

# LONG-TERM OUTCOMES OF TREATMENT-RESISTANT DEPRESSION IN PATIENTS UNDERGOING REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS): A SYSTEMATIC REVIEW OF EFFICACY AND SAFETY

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## ABSTRACT

**Introduction:** Treatment-resistant depression (TRD) is a major clinical challenge, as many patients do not respond to conventional antidepressants. Repetitive transcranial magnetic stimulation (rTMS) emerges as a promising alternative for resistant cases by stimulating brain regions associated with mood regulation. **Objective:** This study aims to analyze the efficacy and safety of rTMS in comparison to electroconvulsive therapy (ECT) and to explore the durability of antidepressant effects and the applicability of rTMS in specific populations. **Methodology:** Through a systematic review, studies were selected in the BVS, Scielo, and PubMed databases using the terms "Repetitive Transcranial Magnetic Stimulation," "Depression," and "Safety." Inclusion criteria involved randomized controlled trials, cohort studies, and systematic reviews on the efficacy and safety of rTMS for TRD. **Results and Discussion:** Results showed that rTMS provides an antidepressant response in non-psychotic TRD cases, with lower dropout rates and fewer cognitive side effects compared to ECT. However, rTMS's initial efficacy tends to decrease without maintenance protocols. Studies indicate a response rate of up to 66.5% after three months, dropping to 46.3% after one year, highlighting the need for maintenance protocols to prolong effects. **Conclusion:** Although rTMS shows lower efficacy in severe cases, such as psychotic depression, its higher patient acceptance and reduced cognitive effects make it an attractive option. Future studies should investigate the maintenance of rTMS effects, particularly in adolescents and patients with comorbidities.

**Keywords:** Repetitive transcranial magnetic stimulation; Treatment-resistant depression; Efficacy; Safety; Electroconvulsive therapy.

## INTRODUCTION

Treatment-resistant depression (TRD) presents a significant challenge in clinical practice, as many patients fail to experience symptom relief from traditional antidepressants. In this context, repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising alternative treatment for resistant cases, particularly in patients who do not adequately respond to conventional therapies. rTMS is a non-invasive method that uses magnetic fields to stimulate

specific brain regions involved in mood regulation, offering an innovative approach to managing depression.

The studies analyzed the efficacy and safety of rTMS present mixed results in terms of immediate effects and the durability of therapeutic benefits. According to a meta-analysis conducted by Health Quality Ontario (2016), rTMS showed a modest but significant improvement in depression scores compared to placebo. However, its effects were less robust and long-lasting compared to electroconvulsive therapy (ECT). This conclusion is supported by Ren et al. (2014), who observed that while ECT achieved better response and remission rates in cases of psychotic depression, rTMS had similar efficacy to ECT in non-psychotic depression cases.

Although ECT stands out in more severe cases, such as psychotic depression, rTMS has proven to be an attractive option due to its minimal side effects and greater patient acceptance. McGirr et al. (2015) reported that 55.6% of patients with TRD achieved a clinical response following an accelerated rTMS protocol, with 37% reaching full remission. Additionally, studies such as Kedzior et al. (2016) emphasize that rTMS has lower dropout rates compared to ECT, which may be associated with more significant cognitive side effects.

Another important point is the durability of the antidepressant effects. According to Senova et al. (2019), approximately 66.5% of patients who initially responded to treatment maintained their response at three months, and 46.3% still showed benefits after one year. However, to sustain these effects, several authors, including Rachid (2018) and D'Andrea et al. (2023), suggest the implementation of maintenance protocols. Rachid (2018) argues that maintenance rTMS can ensure remission for up to eight years, making it an effective strategy to prevent relapses.

Recently, new stimulation modalities have been studied, such as intermittent theta burst stimulation (iTBS), which has shown similar efficacy to rTMS but with the advantage of being administered in a shorter time, as highlighted by Lan et al. (2023). This could improve treatment adherence and reduce associated costs.

Based on the evidence reviewed, this study aims to investigate the efficacy and safety of rTMS in the treatment of treatment-resistant depression, with a focus on comparison with ECT and the durability of antidepressant effects. Additionally, it seeks to explore the viability

of rTMS in specific populations, such as adolescents and patients with post-traumatic depression, contributing to the development of more effective guidelines for managing TRD.

## **METHODOLOGY**

This study is a systematic review on the long-term outcomes of treatment-resistant depression in patients undergoing repetitive transcranial magnetic stimulation (rTMS), focusing on treatment efficacy and safety. To formulate the research question, the PICO strategy was used, with P (Population): patients with treatment-resistant depression; I (Intervention): rTMS; Co (Outcome): long-term efficacy and safety of rTMS. The guiding question formulated was: “What is the long-term impact of rTMS on efficacy and safety in patients with treatment-resistant depression?”

For the terms selection, a search was conducted using the Descritores em Ciências da Saúde (DeCS), and the terms utilized included “Repetitive Transcranial Magnetic Stimulation,” “Depression,” and “Safety.” Searches were carried out in the Biblioteca Virtual em Saúde (BVS), Scielo, and PubMed databases, utilizing “and” and “or” operators to combine terms. The search was conducted from August 21, 2024, to October 25, 2024, covering articles in English, Portuguese, and Spanish.

The inclusion criteria comprised randomized controlled trials, cohort studies, case-control studies, and systematic reviews on the efficacy and safety of rTMS for treatment-resistant depression, published within the last decade. Articles addressing maintenance rTMS protocols and relapse prevention were included.

Exclusion criteria included studies involving individuals with psychiatric disorders other than treatment-resistant depression, studies with concurrent use of other invasive therapies, and those with methodologies inadequate for assessing long-term efficacy and safety. Additionally, case reports and reviews lacking rigorous methodology or involving subjects that did not meet the established population criteria were excluded.

## **RESULTS AND DISCUSSION**

The studies analyzed on the efficacy and safety of rTMS in the treatment of treatment-resistant depression (TRD) present a variety of results, both in terms of immediate effects and

the durability of therapeutic benefits. Overall, rTMS is emerging as a promising alternative, particularly for patients who do not achieve satisfactory results with traditional antidepressants.

Health Quality Ontario (2016) conducted a comprehensive meta-analysis comparing rTMS with placebo treatments and electroconvulsive therapy (ECT). Their findings indicate that although rTMS provided a small but significant improvement in depression scores compared to placebo, the effects were not as robust or long-lasting as those obtained with ECT. This conclusion is consistent with the work of Ren et al. (2014), who directly compared rTMS and ECT, highlighting that, for patients with psychotic depression, ECT achieved better response and remission rates, while rTMS showed similar efficacy to ECT in non-psychotic depression cases.

However, the efficacy of rTMS should not be underestimated. Gaynes et al. (2014) noted that patients with multiple antidepressant failures experienced a significant reduction in depression scores when treated with rTMS. This finding aligns with McGirr et al. (2015), who reported that 55.6% of patients with TRD achieved a clinical response after an accelerated rTMS protocol, with 37% of these patients reaching full remission. This study also highlights the acceptability of rTMS among patients, with low dropout rates, contrasting with the higher dropout rates and side effects associated with ECT, as discussed by Kedzior et al. (2016).

Another important point raised by the studies is the durability of the antidepressant effects. Senova et al. (2019) conducted a meta-analysis focused on the sustainability of rTMS benefits, showing that among patients who responded to the initial treatment, approximately 66.5% maintained their response at three months, 52.9% at six months, and 46.3% up to one year. This durability is a critical aspect of the debate between rTMS and ECT, as ECT, although more effective initially, may be perceived as more invasive and associated with higher risks of cognitive side effects, as suggested by Reddy and Vijay (2017) and Kedzior et al. (2017).

Magavi et al. (2017) bring into the discussion the application of rTMS in younger populations, specifically adolescents with TRD. Although most studies have focused on adults, this study suggests that rTMS may also be effective in adolescents, with improvements reported within 2 to 8 weeks of treatment. However, since the reviewed studies were uncontrolled, Magavi et al. (2017) emphasize the need for controlled clinical trials to confirm these findings in adolescents.

The issue of prolonged rTMS use, particularly in terms of maintenance, is highlighted by Rachid (2018) and D'Andrea et al. (2023). Both studies underscore the importance of maintenance protocols to prevent relapses. Rachid (2018) points out that maintenance of rTMS can provide remission in patients for periods of up to eight years, a significant finding given the

high risk of relapses in TRD patients. Similarly, D'Andrea et al. (2023) observed that administering maintenance rTMS twice a month was effective in significantly reducing relapse risk, particularly after five months of the initial treatment.

Lan et al. (2023) introduce an interesting comparison between high-frequency rTMS and intermittent theta burst stimulation (iTBS), a newer and shorter-duration modality. While both treatments showed similar efficacy in terms of response and remission rates, iTBS has the advantage of being administered in a significantly shorter time, which may improve treatment adherence and reduce overall treatment costs.

In terms of safety, most studies indicate that rTMS is well-tolerated, with mild side effects such as scalp pain and headaches. Xie et al. (2023) confirm this safety in their study on patients with post-stroke memory disorders, reporting that rTMS not only improved cognitive function in these patients but was also safe, with no significant adverse effects.

Additionally, Bulteau et al. (2020) focused on the cost-effectiveness of rTMS, arguing that the use of rTMS, both in curative interventions and in maintenance protocols, can be a cost-effective strategy for TRD patients, especially when compared to the high costs of long-term antidepressant treatments and the frequent relapses associated with these treatments.

Finally, the study by Chang et al. (2023) adds to the discussion by exploring the application of rTMS in patients with post-traumatic depression after traumatic brain injury. Their results showed that rTMS had a positive impact on reducing depressive symptoms in these patients, although the effects diminished after one to two months, suggesting that maintenance treatments or longer protocols may be necessary to sustain the benefits in specific populations.

In summary, the reviewed studies indicate that rTMS is a viable and safe alternative for the treatment of treatment-resistant depression, particularly in non-psychotic cases. Short-term efficacy is well-documented, but the durability of the effects varies, depending on the presence or absence of maintenance protocols. Furthermore, compared to ECT, rTMS shows slightly lower efficacy in more severe cases, such as psychotic depression, but it is associated with better patient acceptance and fewer cognitive side effects, making it an attractive option for a growing number of patients and physicians.

## **CONCLUSION**

The review of studies indicates that rTMS demonstrates significant efficacy in treating treatment-resistant depression (TRD), particularly in non-psychotic cases, offering a safe and

well-tolerated alternative. Although its initial effects in symptom reduction are promising, the therapeutic benefits of rTMS in terms of response and remission are still lower than those of ECT in more severe cases, such as psychotic depression. Nonetheless, rTMS is associated with better patient acceptance, lower dropout rates, and fewer cognitive side effects.

Among the limitations observed, there is a variation in the durability of the antidepressant effects of rTMS, which tends to diminish after a few months without maintenance protocols, limiting its long-term efficacy for some patients. Additionally, cost-effectiveness analyses and the impact of rTMS on different populations, such as adolescents and patients with traumatic brain injuries, require more controlled and specific studies, given the variability of responses within these groups.

Future research should focus on more structured maintenance protocols to extend the durability of rTMS's therapeutic effects, assessing different application frequencies to prevent relapses without compromising treatment adherence. Furthermore, randomized studies in adolescents and patients with psychiatric or neurological comorbidities could strengthen the understanding of rTMS's efficacy and safety in these populations, as well as better define the role of modalities like iTBS.

In summary, rTMS continues to evolve as a viable and safe therapeutic option for TRD, especially among patients with multiple antidepressant failures. However, its sustained efficacy depends on further investigation into maintenance protocols and robust evaluations in diverse groups, aiming to expand its clinical use and consolidate its long-term role in the treatment of treatment-resistant depression.

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