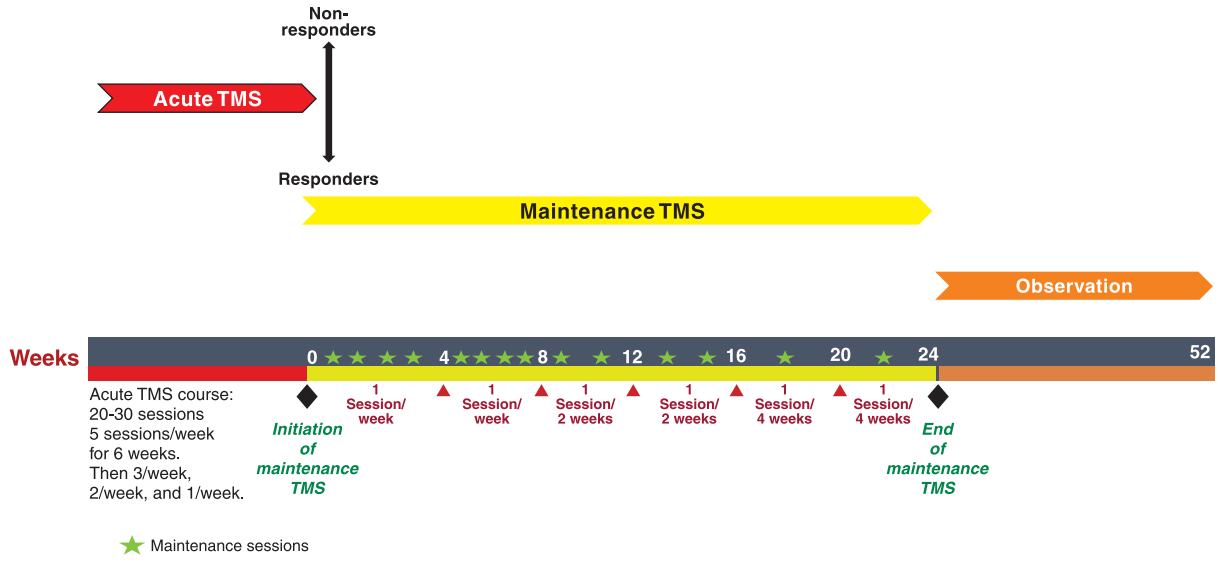

Figure 1 Proposed clinical trial design for maintenance transcranial magnetic stimulation.

stimulations per month reported a significantly reduced risk of relapse overall.

Temporal distance from acute maintenance protocol

Studies have shown that a 4-week gap between acute and maintenance protocols does not result in adverse outcomes, supporting the idea of a 4-week interval as optimal.[2]

Duration of maintenance protocol

The current literature shows that the risk of relapse is most pronounced 5 months after acute TMS treatments, so it would be reasonable to have a maintenance protocol lasting at least 5 months following the acute treatment phase.[10]

Proposed clinical trial design

A randomized, double-blinded, sham-controlled clinical trial. The target population will include MDD patients who are acute TMS responders. Initially, patients will undergo a full course of acute TMS, with the location and frequency determined by the researcher. Subsequently, acute responders will be randomly assigned to either the active or sham groups. Maintenance TMS will begin immediately after the completion of acute stimulation and continue for a duration of 24 weeks. The frequency of sessions will be structured as follows: one session per week for the first 2 months, followed by one session every other week for the subsequent 2 months, and, finally, one session every 4 weeks for the remaining 2 months. The study will have a total duration of 52 weeks, allowing for an extended follow-up period to assess the long-term outcomes and sustainability of the antidepressant effects (Figure 1).

In conclusion, the existing literature suggests that maintenance TMS holds significant potential as a valuable tool in the management of MDD and TRD. It demonstrates promising results in reducing relapse rates among responders, thereby emphasizing the need for its inclusion in the treatment approach. However, further research is warranted to fully elucidate the effectiveness of maintenance TMS in MDD treatment. To address this gap, a proposed clinical trial design is outlined, aiming to provide valuable insights and a long follow-up period to enhance our understanding of maintenance TMS. By establishing an evidence-based protocol, we can advance towards more effective and sustainable long-term outcomes for patients with MDD, while also ensuring the safety and efficacy of additional TMS treatments.

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