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REVIEW ARTICLE

Systematic review and meta-analysis: Combining transcranial magnetic stimulation or direct current stimulation with pharmacotherapy for treatment of substance use disorders

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Abstract

Background and Objectives: Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have evidence for their potential in the treatment of substance use disorders (SUD). Medication for addiction treatment (MAT) is underutilized and not always effective. We identified randomized controlled trials (RCTs) and case studies that evaluated the effectiveness of TMS or tDCS used concurrently with MAT in SUD treatment.

Methods: A systematic review of published literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted on 6/1/2023 by a medical librarian. Craving-related scales were extracted for an effect size calculation. The Physiotherapy Evidence Database (PEDro) scale assessed study quality.

Results: Eight studies (7 RCT, 1 case) including 253 individuals were published from 2015 to 2022, 5 of which had available data for meta-analysis. TMS or tDCS combined with MAT significantly reduced craving-related measures relative to sham stimulation (Hedges' $g = -0.42$, confidence interval: −0.73 to −0.11, $p < .01$). Opioid use disorder, methadone, and the dorsolateral prefrontal cortex were the most commonly studied SUD, MAT, and target region.

Discussion and Conclusions: Our results show a significant effect; however, is limited by a small number of studies with heterogeneous methodology across intervention methods and SUDs. Additional trials are needed to fully assess the clinical impact and mechanisms of combined brain stimulation and pharmacotherapy. We discuss a possible mechanism for synergism from these treatment combinations.

Scientific Significance: Adds the first systematic review of combination treatment with TMS or tDCS and MAT in SUD patients to the literature and estimates its overall effect size.

INTRODUCTION

Substance use disorders (SUD) are chronic conditions that are prevalent worldwide and characterized by periods of remission and relapse. Food and Drug Administration (FDA) approved medications exist for tobacco, alcohol, and opioid use disorders (OUD); however, overall utilization is low. Approximately one-sixth of patients with an alcohol use disorder (AUD) and one-quarter of patients with an OUD receive medication for addiction treatment (MAT).[1] Furthermore, those struggling with cannabis, cocaine, or methamphetamine have no FDA-approved interventions. With deaths by drug overdose per year passing 100,000 in 2021 for the first time,[2] additional treatment options are urgently needed.

Noninvasive brain stimulation (NIBS), including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), has shown positive results in reducing substance-related cravings in those with SUDs.[3–5] Cravings are the subjective experience of wanting or desiring a drug or alcohol. While the intoxication and withdrawal characteristics vary across substances, cravings are ubiquitous. Clinically, cravings are also a target for MAT. Prospective studies have supported craving's importance, with increased alcohol craving at residential program admission and discharge being predictive of future alcohol use.[6] This is similarly seen in drug-related cravings. A meta-analysis of over 50,000 individuals found that for every 1-point increase in scales of cue-related craving, there was an increased odds ratio of 2 for future substance use.[7]

TMS and tDCS differ in design, yet, they share the same goal: modulation of addiction-related neural circuitry. Increases in cravings following drug-related cues have been correlated with increased neural activity in the ventromedial PFC (vmPFC).[8] Using drug and alcohol-related cues to trigger cravings, thereby potentially activating pathological neural circuits, may provide a mechanism to both benefit NIBS treatment and be assessed longitudinally.

There is limited information regarding the utility of combining either TMS, such as repetitive TMS (rTMS), deep TMS (dTMS), or theta burst stimulation (TBS), or tDCS with MAT for SUD treatment. A review of the TMS depression literature suggests that concomitant medication may impact responses to treatment. Large trials evaluating the anti-depressant efficacy of TMS often require medication washout; however, a trial of 181 patients with major depressive disorder who were continued on pharmacology noted that the 6-week response rates were significantly lower in those taking benzodiazepines and significantly higher in those taking stimulants, relative to individuals not on those medication classes.[9] NIBS-related measures of neuroplasticity have also been shown to be disrupted or enhanced through psychoactive medication.[10,11]

We set out to systematically review the literature regarding the combination use of either TMS or tDCS with MAT to treat SUDs. Additionally, we outline a mechanism for the possible synergistic effect of treatment combination.

Transcranial magnetic and direct current stimulation

TMS is governed by electromagnetic induction. By passing an electrical current through a wire coil outside of the skull, an orthogonal magnetic field is created within the brain. Changes within this magnetic field, caused by the pulsing of current in the coil, induce an electrical current (i.e., stimulation) in the brain at the coil's focal point. Multiple TMS parameters, such as target location, stimulation frequency, intensity, interval length, and total number of individual treatment sessions, may be adjusted. Treatment leads to neuroplastic changes, with low-frequency stimulation (typically 1 Hz) considered to induce long-term depression (LTD), while high frequency (typically 5–10 Hz or greater) leads to long-term potentiation (LTP). Variations include dTMS, which utilizes differing coil geometries that allow for stimulation of deeper brain areas, and TBS, which is a patterned delivery that is more consistent with endogenous brain activity and results in treatments taking less total time. Continuous TBS (cTBS) decreases cortical excitability while intermittent TBS (iTBS) increases cortical excitability.[12] Larger neural networks may be modulated by targeting neural circuits, as evidenced by changes seen in functionally connected distant brain regions.

tDCS differs in that both an anode (current entry point) and cathode (current exit point) electrodes are placed on the scalp, through which a weak electrical current (typically 1–2 mA) is used to stimulate the desired brain regions. Brain tissue near the anode typically increases in cortical excitability (via depolarization of neurons), whereas tissue under the cathode typically will decrease in cortical excitability (via hyperpolarization of neurons).[13] Similarly to TMS, these drive neuroplastic changes in LTP and LTD (see Reviews[3,11,13,14]). While the specific mechanisms leading to long-term changes are not fully understood, gamma-aminobutyric acid (GABA), glutamate (GLU), and dopamine (DA), as discussed later, are clearly involved.

Current evidence for TMS/tDCS in SUD treatment

TMS and tDCS are being investigated in a wide range of SUDs. Much of the literature focuses on stimulation at the left dorsolateral prefrontal cortex (DLPFC), in-line with historical treatment location for depression. A recent review of SUD sham-controlled rTMS clinical trials in individuals with nicotine, alcohol, or illicit drug dependence found that excitatory stimulation of left DLPFC had a Hedges' *g* effect size of −0.62 (confidence interval [CI]: −0.89 to −0.35) for craving reduction. In contrast, excitatory stimulation of the right DLPFC did not have a significant effect on cravings.[4] In 2020, the FDA approved dTMS for treating tobacco use disorder, supported by a multi-site, worldwide, 18-week study by Zangen et al. In this study, patients received 15 dTMS treatment sessions over 3 weeks, followed by weekly treatments for 3 weeks; all treatments were preceded by a cue-induced craving procedure. 123 people received active treatment targeting bilateral prefrontal cortex (PFC) and insula, while 139 received sham treatment. At study-end, the primary

outcome of the 4-week continuous quit rate was significantly higher in active treatment than sham (28.0% vs. 11.7%, $p = .007$).[15] This was further supported by a review and meta-analyses in 2022, showing NIBS's significant effect on nicotine cessation with a Hedges' *g* effect size of 0.76 (CI: 0.37 to 1.10).[16] Currently, tobacco use disorder is the only SUD approved for stimulation treatment by the FDA, however, insurance carriers often do not cover the procedure. tDCS currently has no FDA approved indication.

Significant craving reductions after NIBS have also been seen in reviews on cocaine,[3] methamphetamine,[17] and alcohol.[18] A distinction seen in these substances from tobacco is less success regarding cessation. Primary findings have shown a decrease in drug-related urges or obsessional thoughts. As there is a strong association between cravings and later substance use, these are notable and important findings. Further research is needed to identify why cessation rates for tobacco have outpaced other substances, in addition to translating these findings into clinical outcomes such as rates of total use, time to return-to-use, and overdose. Additionally, as mental health diagnoses are highly comorbid with SUDs, the impact of co-occurring conditions and active versus in remission affective symptoms on treatment outcomes will be important for further investigation.

METHODS

Data sources and search strategies

A comprehensive search of several databases was performed on June 1, 2023. Results were limited to English Language. Date limits were set from 1980 forward. Databases searched (and their content coverage dates) were Ovid MEDLINE(R) (1946+ including epub ahead of print, in-process, and other nonindexed citations), Ovid Embase (1974+), Ovid APA PsycInfo (1967+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), and Scopus via Elsevier (1970+). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed.[19] Review was registered on Open Science Foundation (available at osf.io/4qezw). Results were exported to Covidence from Endnote, and duplicates were removed. Methodological quality of studies was based on the PEDro scale, completed by author NLB.[20]

Inclusion/exclusion criteria

The search strategies were designed and conducted by a medical librarian with input from the study investigators. Controlled vocabulary supplemented with keywords was used. Included studies investigated concurrent treatment with either TMS or tDCS with FDA approved MAT in a SUD population, with primary or secondary outcomes including changes in cravings, urges or obsessional thoughts, and overall substance use changes. If outcomes were changes in mood symptoms within a SUD treatment population, but outcomes related to substance use were not measured or documented, the study was not included. Clinical trials and case reports were included, whereas poster or lecture abstracts, dissertations, and book chapters were not. NLB completed the review and data extraction, with SA and TSO available for discussion.

Meta-analysis

A priori we chose a random effects model with restricted maximum likelihood measures (REML) due to expected heterogeneity from including both TMS and tDCS stimulation, inhibitory and excitatory frequencies, multiple scales, and multiple SUDs. Anticipating few studies meeting search criteria, we did not plan for subgroup analysis based on limited power to find differences. Cravings are a commonly assessed metric, however, the scale used to assess these vary. The visual analog scale (VAS), the Desire for Drug Questionnaire (DDQ), and the obsessive compulsive drug use scale (OCDUS) are commonly used. For studies that included more than one measure, effect sizes were averaged across scales so that each study contributed only one value. Missing data was excluded. Only randomized clinical trials (RCT) were included.

Calculations were performed in R v4.3.0[21] with packages dplyr and metafor, and figures created with functions *forest* and *funnel*.

RESULTS

Study selection

Figure 1 outlines the search process of included studies. Four hundred and four studies were identified, 401 were screened after duplication removal, and 143 were reviewed at the full text level. One hundred and thirty-five were excluded, primarily for issues with study intervention or design. Eight studies met complete search criteria (seven RCTs and one case report), comprising 253 patients. See Table 1 for details on each study. Based on the PEDro scale, studies scored 8 or 9 points (of a possible 11), indicating moderate to high quality (see Table 2 for grading breakdown). The most common reasons for deductions were the stimulation technician or the data analyst not being blinded.

Stimulation type: rTMS

Four trials evaluated adding rTMS (one low-frequency, two high-frequency, and one cTBS) to nicotine replacement therapy (NRT) patches for the treatment of tobacco use disorder[22] or to either buprenorphine-naloxone,[23] methadone,[24] or naltrexone[25] in the treatment of OUD. The earliest study was in 2015 by Trojak et al., who combined 10 sessions of 1 Hz rTMS over 2 weeks targeting the right DLPFC (MRI-guided) with 21 mg NRT patch in treating smoking

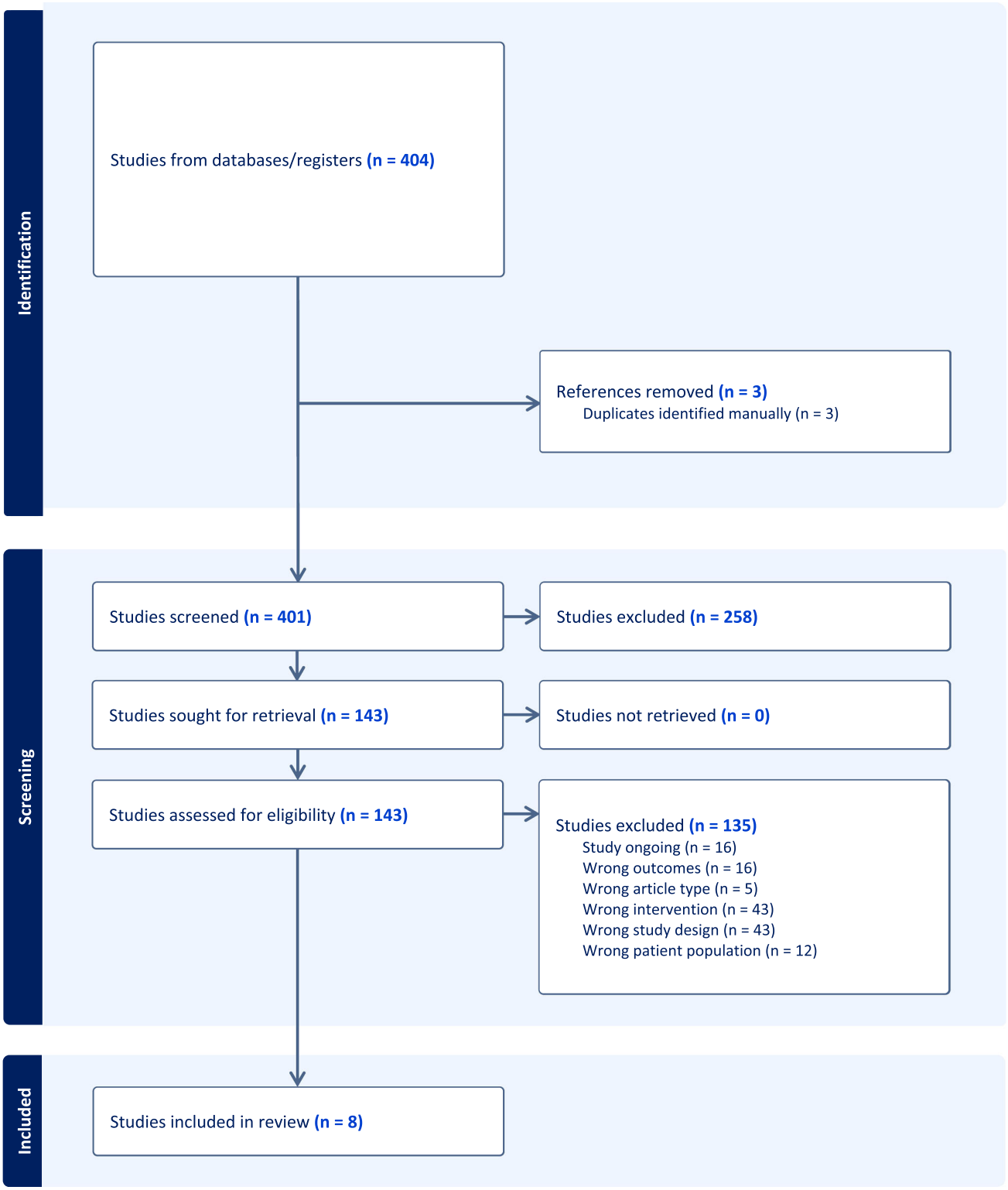

FIGURE 1 PRISMA flow diagram.

cessation. After completion of rTMS, NRT was tapered off over 4 weeks. At the end of Week 2, 16 out of 18 individuals in active treatment met cessation criteria, whereas only 9 of 18 individuals in sham stimulation met cessation criteria ($p = .027$). At study follow-up at 6 and 12 weeks, cessation rates were not significantly different between groups (~27%–40%). Cravings significantly decreased for both groups, however, did not separate based on intervention arm.[22]

In 2021, Tsai et al. enrolled 20 patients with OUD from a methadone treatment program (MTP) and evaluated the effect of 11 sessions (daily for 5 days, then twice weekly for 3 weeks) of 15 Hz

TABLE 1 Characteristics of included studies.

Study	Study design	Substance	Medication	Sample (received active stimulation)	Stimulation type	Stimulation target	Frequency (Hz) or current (mA)	Total sessions	Total pulses or time	Type of sham	Assessment time points	Craving-related sales
2015 Trojak et al.	Parallel	Tobacco	NRT	37 (18)	rTMS	R DLPFC	1 Hz	10	3600 pulses	Sham coil	Pre, post 10-day TMS + NRT, 6-week FU, 12-week FU	VAS
2018 Sharifi-Fardshad et al.	Crossover	Heroin	Methadone	40 (20)	tDCS	R DLPFC/L DLPFC	2 mA	1 and 1	20 min each	30 s of stimulation	Pre, post	DDQ
2019 Taremian et al.	Parallel	Opium	Methadone	60 (20)	tDCS	R DLPFC	2 mA	10	200 min	30 s of stimulation	Pre, post	DDQ, OCDUS
2020 Bimorgh et al.	Parallel	Opioid	Methadone	27 (14)	tDCS	R DLPFC	2 mA	7	140 min	30 s of stimulation	Pre, post	none
2020 Mahoney et al.	Case study	Opioid, cocaine	Buprenorphine	1 (1)	rTMS	L DLPFC	10 Hz	7	14,000 pulses	-	Pre and post each TMS session	VAS
2021 Tsai et al.	Parallel	Opioid	Methadone	20 (11)	rTMS	L DLPFC	15 Hz	11	26,400 pulses	Sham coil	Pre and post each TMS session	OCDUS
2022 Ankit et al.	Parallel	Opioid	Naltrexone	40 (20)	cTBS	R OFC	50 Hz	14	12,600 pulses	Tilted coil	Pre, post 7-day TMS, post 14-day TMS	DDQ, OCDUS
2022 Kumar et al.	Parallel	Opioid	Buprenorphine	28 (14)	tDCS	L DLPFC	2 mA	10	200 min	30 s of stimulation	Pre, post	VAS

Abbreviations: cTBS, continuous theta burst stimulation; DDQ, desire for drugs questionnaire; DLPFC, dorsolateral prefrontal cortex; dTMS, deep transcranial magnetic stimulation; FU, follow-up; L, left; NRT, nicotine replacement therapy; OCDUS, obsessive compulsive drug use scale; OFC, orbitofrontal cortex; R, right; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; pre, baseline measure; post, after completing all stimulation sessions; VAS, visual analog scale.

TABLE 2 Study quality scoring based on the Physiotherapy Electronic Database (PEDro) scale.

Study	PEDro question numbers											Total score
	1	2	3	4	5	6	7	8	9	10	11	
2015 Trojak et al.	1	1	1	1	1	0	0	1	1	1	1	9
2018 Sharifi-Fardshad et al.	1	1	1	1	1	0	0	1	1	1	1	9
2019 Taremian et al.	1	1	1	1	1	0	0	1	1	1	1	9
2020 Bimorgh et al.	1	1	1	1	1	0	0	1	1	1	1	9
2020 Mahoney et al.	-	-	-	-	-	-	-	-	-	-	-	-
2021 Tsai et al.	1	1	1	1	1	0	0	1	1	1	0	8
2022 Ankit et al.	1	1	1	1	1	0	0	1	1	1	1	9
2022 Kumar et al.	1	1	1	1	1	0	0	1	1	1	1	9

Note: Of note, Mahoney et al. is a case report and cannot be graded as a randomized clinical trial.

rTMS (11 active stimulation, 9 sham) targeting the left DLPFC with concurrent methadone (dose range 40–65 mg daily). At 12-week study follow-up, no significant difference was seen in reported craving or heroin use, nor in urine morphine test results. They note that active treatment did result in significant improvements in mood (Hamilton Depression Rating Scale) and concentration (Barratt Impulsiveness Scale).[24] Ankit et al. followed this study 1 year later, enrolling 40 patients (20 active stimulation, 20 sham) with OUD who initially underwent opioid detoxification with clonidine and then were started on naltrexone 50 mg daily. After 8–10 days of opioid abstinence, treatment incorporated 14 once-daily sessions over 2 weeks of 50 Hz cTBS targeting the right orbitofrontal cortex (OFC) at the right frontopolar two (Fp2) electrode site. Cravings decreased for both groups, however, did not separate from one another. This trial incorporated serum measures of brain-derived neurotrophic factor (BDNF) due to its significance in mesolimbic and mesocortical DA neurons; ultimately there was no significant difference between active and sham treatment for BDNF at study endpoint (~3–4 weeks in length, varied due to length of initial detoxification period).[25]

In 2020, a case report was published where a patient with both OUD and cocaine use disorder on buprenorphine-naloxone was treated with seven sessions of 10 Hz rTMS over 3 weeks targeting the left DLPFC. They measured cue-induced craving before and after each rTMS session and found an average-session craving reduction of 60%–80% for heroin and cocaine. Notably, cue-elicited cravings before rTMS were successfully extinguished following the treatment.[23]

Stimulation type: tDCS

Three trials evaluated adding tDCS to methadone, while a fourth incorporated it with buprenorphine-naloxone for the treatment of OUD. In 2018, Sharifi-Fardshad et al. recruited 40 individuals with OUD from a MTP for a crossover study. Participants received one session of 2 mA anode stimulation at the right DLPFC with the cathode at the left DLPFC, followed 3 days later by one session of 2 mA anode stimulation at the left DLPFC and cathode at the right DLPFC. Anode stimulation at the right DLPFC resulted in significantly reduced self-report of all drug desire, negative reinforcement and deficit of control (subscales of Desire for Drug Questionnaire [DDQ]).[26] In another MTP sample from 2019, Taremian et al. recruited 60 individuals with OUD on methadone (mean dose 90 mg) for three groups: (1) tDCS + methadone, (2) sham stimulation + methadone, and (3) methadone monotherapy. Participants received 10 stimulation sessions of 2 mA over 10 days with anode at the right DLPFC and cathode at the left DLPFC. The active stimulation group resulted in significantly lower opium craving (effect size of 0.48), DDQ total score, depression (Beck's Depression Inventory) and anxiety (Beck's Anxiety Inventory) as measured on day of final treatment.[27] In 2020, Bimorgh et al. also recruited 27 individuals with OUD from an MTP to trial methadone augmentation with seven sessions of 2 mA tDCS over 2 weeks with anode at the right DLPFC and cathode at the left DLPFC. Fourteen individuals received active stimulation and 13 received sham, with postintervention data collected on the final stimulation day. There was no difference in primary outcome of relapse rate (1 of 14 in active group, 3 of 13 in sham, $p = .33$). They also utilized the Depression, Anxiety, and Stress Scale-21 (DASS-21) and noted that the intervention group had significantly lower ratings on all subscales.[28]

Kumar et al. evaluated changes in withdrawal, craving, and GLU/GABA levels following tDCS in a group of 28 males (14 active stimulation, 14 sham) with OUD who were initially in opioid withdrawal and started 6 mg of buprenorphine-naloxone at trial onset and were maintained at that dose.[29] Stimulation consisted of 10 sessions of 2 mA over 5 days with anode at the left DLPFC. With assessments done on Day 7, there were no differences seen in symptoms of withdrawal, craving or levels of GLU or GABA (measured via magnetic resonance spectroscopy (MRS) at the stimulation site). The authors posit that the lack of differences was due to participant's recent initiation of buprenorphine-naloxone and confounds associated with opioid withdrawal in general.[29]

Meta-analysis

Data was incorporated from five trials, none of which had missing data. The Hedges' *g* effect size for either TMS or tDCS in addition to MAT treatment in a SUD patient group was −0.42 (CI: −0.73 to −0.11, $p = .008$) as compared with sham stimulation. τ^2 was 0 (SE = 0.089) and I^2 was 0; the observed variance in studies was less than predicted based on within study variability, which explains the 0 values on measures of heterogeneity. The forest plot can be seen in Figure 2 and the funnel plot in Figure 3. No asymmetry was apparent in the funnel plot and none of the studies fell outside the confidence region. Due to the small number of studies, we were unable to conduct meaningful sensitivity analyses. Studies not included were due to being a case study,[23] not having a sham control group,[26] or not measuring cravings.[28]

DISCUSSION

There are two main takeaways from our review. First, the literature on combining TMS or tDCS with MAT in individuals with SUDs is in its early stages. The literature that does exists is primarily in OUD, particularly in those on methadone maintenance treatment. This may be unsurprising, given that patients attend MTPs regularly for medication dosing, which may minimize study discontinuation when attempting to augment treatment in a clinical trial. The lack of existing research may also be secondary to NIBS having limited FDA approved indications thus far, particularly in addiction treatment. Our second main takeaway is the significant effect of combination treatment on the reduction in craving-related scales. While this finding is preliminary based on the limited data available, it is encouraging. Continued trials utilizing NIBS as monotherapy with primary outcomes of overall substance use and reported cravings will be important steps in building evidence toward eventual treatment combination. However, as outlined below, we feel there is currently a compelling case for their integration.

TMS/tDCS and MAT's impact on neurotransmitters and cortical excitability: A case for synergism

Synergistic or complementary treatments are widely used in medicine. Examples include the use of multiple antihypertensives with differing mechanisms to treat resistant blood pressures, pairing antiretrovirals with reverse transcriptase or protease inhibitors in the treatment of human immunodeficiency virus, and managing blood glucose by implementing both basal and bolus insulins along with drugs like metformin—the stacking of treatments in the management of chronic diseases is ubiquitous. This is also seen in psychiatry, exemplified by combining antidepressants of different classes or through augmentation with atypical antipsychotics in treatment-resistant depression.[30]

Specific to addiction treatment, psychotherapy has been a foundational approach incorporated with pharmacology since the advent of MAT. Pharmacology has also been dually prescribed, particularly in tobacco cessation, with options of varenicline, bupropion, and NRT; however, with inconsistent benefits relative to monotherapy and a higher risk for side effects. Specific to alcohol, the combination of acamprosate and naltrexone has been compared with each individually and to placebo.[31] Acamprosate's mechanism is not fully known; however, it is believed to modulate *N*-methyl-D-aspartate (NMDA) receptors and $GABA_A$ transmission, thereby suppressing GLU overall. Naltrexone is a mu-opioid antagonist also FDA approved for the treatment of OUD. The combination of these two are, therefore, mechanistically distinct. Kiefer et al. evaluated time to alcohol relapse over 12 weeks in 160 patients with "alcoholism" and noted significantly lower rates in those on acamprosate with naltrexone relative to acamprosate or placebo monotherapy; however, they did not separate from those solely on

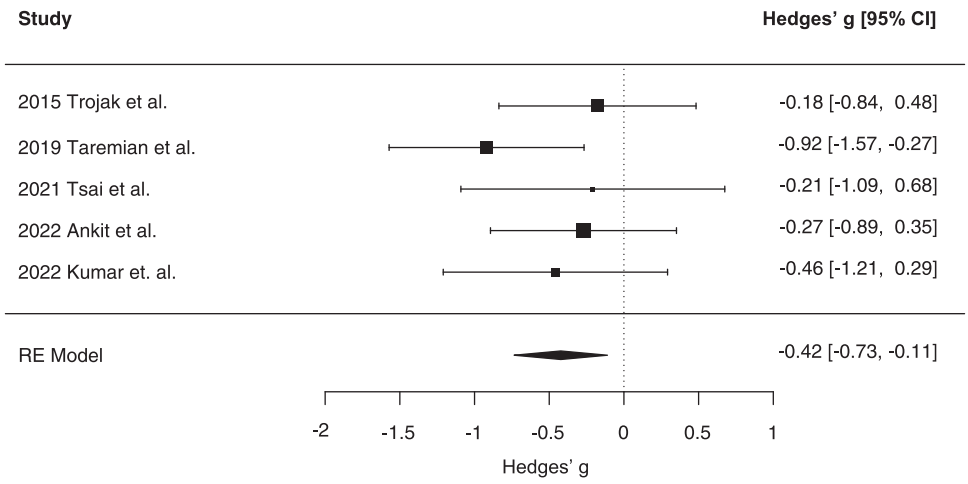

FIGURE 2 Forest plot. Meta-analysis of randomized clinical trials incorporating either transcranial magnetic stimulation or transcranial direct current stimulation with medication for addiction treatment in individuals with substance use disorders. Hedges' *g* effect size displayed, along with confidence intervals for each study and the aggregated analysis.

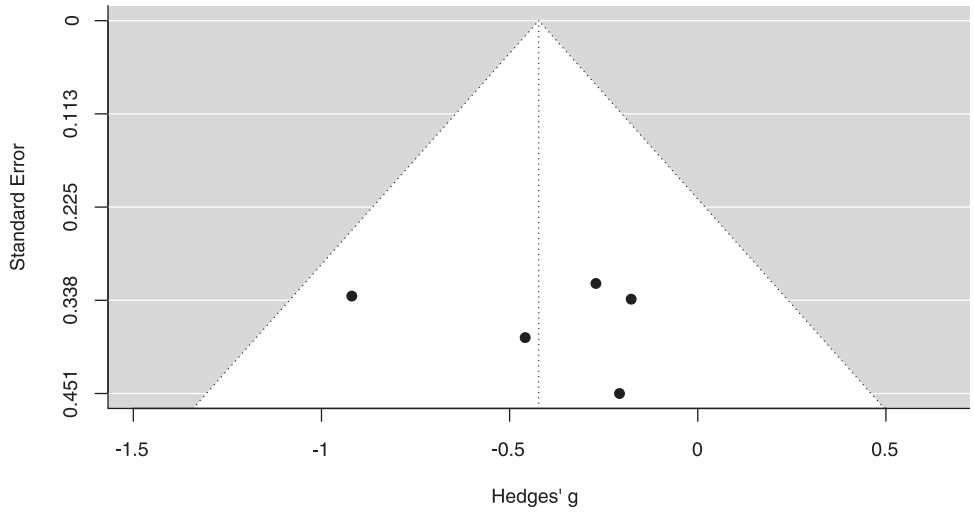

FIGURE 3 Funnel plot. Hedges' *g* effect size versus the standard error measured in randomized clinical trials incorporating either transcranial magnetic stimulation or transcranial direct current stimulation with medication for addiction treatment in individuals with substance use disorders.

naltrexone.[31] In OUD treatment, combining FDA approved pharmacology is contraindicated due to methadone, an opioid agonist, buprenorphine, a partial opioid agonist, and naltrexone having opposing mechanisms on the same receptor class.

Combining NIBS with MAT is appealing due to the distinct mechanisms of action. While pharmacology primarily acts locally on cell receptors, NIBS allows for dynamic changes in neurotransmitters by external means. Particularly relevant to the field of addiction psychiatry are GABA and GLU. While DA modulation may be considered a final endpoint in most substances of addiction,[32] this is primarily mediated through glutamatergic plasticity.[33] Repeated exposure to addictive substances and drug-related cues leads to GLU dysregulation and subsequent neural changes, particularly in the nucleus accumbens, which is pivotal for developing engrained behaviors that may place individuals at risk for continued substance use.[33] Compared with healthy controls, individuals with OUD have significantly lower levels of GABA and higher levels of GLU in the PFC.[34] GABA and GLU are essential mechanisms of network-based neural transmission, making these neurotransmitters logical targets in the treatment of SUDs. GABA and GLU are also mediators of treatment in depressive disorders, with the primary mechanisms of action for esketamine being NMDA antagonism and brexanolone being a positive allosteric modulator of $GABA_A$. The modulation of GABA and GLU may be highly relevant for dual-diagnosis patients.

Previous reviews have outlined NIBS impact on cortical DA, GABA, and GLU.[10,13,35] While individual differences occur, some trends can be outlined. High-frequency stimulation of the PFC has corresponded with increases in striatal DA.[13] Li et al. utilized this mechanism to propose that the increase in DA following high-frequency rTMS leads to the reduction in cue-provoked cravings seen in their sham-controlled trial targeting the left DLPFC in nontreatment seeking individuals smoking at least 10 cigarettes daily.[36] However, DA changes are likely secondary to primary action on the GLU and GABA system. MRS has shown an increase in GLU following high-frequency rTMS to the left DLPFC.[13] This is in contrast to TBS, where iTBS decreases GABA/GLU ratio versus cTBS increasing the GABA/GLU ratio; notably, minimal effect is seen on GLU, suggesting that this change is primarily driven by GABA.[37]

Cortical excitability reflects neuron responsivity to a stimulus and is a function of the GABA and GLU system. TMS provides a way to evaluate changes in cortical excitability through measures such as cortical inhibition (CI). A conditioning stimulus (TMS pulse) is used to activate inhibitory neurotransmitters (such as GABA), which is then followed by a test pulse. Measuring the difference in motor evoked potentials (MEP) provides data on if the cortex is hypo- or hyperexcitable. Therefore, changes in cortical excitability are mechanistically appealing in addiction research due to the established literature on changes in the glutamatergic system.

Alcohol is a prime example of how a substance can dramatically impact the balance of GLU and GABA. Acute alcohol intoxication potentiates the effect of GABA on $GABA_A$ receptors, creating an imbalance with GLU. Over time, chronic use downregulates $GABA_A$ receptors and upregulates NMDA receptors, leading to a hyperglutamatergic state. Abrupt alcohol discontinuation removes its compensatory effect, leading clinically to withdrawal. Acamprosate is beneficial long-term in reducing the return to drinking, with additional mechanistic evidence that it may also help in the immediate withdrawal period. As acamprosate modulates NMDA receptors and $GABA_A$ transmission, this contributes to a dampening effect on GLU.[38] In patients having recently discontinued alcohol use, acamprosate relative to placebo was associated with a significant reduction of GLU in the frontal lobe as measured by MRS with a Cohen's d effect size of 0.95.[39]

However, cortical excitability changes may be long-standing after discontinuation of alcohol use. Evaluation of individuals in recovery from alcohol with a range of 1 week to 2 years showed a significant

reduction in CI relative to healthy controls. This may indicate a persistent state of cortical hyperexcitability and reduced GABA activity.[40] Acamprosate's impact on cortical excitability has also been evaluated in healthy individuals. Compared with placebo, MEP did not change between groups; however, the motor threshold in individuals receiving acamprosate significantly increased. This suggests that acamprosate decreased overall excitability, and as MEP did not change, this may be driven by subcortical mechanisms.[41]

This line of evidence builds the potential for NIBS and acamprosate to have a synergistic effect in the treatment of AUD. cTBS reduces cortical excitability by modulating and strengthening GABA synapses,[12,37] while acamprosate has an overall dampening effect on GLU[38,39] with clinical benefits on decreasing return to drinking. A multi-modal treatment approach such as this may be more impactful in helping patients change their overall recovery trajectory.

These changes occur within larger brain networks. Recent reviews[3,5,35] suggest that NIBS is well-suited for their modulation. Reviews by Hanlon et al.,[3,35] Dunlop et al.[5] and their cited literature point towards an overall change in baseline functional connectivity and cue-related reactivity, particularly in the PFC and limbic pathways. Changes in PFC circuits in individuals with a history of substance dependence have been correlated with decreased inhibitory control, and specific to the vmPFC, heightened cue-related hyperactivity and cravings.[8] Modulating these circuits to normalize their responsiveness,[42] potentially by targeting vmPFC, has been proposed as a therapeutic option.[3,43]

MAT also shows the potential to enhance network connectivity. In a placebo-controlled study of 21 males with active alcohol use, naltrexone significantly increased functional connectivity between the vmPFC, as previously noted to be related to cravings, and the anterior cingulate cortex (ACC), which is involved with inhibitory control and emotional regulation.[44] A similar strategy as previously laid out for acamprosate could be reasoned for naltrexone—medication and NIBS being prescribed with synergism in mind. Other rationales may include varenicline in tobacco cessation, which has been shown to increase DA,[45] combined with NIBS, as described previously, has strong evidence for efficacy in tobacco cessation and also is associated with increases in DA locally.[13] It is relevant to note that changes in excitability following medication administration may be different in healthy controls compared with patients with SUD. A recent review of medications' impact on tDCS noted that nicotine spray dosing had differential impact on excitability at the cathode and anode electrodes and that varenicline was associated with prolonged excitability at the cathode[11]; both studies were in nonsmoking individuals. Further research and clinical trials are needed to fully understand concomitant pharmacology and NIBS in individuals with SUDs.

LIMITATIONS

The current literature on this topic is limited and primarily consists of small trials in OUD, half of which occurred within an MTP. The generalizability of those studies is limited for two main reasons. Methadone is a highly regulated medication, with countries having unique regulations, and in the USA regulations may vary from state to state. As these MTPs were only in Iran and Taiwan, it is unclear how the results may generalize to other countries. It is also unclear how these findings generalize to other SUDs and will require investigation within each substance. Overall, these trials were also diagnostically exclusive. Extrapolating these results to patients with comorbid addictions or active mental health symptoms of depression or psychosis is also unclear. The studies included did not explore the incorporation of psychotherapy, which may be particularly relevant for SUDs without approved medications. The total number of treatment sessions varied, ranging from 1 to 14. It is likely that repeated treatments are required for enduring changes, however, it is unclear when to conclude treatment versus tapering off or continued maintenance treatments. Sham conditions were typically utilized, however differed in the tDCS trials where 30 s of stimulation was used and then tapered off versus TMS where either a sham coil was incorporated, or the treatment coil was tilted away from the patient. It is possible that lower quality sham arms may have suppressed a possible placebo response, thereby inflating the reported effect of active treatment. The DLPFC was the primary stimulation target, with 3 studies targeting the right side,[22,27,28] 3 studies targeting the left,[23,24,29] and 1 study with a cross-over design that stimulated either side with 72 h in-between.[26] Ankit et al. stimulated the right OFC as the lone alternative location.[25] It is unclear if these are the ideal treatment sites, or if they translate effectively to other SUDs.

The quality of the meta-analysis is a direct function of the studies included. Measures of craving varied amongst studies; grouping scales that were craving-related as the outcome is an additional limitation, and would be enhanced from consistent use of one validated scale. A standard way to illicit cravings may also help decrease variation across trials. Previous research has suggested that cue-provocation may be beneficial in substance use-related outcomes,[3,15,46] however the relative importance of this is unknown across SUDs, nor the significance for individuals with multiple SUDs. While our effect size was significant, the confidence interval was large, therefore the impact of this effect is not clear. Additionally, we grouped studies regardless of stimulation: TMS, tDCS, excitatory frequencies, and inhibitory frequencies were combined due to limited number of studies available. Our goal was to determine if there was an effect when incorporating stimulation with MAT, and future research will be needed to determine specific parameters. In light of these limitations, we note that the calculated effect size is exploratory and requires validation in larger trials. While we focused on rTMS and tDCS, less common but still relevant NIBS for future consideration include galvanic vestibular stimulation, random noise stimulation, transcranial alternating current stimulation, transcranial ultrasound stimulation, and vagus nerve stimulation.[47] Future trials would also benefit from blinded stimulation technicians and data analysts, which were often missing in these studies. These steps may help limit the introduction of bias. See Table 3 for the PRSIMA recommended checklist.

TABLE 3 PRISMA 2020 checklist.

Section and topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Cover page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Completed
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4th para
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3rd para
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2nd para
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	1st para
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	2nd para
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2nd para
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2nd para
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2nd para
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2nd para
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	1st para
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	3rd para
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]).	3rd para
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	3rd para
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4th para

TABLE 3 (Continued)

Section and topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	3rd and 4th para
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	3rd para
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	3rd para
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	3rd para
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	3rd para
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	[Figure 1]
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Inclusion/exclusion criteria
Study characteristics	17	Cite each included study and present its characteristics.	Table 1; Stimulation type para(s)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 2; para 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	[Figure 2]
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Stimulation type: rTMS and tDCS sections
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Stimulation type: rTMS and tDCS sections
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Para 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Para 7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	[Figure 2 and 3]
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	[Figure 2 and 3]
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Para 12
	23b	Discuss any limitations of the evidence included in the review.	Para 11
	23c	Discuss any limitations of the review processes used.	Para 12

(Continues)

TABLE 3 (Continued)

Section and topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Main discussion; para 12; conclusions
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods, para 1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods para 1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review.	Acknowledgments
Competing interests	26	Declare any competing interests of review authors.	Declaration of interest
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Data statement

Note: For more information, visit: http://www.prisma-statement.org/.
Source: Page et al.[19]

CONCLUSION

Our meta-analysis found a significant reduction in craving-related measures. The concomitant use of TMS or tDCS with MAT for the treatment of SUD is near its beginning, emphasized by only 8 studies meeting our systematic review criteria. TMS and tDCS have building evidence for their individual effectiveness in craving reduction in multiple addictions. These treatments modulate brain networks and directly impact GABA and GLU, which are key mediators of neural transmission. Alcohol is a quintessential example of how chronic substance use dysregulates the glutamatergic system. We outline how a potential synergistic effect of TMS or tDCS with MAT may have a more dramatic treatment effect, specifically on this system. We hypothesize that inhibitory stimulation, such as cTBS, at the mPFC concurrent with acamprosate treatment would be a more effective than monotherapy AUD treatment. This is grounded in the literature, with each treatment having a suppressive effect on GLU, which is elevated with loss of alcohol, and that their mechanism of actions on GLU differ from one another. Ultimately, we feel this thinking is translatable to other SUDs and medications, however, requires extensive additions to the limited literature that we reviewed. Currently, the majority of studies have been in OUD, specifically combining tDCS with methadone, however, there is lacking representation from other addictions.

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The authors alone are responsible for the content and writing of this paper.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data used was extracted from the original study articles or online supplemental information. Analytic code and templates used to assist with the review process are available upon reasonable request.

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REFERENCES

1. Mauro PM, Gutkind S, Annunziato EM, Samples H. Use of medication for opioid use disorder among US adolescents and

adults with need for opioid treatment, 2019. *JAMA Netw Open*. 2022;5(3):e223821. doi:10.1001/jamanetworkopen.2022.3821
2. Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. 2023. Accessed June 15, 2023. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm
3. Hanlon CA, Dowdle LT, Austelle CW, et al. What goes up, can come down: novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. *Brain Res*. 2015;1628(Pt A):199-209. doi:10.1016/j.brainres.2015.02.053
4. Zhang JJQ, Fong KNK, Ouyang R, Siu AMH, Kranz GS. Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis. *Addiction*. 2019;114(12):2137-2149. doi:10.1111/add.14753
5. Dunlop K, Hanlon CA, Downar J. Noninvasive brain stimulation treatments for addiction and major depression. *Ann NY Acad Sci*. 2017;1394(1):31-54. doi:10.1111/nyas.12985
6. Schneekloth TD, Biernacka JM, Hall-Flavin DK, et al. Alcohol craving as a predictor of relapse. *Am J Addict*. 2012;21(suppl 1):S20-S26. doi:10.1111/j.1521-0391.2012.00297.x
7. Vafaie N, Kober H. Association of drug cues and craving with drug use and relapse: a systematic review and meta-analysis. *JAMA Psychiatry*. 2022;79(7):641-650. doi:10.1001/jamapsychiatry.2022.1240
8. Volkow ND, Michaelides M, Baler R. The neuroscience of drug reward and addiction. *Physiol Rev*. 2019;99(4):2115-2140. doi:10.1152/physrev.00014.2018
9. Hunter AM, Minzenberg MJ, Cook IA, et al. Concomitant medication use and clinical outcome of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder. *Brain Behav*. 2019;9(5):e01275. doi:10.1002/brb3.1275
10. Ziemann U, Reis J, Schwenkreis P, et al. TMS and drugs revisited 2014. *Clin Neurophysiol*. 2015;126(10):1847-1868. doi:10.1016/j.clinph.2014.08.028
11. McLaren ME, Nissim NR, Woods AJ. The effects of medication use in transcranial direct current stimulation: a brief review. *Brain Stimul*. 2018;11(1):52-58. doi:10.1016/j.brs.2017.10.006
12. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005;45(2):201-206. doi:10.1016/j.neuron.2004.12.033
13. Moretti J, Poh EZ, Rodger J. rTMS-induced changes in glutamatergic and dopaminergic systems: relevance to cocaine and methamphetamine use disorders. *Front Neurosci*. 2020;14:137. doi:10.3389/fnins.2020.00137
14. Mahoney, III JJ, Hanlon CA, Marshalek PJ, Rezai AR, Krinke L. Transcranial magnetic stimulation, deep brain stimulation, and other forms of neuromodulation for substance use disorders: review of modalities and implications for treatment. *J Neurol Sci*. 2020;418:117149. doi:10.1016/j.jns.2020.117149
15. Zangen A, Moshe H, Martinez D, et al. Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial. *World Psychiatry*. 2021;20(3):397-404. doi:10.1002/wps.20905
16. Song S, Zilverstand A, Gui W, Pan X, Zhou X. Reducing craving and consumption in individuals with drug addiction, obesity or overeating through neuromodulation intervention: a systematic review and meta-analysis of its follow-up effects. *Addiction*. 2022;117(5):1242-1255. doi:10.1111/add.15686
17. Chang CH, Liou MF, Liu CY, Lu WH, Chen SJ. Efficacy of repetitive transcranial magnetic stimulation in patients with methamphetamine use disorder: a systematic review and meta-analysis of double-blind randomized controlled trials. *Front Psychiatry*. 2022;13:904252. doi:10.3389/fpsyt.2022.904252
18. Antonelli M, Fattore L, Sestito L, Di Giuda D, Diana M, Addolorato G. Transcranial magnetic stimulation: a review about its efficacy in the treatment of alcohol, tobacco and cocaine addiction. *Addict Behav*. 2021;114:106760. doi:10.1016/j.addbeh.2020.106760
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
20. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother*. 2009;55(2):129-133. doi:10.1016/s0004-9514(09)70043-1
21. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2022. Accessed June 20, 2023. https://www.R-project.org/
22. Trojak B, Meille V, Achab S, et al. Transcranial magnetic stimulation combined with nicotine replacement therapy for smoking cessation: a randomized controlled trial. *Brain Stimul*. 2015;8(6):1168-1174. doi:10.1016/j.brs.2015.06.004
23. Mahoney JJ, Marshalek PJ, Rezai AR, Lander LR, Berry JH, Haut MW. A case report illustrating the effects of repetitive transcranial magnetic stimulation on cue-induced craving in an individual with opioid and cocaine use disorder. *Exp Clin Psychopharmacol*. 2020;28(1):1-5. doi:10.1037/pha0000289
24. Tsai TY, Wang TY, Liu YC, et al. Add-on repetitive transcranial magnetic stimulation in patients with opioid use disorder undergoing methadone maintenance therapy. *Am J Drug Alcohol Abuse*. 2021;47(3):330-343. doi:10.1080/00952990.2020.1849247
25. Ankit A, Das B, Dey P, Kshitiz KK, Khess CRJ. Efficacy of continuous theta burst stimulation—repetitive transcranial magnetic stimulation on the orbito frontal cortex as an adjunct to naltrexone in patients of opioid use disorder and its correlation with serum BDNF levels: a sham-controlled study. *J Addict Dis*. 2022;40(3):373-381. doi:10.1080/10550887.2021.2007716
26. Sharifi-Fardshad M, Mehraban-Eshtehardi M, Shams-Esfandabad H, Shariatirad S, Molavi N, Hassani-Abharian P. Modulation of drug craving in crystalline-heroin users by transcranial direct current stimulation of dorsolateral prefrontal cortex. *Addict Health*. 2018;10(3):173-179. doi:10.22122/ahj.v10i3.613
27. Taremian F, Nazari S, Moradveisi L, Moloodi R. Transcranial direct current stimulation on opium craving, depression, and anxiety: a preliminary study. *J ECT*. 2019;35(3):201-206. doi:10.1097/YCT.0000000000000568
28. Sadeghi Bimorgh M, Omidi A, Ghoreishi FS, Rezaei Ardani A, Ghaderi A, Banafshe HR. The effect of transcranial direct current stimulation on relapse, anxiety, and depression in patients with opioid dependence under methadone maintenance treatment: a pilot study. *Front Pharmacol*. 2020;11:401. doi:10.3389/fphar.2020.00401
29. Kumar AS, Khanra S, Goyal N, Dharani R, Roy C. Adjunctive high-definition transcranial direct current stimulation in brain glutamate-glutamine and γ-aminobutyric acid, withdrawal and craving during early abstinence among patients with opioid use disorder on buprenorphine-naloxone: a proton magnetic resonance spectroscopy-based pilot study. *J ECT*. 2022;38(2):124-132. doi:10.1097/YCT.0000000000000820
30. Tundo A, Filippis R, Proietti L. Pharmacologic approaches to treatment resistant depression: evidences and personal experience. *World J Psychiatry*. 2015;5(3):330-341. doi:10.5498/wjp.v5.i3.330
31. Kiefer F, Jahn H, Tarnaske T, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2003;60(1):92-99. doi:10.1001/archpsyc.60.1.92
32. Nestler EJ. Is there a common molecular pathway for addiction? *Nat Neurosci*. 2005;8(11):1445-1449. doi:10.1038/nn1578
33. Kalivas PW, Lalumiere RT, Knackstedt L, Shen H. Glutamate transmission in addiction. *Neuropharmacology*. 2009;56(suppl 1):169-173. doi:10.1016/j.neuropharm.2008.07.011

34. Li JN, Liu XL, Li L. Prefrontal GABA and glutamate levels correlate with impulsivity and cognitive function of prescription opioid addicts: A ^{1}H-magnetic resonance spectroscopy study. *Psychiatry Clin Neurosci*. 2020;74(1):77-83. doi:10.1111/pcn.12940
35. Hanlon CA, Dowdle LT, Henderson JS. Modulating neural circuits with transcranial magnetic stimulation: implications for addiction treatment development. *Pharmacol Rev*. 2018;70(3):661-683. doi:10.1124/pr.116.013649
36. Li X, Hartwell KJ, Owens M, et al. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. *Biol Psychiatry*. 2013;73(8):714-720. doi:10.1016/j.biopsych.2013.01.003
37. Stagg CJ, Wylezinska M, Matthews PM, et al. Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy. *J Neurophysiol*. 2009;101(6):2872-2877. doi:10.1152/jn.91060.2008
38. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. *Br J Clin Pharmacol*. 2014;77(2):315-323. doi:10.1111/bcp.12070
39. Umhau JC, Momenan R, Schwandt ML, et al. Effect of acamprosate on magnetic resonance spectroscopy measures of central glutamate in detoxified alcohol-dependent individuals: a randomized controlled experimental medicine study. *Arch Gen Psychiatry*. 2010;67(10):1069-1077. doi:10.1001/archgenpsychiatry.2010.125
40. Naim-Feil J, Bradshaw JL, Rogasch NC, et al. Cortical inhibition within motor and frontal regions in alcohol dependence post-detoxification: a pilot TMS-EEG study. *World J Biol Psychiatry*. 2016;17(7):547-556. doi:10.3109/15622975.2015.1066512
41. Wohlfarth K, Schneider U, Haacker T, et al. Acamprosate reduces motor cortex excitability determined by transcranial magnetic stimulation. *Neuropsychobiology*. 2000;42(4):183-186. doi:10.1159/000026691
42. Seo D, Lacadie CM, Tuit K, Hong KI, Constable RT, Sinha R. Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry*. 2013;70(7):727-739. doi:10.1001/jamapsychiatry.2013.762
43. Hanlon CA, Dowdle LT, Gibson NB, et al. Cortical substrates of cue-reactivity in multiple substance dependent populations: transdiagnostic relevance of the medial prefrontal cortex. *Transl Psychiatry*. 2018;8(1):186. doi:10.1038/s41398-018-0220-9
44. Elton A, Dove S, Spencer CN, Robinson DL, Boettiger CA. Naltrexone acutely enhances connectivity between the ventromedial prefrontal cortex and a left frontoparietal network. *Alcohol Clin Exp Res*. 2019;43(5):965-978. doi:10.1111/acer.13999
45. Perez XA, Khroyan TV, McIntosh JM, Quik M. Varenicline enhances dopamine release facilitation more than nicotine after long-term nicotine treatment and withdrawal. *Pharmacol Res Perspect*. 2015;3(1):e00105. doi:10.1002/prp2.105
46. Dinur-Klein L, Dannon P, Hadar A, et al. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. *Biol Psychiatry*. 2014;76(9):742-749. doi:10.1016/j.biopsych.2014.05.020
47. Bhattacharya A, Mrudula K, Sreepada SS, et al. An overview of noninvasive brain stimulation: basic principles and clinical applications. *Can J Neurol Sci*. 2022;49(4):479-492. doi:10.1017/cjn.2021.158

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