INPLASY

# Transcranial Magnetic Stimulation (TMS) for the treatment of amphetamine and amphetamine-type stimulants (ATS) addiction – A systematic review and meta-analysis

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**ADMINISTRATIVE INFORMATION**

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**Conflicts of interest -** None declared.

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**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 January 2024 and was last updated on 09 January 2024.

## INTRODUCTION

**Review question / Objective** The aim of this systematic review and meta-analysis is to evaluate the efficacy of TMS in the treatment of amphetamine and amphetamine-type abuse.

**Rationale** Amphetamine and amphetamine-type stimulants (ATS) are strong synthetic molecules that affect the transmission of different neurotransmitters, such as dopamine, serotonin, and norepinephrine. These substances can be therapeutically used to address attention deficit hyperactivity disorder (ADHD) in both children and adults, as well as for the management of narcolepsy. Additionally, they are occasionally used on a short-term basis to treat obesity [1-3]. While they can temporarily enhance alertness, attention, and physical performance, as well as induce a sense of euphoria, a prolonged use can lead to a number of side effects, including weight loss, impaired cognitive functioning, insomnia, and persistent psychotic symptoms, especially at high dosages [4, 5]. Disorders related to the use of amphetamine and ATS entail the non-medical, recreational, consumption of these substances (abuse). These conditions are characterized by a repeated pattern of substance use, eventually resulting in significant clinical impairment or distress. Despite numerous approaches attempted in recent years, to date there is no consensus on the treatment of choice for amphetamine and ATS addiction; few drugs and non-pharmacological approaches are currently used to manage these patients, although with inconstant results [6].

Among non-invasive brain stimulation techniques, transcranial magnetic stimulation (TMS) has shown potential therapeutic effects for the treatment of amphetamine and ATS addiction. However, the

optimal location and frequency of stimulation for this treatment have not been determined yet. Pathophysiologically, researchers suggest a growing link between addiction cravings and the "reward circuit," which is mainly associated with the dopamine pathway. In this context, studies have indicated that TMS of the dorsolateral prefrontal cortex might potentially reduce the urge to use these substances [7].

Given the variety of studies currently available, a systematic review and meta-analysis on the safety and impact of TMS for treating Amphetamine and Methamphetamine Use Disorders holds the potential to offer a comprehensive synthesis of the whole findings published in this "cutting-edge" topic. Moreover, compared to a single primary study, this approach is likely to yield more robust results, which would be reliably translated in clinical and rehabilitative settings. By systematically evaluating and combining data from multiple studies, this review can provide a broader and deeper understanding of the effectiveness of TMS in addressing amphetamine and methamphetamine use disorders.

**Condition being studied** This systematic review and meta-analysis examine the effects of TMS on individuals with amphetamine and ATS addiction. Subjects with these conditions display specific behavioral and psychological symptoms[8]. Namely, behavioral symptoms include compulsive seeking and use of the substances and risky behaviors, such as driving under influence or unprotected sex, and neglect of personal and professional responsibilities, whereas psychological symptoms are intense cravings, mood disturbances, aggression, paranoia, and, in some cases, psychotic features resembling schizophrenia [9]. Pharmacologically, the chronic use leads to tolerance, a need for increasingly higher doses to achieve the same effect, and severe withdrawal symptoms, including depression and fatigue when the substance is not used. Long-term use can result in significant brain changes, cardiovascular problems, dental issues (known as "meth mouth"), and an increased risk of infectious diseases due to impaired immune functioning and risky behaviors [10, 11]. Additionally, amphetamine and ATS addiction often coexists with other mental health disorders, thus complicating treatment and recovery rate.

## METHODS

**Search strategy** We intend to conduct a systematic search in the following databases: Cochrane CENTRAL, PubMed, and PsycINFO. We will also search in the clinical trials databases to perform a comprehensive search. Our search will utilize the following search string, that will be adapted, if necessary, for the specific database search formatting:

"(amphetamine OR methamphetamine OR MDMA OR ecstasy OR dextroamphetamine OR stimulant OR stimulants) AND (abstinence OR dependent OR dependence OR addict* OR withdrawal OR misuse OR abuse) AND (TMS OR "transcranial magnetic stimulation" OR rTMS OR "repetitive transcranial magnetic stimulation" OR "repetitive TMS" OR "high frequency rTMS" OR "low frequency rTMS" OR "theta burst stimulation" OR "TBS" OR "theta burst" OR cTBS OR "continuous theta burst stimulation" OR iTBS OR "intermittent theta burst stimulation" OR "accelerated rTMS" OR "accelerated HF-rTMS" OR "HF-rTMS")".

**Participant or population** We will include adults 18 to 65 years old with a diagnosis of amphetamine and ATS addiction according to the current international diagnostic criteria (DSM-5, DSM-5TR or ICD).

**Intervention** We will include studies that employ any paradigm of TMS for treating amphetamine-related addiction disorders. This encompasses repetitive TMS (rTMS), at both high-frequency (HF-rTMS, which usually excites the stimulation area) and low-frequency rTMS (LF-rTMS, which suppresses the stimulated area), as well as theta burst stimulation (TBS), including both continuous (cTBS, typically producing an inhibitory response) and intermittent TBS (iTBS, which is generally considered excitatory). We will also include studies with accelerated rTMS (a-rTMS).

**Comparator** Sham (fictitious), active comparator.

**Study designs to be included** Randomized clinical trials (RCTs) and cross-over trials, considering only the first phase of the trial (i.e., before the crossover), to prevent the carry-over effect.

**Eligibility criteria** All the following criteria must be satisfied for inclusion: 1 Participants or population: we will include adults from 18 to 65 years old with a diagnosis of amphetamine and ATS addiction according to DSM-5, DSM-5TR or ICD; 2. Intervention: studies focused on the use of TMS, either as a monotherapy or as an add-on administration. This encompasses both HF-rTMS and LF-rTMS, cTBS and iTBS. We will also include studies with a-rTMS;3. Comparator: studies where the comparator is sham or active comparator;4. Study design: We will include RCTs and cross-over trials, considering only the first phase of the trial

(i.e., before the crossover), to prevent the carry-over effect;5. Clinical outcomes: studies that report at least one of the following: assessment of craving and cue-induced craving, impulsivity, cognitive functions (i.e., attention, memory, cognitive control, executive functions, social and emotional cognition, sleep quality, depression and anxiety levels); 6. Language: english and italian.

**Information sources** We intend to conduct a systematic search in the following databases: Cochrane CENTRAL, PubMed, and PsycINFO. We will also search in the clinical trials databases to perform a comprehensive search.

**Main outcome(s)**
1. Changes in craving;
2. Changes in cue-induced craving;
3. Changes in impulsivity;
4. Cognitive functions changes (i.e., attention, memory, cognitive control, executive functions, social and emotional cognitions).

**Additional outcome(s)**
1. Anxiety level changes;
2. Depression level changes;
3. Sleep quality;
4. Social functioning changes;
5. Intervention's side effects.

**Data management** Data will be extracted in a relational database by four independent reviewers. If any discrepancy will occur during data extraction, the conflict will be independently solved by a fifth experienced author.

**Quality assessment / Risk of bias analysis** We will conduct a risk of bias assessment using the Risk of Bias 2 tool developed by Cochrane. Assessments will be performed exclusively on the main outcomes and will be carried out by two authors independently. Any discrepancies will be resolved by a third, experienced author. Moreover, in the context of our systematic review and meta-analysis, we pay special attention to the assessment of the quality of evidence related to primary outcomes. This process will be conducted following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. Also this assessment will be performed by two authors independently, with discrepancies resolved by a third, more experienced author.

**Strategy of data synthesis** We will use the R-Studio software, specifically the meta package, for data analysis. To measure the outcomes expressed as continuous data, we will calculate the standardized mean difference. For outcomes expressed as binary data, we will calculate the odds ratio and relative risk. Each effect size will be accompanied by a significance test to calculate the p value. We will also conduct heterogeneity tests for each outcome, including the calculation of Q, p, I^2, and Tau.

**Subgroup analysis** We plan to conduct subgroup analysis based on the type of stimulation (i.e., LF-rTMS, HF-rTMS, cTBS, iTBS, a-TMS) and the number of stimulation sessions (one session vs. multiple sessions). We also aim to conduct subgroup analysis based on the different type of substance use.

**Sensitivity analysis** We will conduct sensitivity analysis in the case of moderate or high heterogeneity detected within the analysis.

**Language restriction** English and italian.

**Country(ies) involved** Italy.

**Keywords** Amphetamine; amphetamine-type stimulants; addiction; stimulants; TMS, TBS; neuromodulation; brain stimulation.

**Dissemination plans** We plan to publish the data coming from the present work in peer reviewed journals and to show them in scientific conferences.

**Contributions of each author**

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