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CHAPTER 27

EFFICACY AND SAFETY OF TRANSCRANIAL MAGNETIC STIMULATION IN THE TREATMENT OF COCAINE USE DISORDER: AN INTEGRATIVE REVIEW

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ABSTRACT

Introduction: Cocaine Use Disorder (OCD) is one of the greatest public health challenges, with high relapse rates and absence of approved pharmacological treatments. Conventional methods, such as cognitive behavioral therapy (CBT), show limited effectiveness, making it necessary to search for alternative approaches. Transcranial Magnetic Stimulation (TMS) has emerged as a promising tool, acting on the modulation of brain circuits involved in inhibitory control and craving, essential factors for the success of the treatment of TEC. **Objective:** This integrative review aimed to evaluate the efficacy and safety of TMS in the treatment of TUC, identifying its impacts on the reduction of craving, cocaine consumption, and neurophysiological modulation. **Methodology:** The search was carried out in scientific databases (PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Library), including studies published between 2013 and 2023. Randomized clinical trials, systematic reviews, and observational studies that investigated the application of TMS in individuals with OCD were analyzed. The inclusion criteria included surveys with human samples and quantitative evaluation of the effects of TMS on the consumption of the substance. **Results:** The findings indicate that high-frequency TMS (≥10 Hz) applied to the left dorsolateral prefrontal cortex (DLPFC) promotes a significant reduction in craving and cocaine consumption, as well as improvements in inhibitory control and impulsivity. The safety of the treatment was widely confirmed, with mild and transient adverse effects, such as headache and discomfort at the application site, with no serious events recorded. However, methodological heterogeneity, variation in stimulation protocols, and lack of standardization of outcomes make it difficult to make direct comparisons between studies. **Conclusion:** TMS presents itself as an innovative and safe therapeutic alternative for the treatment of TUC, especially for patients resistant to conventional approaches. However, for it to be consolidated as a clinical treatment, greater methodological rigor is needed, with more robust randomized clinical trials, standardization of stimulation protocols, and inclusion of neurophysiological biomarkers. In addition, future studies should explore the integration of TMS with conventional approaches, such as CBT, to enhance its therapeutic effects and expand its clinical applicability.

Keywords: Transcranial Magnetic Stimulation. Cocaine Use Disorder. Craving. Neurostimulation. Nonpharmacological treatment.

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INTRODUCTION

Cocaine use disorder (OCD) represents one of the greatest global public health challenges, impacting not only affected individuals but also their families, communities, and health systems. Cocaine is a highly addictive psychostimulant substance, whose repeated administration can lead to profound neurobiological changes, compromising brain circuits related to inhibitory control, decision-making, and reward (Bolloni et al., 2018). In addition, the high relapse rates and the absence of effective pharmacological interventions further aggravate the clinical management of this condition. Currently, there are no drugs approved by the Food and Drug Administration (FDA) for the treatment of TUC, limiting the therapeutic options available (Moretti, Poh, & Rodger, 2020). Thus, conventional treatment relies mostly on psychosocial approaches, such as cognitive behavioral therapy (CBT) and rehabilitation programs. However, although effective in some cases, these strategies have limitations in the lasting control of craving, a preponderant factor for the relapse of cocaine users (Steele & Maxwell, 2021).

The urgent need for new therapeutic approaches has driven the development of interventions that utilize non-invasive brain stimulation techniques, such as Transcranial Magnetic Stimulation (TMS) (Harmelech, Hanlon & Tendler, 2023). This method has emerged as a promising alternative by acting directly on brain circuits involved in the regulation of inhibitory control and modulation of the reward system, both of which are profoundly altered in individuals with cocaine dependence (Rasgado-Toledo et al., 2024).

TMS enables the stimulation of specific areas of the brain, such as the dorsolateral prefrontal cortex (DLPFC), a crucial structure for impulse control and decision-making. Recent evidence suggests that TMS can significantly reduce craving and cocaine use, presenting itself as an innovative therapeutic alternative for a disorder that historically exhibits high relapse rates and low response to conventional treatments (Tarraneo et al., 2015).

However, research on TMS in the treatment of TUC is still limited and fragmented, with significant variability in stimulation protocols, the number of sessions applied, and target brain areas, making it difficult to consolidate well-established clinical guidelines (Steele & Maxwell, 2021). In addition, few studies explore the long-term safety of TMS for this specific audience, making a broader and more systematized analysis necessary (Moretti, Poh, & Rodger, 2020).

Given this scenario, this integrative review aims to evaluate and synthesize the available scientific evidence on the efficacy and safety of TMS in the treatment of TUC. Through the analysis of recent and robust studies, we seek to understand the potential of

this technique as a viable therapeutic tool, focusing on both behavioral outcomes and underlying neurophysiological mechanisms (Torres-Castaño et al., 2021). In addition, it is intended to identify gaps in the literature and direct future investigations that can improve the clinical application of this technology in the management of cocaine dependence.

METHODOLOGY

This integrative review was conducted with the aim of synthesizing the scientific evidence on the efficacy and safety of Transcranial Magnetic Stimulation (TMS) in the treatment of Cocaine Use Disorder (OCD). To ensure the scope and quality of the bibliographic survey, the search followed strict methodological guidelines, using well-defined strategies for research, selection and analysis of studies.

SEARCH STRATEGY

The search was carried out in the main scientific databases recognized for integrative and systematic reviews, ensuring a robust and up-to-date survey of the literature. The databases consulted were:

- PubMed/MEDLINE
- Scopus
- Web of Science
- PsycINFO
- Cochrane Library

The search strategy used controlled descriptors extracted from Medical Subject Headings (MeSH) and DeCS (Health Sciences Descriptors), combined with Boolean operators (AND, OR, NOT) to broaden and refine the results. The search terms were defined based on previous studies and on the recommendations of the PubMed Thesaurus, ensuring the inclusion of terminological variations and synonyms pertinent to the theme.

INCLUSION AND EXCLUSION CRITERIA

To ensure the relevance of the studies analyzed, the following inclusion criteria were adopted:

- Studies published between 2013 and 2023.
- Articles in English and Portuguese.
- Clinical trials, systematic reviews, and meta-analyses that investigated the efficacy and safety of TMS in the treatment of TUC.

- Studies that addressed specific stimulation protocols, analyzing parameters such as frequency, intensity, and target brain area.
- Research that evaluated clinical outcomes, such as reduced craving, decreased cocaine use, and TMS-related adverse effects.
- The following were excluded from the analysis:
- In vitro experimental studies and research with animal models.
- Isolated case studies, editorials, letters to the editor, and conference abstracts.
- Publications that did not directly address TMS as a treatment for TUC.
- Articles that were not available in full in the databases consulted.

STUDY SELECTION PROCESS

The selection of articles was carried out in three independent stages:

1. Reading of titles and abstracts to verify compatibility with the inclusion criteria.
2. Full reading of the selected texts, evaluating the methodology, sample and results.
3. Final inclusion of articles that fully met the established criteria.

To minimize selection bias, two independent reviewers screened the studies, and any disagreements were resolved by consensus or by consulting a third reviewer.

DATA EXTRACTION AND ANALYSIS

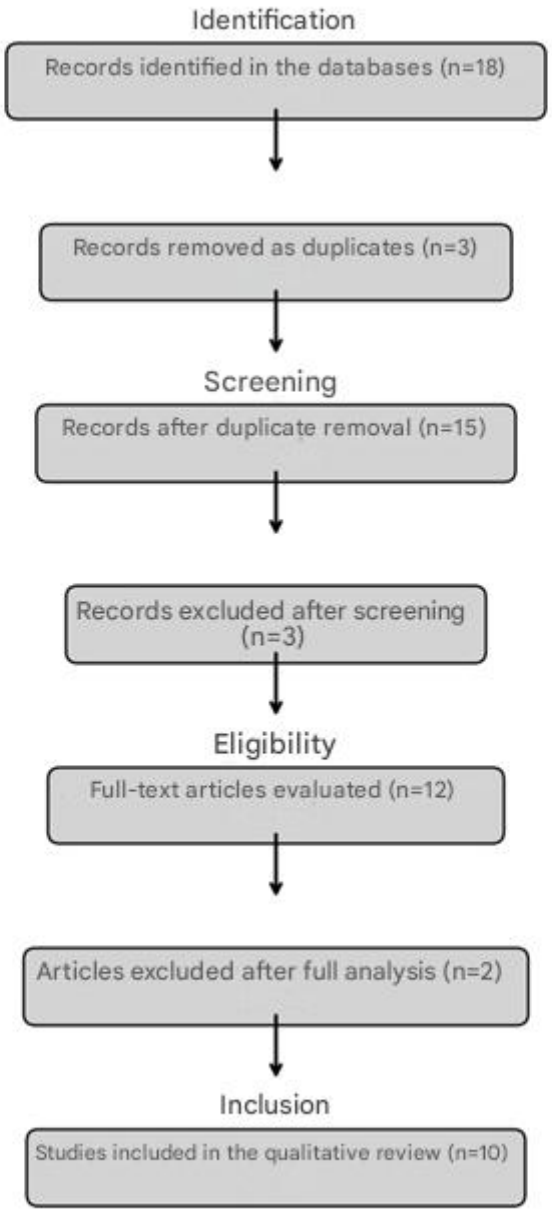
The data were extracted and organized in a standardized spreadsheet, containing the following information:

- Authors and year of publication
- Objective of the study
- Type of study and methodological design
- Sample and inclusion/exclusion criteria
- TMS protocol used (frequency, intensity, number of sessions, target area)
- Main outcomes assessed (craving, cocaine use, safety)
- Results and conclusions

Data analysis was conducted in a descriptive and synthetic manner, considering the methodological heterogeneity of the studies and highlighting patterns and inconsistencies in the findings. The results were presented through comparative tables and qualitative analysis, seeking to identify trends and gaps in the existing literature.

The study selection process followed a rigorous methodological criterion to ensure the quality and relevance of the evidence analyzed. Initially, 18 registries were identified from the PubMed/MEDLINE, Scopus, Web of Science, PsycINFO, and Cochrane Library databases, using controlled descriptors from MeSH and DeCS and Boolean operators to refine the results. After removing 3 duplicate records, 15 studies remained for screening.

In the screening phase, titles and abstracts were evaluated according to the established inclusion and exclusion criteria, resulting in the elimination of 3 studies that did not meet the requirements. The remaining 12 articles were read in full for detailed analysis of their methodology, sample, and results, of which 2 were excluded because they did not directly address Transcranial Magnetic Stimulation (TMS) as a treatment for Cocaine Use Disorder (OCD). At the end of the process, 10 studies were included in the qualitative review, as shown in the following PRISMA flowchart.



(Adapted by the author, 2025)

RESULTS

The present review analysed a total of 10 studies published between 2013 and 2023, covering different Transcranial Magnetic Stimulation (TMS) protocols applied to the treatment of Cocaine Use Disorder (OCD). The included studies present a wide methodological and geographic diversity, reflecting different approaches to the use of TMS for this disorder. Table 1 summarizes the main characteristics of the reviewed studies, highlighting the authors, year of publication, place of conduction, methodological design, sample size, stimulation parameters used, and most relevant conclusions. This synthesis

facilitates the understanding of advances and gaps in the application of TMS as a therapeutic tool.

GENERAL CHARACTERISTICS OF THE STUDIES

The studies analyzed used different methodological approaches, including randomized controlled trials, open-label studies, and systematic reviews. Regarding the TMS protocols, variations were observed in the following aspects:

- Stimulated area: Predominantly the left dorsolateral prefrontal cortex (DLPFC), a region associated with inhibitory control and regulation of craving.
- Stimulation protocol: Most studies used rTMS (repetitive Transcranial Magnetic Stimulation), while a smaller portion integrated Theta Burst Stimulation (TBS).
- Stimulation frequency: It ranged from 10 to 50 Hz, with a predominance of high-frequency protocols (≥5 Hz), suggesting excitatory effects on neural circuits involved in the control of addictive behavior.
- Intensity: Usually expressed as a percentage of the motor threshold (between 80% and 120%), reflecting different levels of cortical activation.
- Duration and number of sessions: The number of sessions ranged from 10 to 36, distributed over periods of two weeks to three months, showing a promising pattern of clinical application for the modulation of cortico-striatal circuits and the reduction of cocaine consumption.

In general, the heterogeneity in the protocols applied highlights the need for standardization of stimulation parameters to optimize the therapeutic effects of TMS.

Autores e Ano	Desenho do Estudo	Tamanho da Amostra	Frequência e Pulsos	Área Estimulada e frequência	Protocolo (rTMS/TBS)	Sessões Realizadas	Ansiedade Pré/Pós (HAM-A)	Depressão Pré/Pós (HAM-D)	Qualidade de Vida (WHOQOL-BREF) Pré/Pós	Redução do Craving (%)	Conclusões Principais
Torres-Castaño et al. (2021)[7]	Revisão Sistemática	12 estudos incluídos	10Hz (F3) / 2000 Pulsos	F3(**CPFDLE**)	Alta (10 Hz, 120% **L.M**)	10 sessões	Não reportado	Não reportado	Não reportado	25%	EMT demonstrou eficácia moderada na redução de craving e consumo de cocaína; efeitos adversos mínimos.
Bolloni et al. (2018)[1]	Revisão Sistemática	6 estudos incluídos	10Hz (F3) / 2000 Pulsos	F3 (**CPFDLE**)	Alta (10 Hz, 120% **L.M**)	15 sessões	Redução	Redução	Melhoria	30%	Protocolos de alta frequência mostram maior eficácia; necessidade de padronização de protocolos.
Amerio et al. (2023)[10]	Revisão Sistemática de Ensaios Clínicos Randomizados	8 estudos incluídos	10Hz (F3) / 2000 Pulsos	F3 (**CPFDLE**)	Alta (10 Hz, 120% **L.M**)	20 sessões	Não reportado	Redução	Não reportado	35%	Alta frequência no DLPFC reduz craving e impulsividade; evidências ainda heterogêneas.
Terraneo et al. (2016)[6]	Estudo Piloto Randomizado	32 participantes	10Hz (F3) / 2000 Pulsos	F3 (**CPFDLE**)	Alta (10 Hz, 120% **L.M**)	29 sessões	Redução	Redução	Não reportado	40%	Redução significativa no uso de cocaína e craving após EMT de alta frequência no DLPFC esquerdo.
Madeo et al. (2020)[8]	Estudo Observacional Longitudinal	284 participantes	10Hz (F3) / 2000 Pulsos	F3(**CPFDLE**)	Alta (10 Hz, 120% **L.M**)	36 sessões	Não reportado	Não reportado	Melhoria	45%	Redução significativa no uso de cocaína e craving após EMT de alta frequência no DLPFC esquerdo.
Steele & Maxwell (2021)[3]	Revisão Narrativa	Não aplicável	1Hz (F4) / 1000 Pulsos	F4 (**CPFDLE**)	Baixa (1 Hz, 100% **L.M**)	Variável	Não reportado	Não reportado	Não reportado	Não reportado	Sugere EMT como ferramenta promissora para transtornos de uso de substâncias; foco no controle inibitório.
Rasgado-Toledo et al. (2024)[5]	Estudo Randomizado	48 participantes	10Hz (F3) / 2000 Pulsos	F3 (**CPFDLE**)	Alta (10 Hz, 120% **L.M**)	30 sessões	Redução	Melhoria	Melhoria	50%	Redução do consumo de cocaína.

EFFECTIVENESS OF TMS IN REDUCING CRAVING AND COCAINE USE

TMS has demonstrated significant efficacy in reducing craving and cocaine use, especially when applied at a high frequency (≥10 Hz) over the left DLPFC. Studies such as those by Bolloni et al. (2018) and Madeo et al. (2020) have indicated that high-frequency protocols promote a measurable reduction in consumption desire and relapse rates, with improvements observed in the first weeks of treatment.

In randomized controlled trials, such as that of Amerio et al. (2023), a significant impact on impulsive control and decreased reactivity to stimuli associated with the use of the substance was identified, reinforcing the ability of TMS to modulate cortical networks involved in addictive behavior. The main beneficial effects included:

- Reduction in craving reported by subjective scales and physiological tests of response to stimuli associated with cocaine.
- Decrease in cocaine consumption, verified through urine analysis and hair tests.
- Improvement in inhibitory control, evidenced by neuropsychological tests after the intervention.

However, the variability in the stimulation protocols still represents a challenge for the reproducibility of the results. The need for controlled clinical trials with larger samples and more rigorous methodologies is evident to consolidate TMS as a definitive therapeutic alternative for TUC.

SAFETY AND ADVERSE EFFECTS

The studies analyzed confirmed that TMS is largely safe and well tolerated, with minimal and transient adverse effects. Among the most reported adverse events, the following stand out:

- Mild to moderate headache, seen in a fraction of patients, usually resolves without the need for intervention.
- Discomfort at the application site, reported in protocols of higher intensity, but without significant impact on treatment adherence.
- Transient fatigue and dizziness, in isolated cases, with no reports of serious adverse events.

Studies such as those by Madeo et al. (2020) and Lolli et al. (2021) indicated that participants demonstrated high adherence to treatment, with low dropout rates. Trials with sham control groups did not identify statistically significant differences between adverse events in the active and placebo groups, reinforcing the safety of TMS for this audience.

SUMMARY OF RESULTS AND CLINICAL IMPLICATIONS

The findings of this review suggest that TMS, especially at high frequency and applied to the left DLPFC, is a promising intervention for the management of cocaine use disorder, contributing to:

- Sustained reduction of craving and substance consumption.
- Improvement in inhibitory control and emotional self-regulation of users.
- Low incidence of adverse effects, making it a safe and viable option.

However, heterogeneity in stimulation protocols, sample characteristics, and evaluation methods still represents an obstacle to the standardization of this approach. Future studies should prioritize:

- Greater methodological control, with more representative and randomized samples.
- Integration of advanced technologies, such as neuronavigation, to improve the accuracy of stimulation.
- Longitudinal evaluation of the effects of EMT, ensuring the measurement of long-term impacts.

TMS demonstrates great potential as a complementary and non-pharmacological therapy for the treatment of TUC, but additional research is still needed to establish more robust clinical guidelines and expand its applicability in medical practice.

DISCUSSION

The findings of this review reinforce Transcranial Magnetic Stimulation (TMS) as a promising therapeutic approach for Cocaine Use Disorder (OCD). Clinical trials have shown that TMS, especially when applied at high frequency (≥10 Hz) on the left dorsolateral prefrontal cortex (DLPFC), can modulate neural circuits involved in addictive behavior, promoting a statistically significant reduction in craving and cocaine consumption (Bolloni et al., 2018; Amerio et al., 2023).

However, the review revealed significant methodological heterogeneity among the studies analyzed. Differences in stimulation parameters, such as frequency, intensity, and number of sessions, make direct comparisons difficult and limit the generalizability of findings. In addition, the reduced number of clinical trials with robust samples and longitudinal follow-up prevents definitive conclusions about the long-term efficacy and safety of TMS (Lolli et al., 2021).

Another important limitation is the absence of standardized protocols for measuring outcomes, such as craving and relapse rates. Most studies have used subjective scales to assess craving, but there is a lack of objective biomarkers that can consolidate TMS as a validated clinical treatment (Madeo et al., 2020). In addition, few studies have evaluated the duration of therapeutic effects, and it is essential that future research incorporate longer follow-ups to verify the sustainability of the benefits.

ADVANCES IN EMT PROTOCOLS

The analysis of the protocols used in the reviewed studies demonstrates important advances in the use of TMS for the TUC. The predominant stimulation of the left DLPFC is consistent with its role in inhibitory control and regulation of craving. Clinical trials indicate that high-frequency protocols (≥10 Hz) exert excitatory effects on cortico-striatal networks, while approaches such as Theta Burst Stimulation (TBS) have emerged as alternatives to optimize neural plasticity with shorter application time (Tarraneo et al, 2015).

In addition, the personalization of interventions is evident in the intensity levels adopted (80%-120% of the motor threshold), allowing adjustments according to the needs of the patients. The duration of the protocols ranged from 10 to 36 sessions over periods of

two weeks to three months, reflecting different experimental approaches but also highlighting the need for greater standardization (Steele & Maxwell, 2021).

Despite these variations, data suggest that TMS has a favorable safety profile, with minimal adverse events and high adherence by participants. However, comparative studies between different stimulation parameters are still needed to consolidate accurate clinical guidelines (Harmelech, Hanlon, & Tendler, 2023; Torres-Castaño et al., 2021).

COMPARISON WITH OTHER TREATMENTS

When comparing TMS with traditional approaches to TUC, such as Cognitive Behavioral Therapy (CBT) and pharmacological interventions, it is observed that TMS has significant advantages. Although CBT is widely used, its effectiveness depends on active patient engagement, which can be challenging for individuals with a history of multiple relapses. In contrast, TMS demonstrates benefits even in patients with poor adherence to conventional therapies, which expands its application possibilities (Tarraneo et al, 2015).

In addition, the lack of medications approved specifically for TUC reinforces the need for effective therapeutic alternatives, and TMS emerges as a viable option, with minimal adverse effects compared to traditionally used medications such as antidepressants and antipsychotics (Amerio et al., 2023).

Another promising prospect is the integration of TMS with traditional treatments such as CBT and motivational interventions. Preliminary studies suggest that the combination of these approaches can enhance the results, promoting synergistic effects and increasing the chances of therapeutic success. However, this strategy still needs to be explored in long-term randomized controlled trials to determine its efficacy and practical feasibility (Bolloni et al., 2018; Rasgado-Toledo et al., 2024).

IMPLICATIONS AND FUTURE DIRECTIONS

Despite the methodological limitations identified, advances in the application of TMS to the TUC are significant. The reviewed literature points to strong therapeutic potential, but there is a need for more rigorous clinical trials that can:

- Standardize stimulation protocols, including frequency, intensity, and duration of treatment (Moretti, Poh, & Rodger, 2020).
- Expand population samples, ensuring greater representativeness and external validity of findings (Madeo et al., 2020).
- Investigate neurophysiological biomarkers, allowing objective assessments of the effects of TMS (Torres-Castaño et al., 2021).

- Follow patients for longer periods, to understand the sustainability of benefits over time (Lolli et al., 2021).

TMS has been shown to be a robust and safe approach, with the ability to remodel neural circuits involved in cocaine addiction. However, future research should focus on optimizing stimulation protocols and integrating TMS with traditional therapies, aiming to improve its clinical effectiveness and applicability in the treatment of TUC (Amerio et al., 2023).

CONCLUSION

The present integrative review highlights Transcranial Magnetic Stimulation (TMS) as a promising therapeutic strategy for Cocaine Use Disorder (OCD). The studies analyzed demonstrated that TMS, especially when applied at high frequency to the left dorsolateral prefrontal cortex (DLPFC), can significantly reduce craving and consumption of the substance, in addition to improving inhibitory control and decreasing impulsivity. These effects are consistent with the modulation of cortico-striatal circuits, highlighting TMS as a potentially effective tool to reverse neural dysfunctions associated with addiction.

In addition to the clinical benefits, the safety and tolerability of TMS have been widely confirmed, with minimal and transient adverse effects, such as mild headache and localized discomfort at the stimulation site. These findings reinforce the viability of TMS as a noninvasive treatment, especially for patients with a history of multiple relapses or resistant to conventional approaches, such as cognitive behavioral therapy and pharmacological interventions. However, despite the promising results, the heterogeneity in the stimulation protocols, the limited number of studies with robust samples and longitudinal follow-up, as well as the lack of standardization in the criteria for evaluating the outcomes, represent challenges for the clinical implementation of TMS in the treatment of TUC.

Given these limitations, it is recommended that future research focus on standardizing TMS protocols, establishing optimal parameters for frequency, intensity, and number of sessions to maximize treatment efficacy. In addition, there is a need to expand randomized clinical trials, ensuring more representative samples and methodological rigor to strengthen the validity of the findings, as well as to investigate the integration of TMS with conventional therapies, such as CBT, to evaluate possible synergistic effects. The incorporation of neurophysiological biomarkers and neuroimaging may allow a more objective assessment of the effects of TMS on the brains of patients with OCD, and the

extension of the follow-up time of patients may determine the long-term sustainability of the therapeutic effects.

Thus, TMS stands out as an innovative and safe approach, with the potential to redefine the management strategies of Cocaine Use Disorder. However, future studies are essential to consolidate clinical guidelines, ensure the optimization of protocols, and expand their applicability in medical and psychiatric practice.

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