



Transcranial Direct Current Stimulation in Opioid Use Disorder: A Systematic Review of the Literature

Victor Anculle-Arauco^{1,2*}, Mohammed S Alnafisah^{1,3}, Karen Czischke L^{1,4},
Ángel L. Rodríguez Lockward^{1,5}, Murilo Simão Cenovicz^{1,6}, Nassima Allouche Colak^{1,7},
Alexandra Frealdo Dumont Alves^{1,8}, Emilia Kvasnicka^{1,9}, Rafael A F Barros¹,
Juliana A M Couto Magalhães¹, Fernando Zanela da Silva Arêas^{1,10}, Rabia Islam^{1,11},
Beatrice Nyawira¹, Pedro Lança Gomes¹, Ana Victoria P. Vigano¹,
Sorivel Sosa^{1,12}, Sara Pinto Barbosa^{1,13}, Flávia Regina Bueno^{1,14}

¹ PPCR - Harvard TH.Chan School of Public Health; ² Hospital Cayetano Heredia, Lima, Perú; ³ Ministry of National Guard and Health Affairs, Riyadh, Saudi Arabia; ⁴ Clínica Alemana, Hospital Padre Hurtado, Santiago, Chile; ⁵ Pontificia Universidad Católica Madre y Maestra; ⁶ Parana Eye Hospital, Curitiba, Brazil; ⁷ Hamad Medical Corporation, Qatar; ⁸ NCFarma Group, BR; ⁹ University Hospital Basel, Basel, Switzerland; ¹⁰ Laboratory of Neurorehabilitation and Neuromodulation, Universidade Federal do Espírito Santo, Vitória, Brazil; ¹¹ Punjab Medical College Faisalabad, Pakistan; ¹² Instituto Dominicano de Estudios Virologicos, Santo Domingo, Republica Dominicana; ¹³ Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, BR; ¹⁴ Research Coordinator at Endpoint Health Inc., BR.

Abstract

Introduction: Opioid use disorder burdens healthcare facilities and causes significant annual mortality and healthcare costs. Its current management focuses on biopsychosocial interactions; however, a high relapse rate prompts the search for new treatment strategies, such as Transcranial Direct Current stimulation.

Methods: A systematic literature search of PubMed, MEDLINE, and clinicaltrials.gov databases was performed. The search terms reflected the conditions and treatment modalities of interest. Trials reporting transcranial direct current stimulation in opioid use disorders were eligible. The primary outcome was craving reduction, measured using different questionnaires. According to the PRISMA guidelines, three research members independently performed article selection and data extraction. Also, was performed Cochrane risk-of-bias tool for each article.

Results: Seven articles were selected from the 16 eligible papers. In total, 233 patients were included in this study. All studies were conducted in Asian countries and included only male subjects, and the follow-up time was limited to less than six months. Most studies (6/7) reported a significant improvement in craving reduction in the active transcranial direct current stimulation group.

Discussion: Most studies concluded that active transcranial stimulation significantly reduced craving scores; however, the studies had high variability in frequency, intensity, and stimulation site. The limited locations of the trials and small sample sizes represent a threat to the external validity of the studies, which emphasizes the need for further large multicenter randomized trials with adequate follow-up periods to test the efficacy of transcranial direct current stimulation in treating opioid use disorder.

Introduction

Costing around \$80 billion a year, the Center for Disease Control has declared opioid use disorder (OUD)

as a worsening epidemic in the US (Imtiaz, M. S. et al. 2021), with approximately 50,000 deaths in the country only in the year 2019 (Opioid Overdose Crisis, 2022). The National Institute of Drug Abuse estimates a 40–60% relapse rate for patients recovering from drug abuse (Saitz R. et al., 2007). Moreover, with OUD emerging as one of the most severe addiction disorders, a 90% relapse rate in six months has been reported despite being on treatment (Asl, S. N. A. et al. 2013).

*Corresponding author: victor.anculle-2022@ppcr.org

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Current treatment evidence focuses on the interaction between pharmacotherapy and psychosocial therapy with counseling (Lupi M. et al., 2017)(Tareman F et al., 2019) [5-6]; however, researchers are exploring new treatment strategies, such as transcranial direct current stimulation (tDCS).

tDCS is a non-invasive brain stimulation technique that induces polarity-dependent alterations in the brain's cortical excitability (Nitsche, M. A et al., 2000)(Nitsche M. A et al., 2003). It has been shown to improve neuropsychiatric conditions, including alcohol, crack, and cocaine addictions, and reduce cravings. Nonetheless, there is a lack of information and reviews in the literature regarding the impact of tDCS on patients with OUD directly [9, 10-12].(Martinotti, G. et al 2019), (Conti, C. L. et al. 2014), (Gorini, A. et al. 2014), (da Silva, M. C. et al. 2013) The objective of this study was to explore the effects of tDCS described in the current literature on patients with OUD.

In this systematic review, we evaluated studies, including clinical trials, that utilized tDCS as a treatment strategy for OUD by reducing cravings in patients in remission. Such evidence could help shed some light on new therapeutics for patients with OUD by assessing the effects of tDCS in these disorders.

Materials and Methods

We searched the MEDLINE and ClinicalTrials.Gov databases to identify studies investigating the use of tDCS in people with OUD that were published from inception until September 2022. Three authors independently selected the manuscripts and extracted data. We included randomized clinical trials, quasi-experimental studies, pilot studies, systemic reviews, preliminary studies, and commentaries. We excluded studies involving patients with abuse disorders other than opioids and evaluations other than cravings; the papers included in this review were fully published in English. Three types of search were carried out, using the following terms; as concept 1, we used transcranial Direct Current Stimulation as the keyword: "*" [tw] OR " [tw] OR " [tw] OR " [Mesh] and Mesh term: "Transcranial Direct Current Stimulation;" as concept 2, we used keywords: "opioid abuse disorder*," "opioid use disorder*," OR "OUD" OR "opioid abuse*"OR "opioid addiction" [tw] OR "opioid dependence" [Mesh] and Mesh term: "opioid-related disorders;" and finally as concept 3, we used cravings as the keyword: "craving*"OR "compulsion" OR "addiction" OR "substance dependence" and as Mesh term: "craving*" OR "compulsion" OR "addiction" OR "substance dependence."Finally, the reviewer performed a final search without a time filter because of

the small number of articles with concepts 1, 2, and 3.

After reading and in a meeting, the articles were evaluated using the Cochrane risk-of-bias tool for randomized trials.

Results

We identified 16 citations; then we screened 16 full-text versions; nine of these were excluded due to Randomized Controlled Trials (n=2), reviews (n=4), Systematic reviews (n=2), and commentary (n=1). After evaluation using the inclusion criteria, seven studies were eligible for inclusion. Figure 1 shows the article selection workflow based on the PRISMA flowchart.

The characteristics of the search are described in Table 1. There were 233 OUD patients in the seven studies, all male. The evaluation tools for craving were the Desire for Drug Questionnaire (DDQ) and VAS craving score in five and two journals, respectively. Additionally, five studies applied more than ten sessions, with an average of 20 minutes, from 10 to 14 days; the rest only used one or two sessions. Six studies reported significant improvement in craving after the tDCS sessions, and only one, though with a small sample size, found no difference between craving scores at the baseline and the end of 20 tDCS.

The risk assessment is presented in Table 2. It is important to note that most studies had an information bias due to a lack of description and selection bias because most participants were male. Additionally, we evaluated the analyses using the Cochrane risk-of-bias tool (Sterne JAC et al., 2019)

Discussion

This review aimed to demonstrate the effectiveness of tDCS on craving-scale-level reduction in patients in remission for OUD. All the included clinical studies were published from inception to September 2022.

We found seven eligible studies enrolling 233 male participants who received active or sham tDCS. All studies showed a significant reduction in the craving scale in the active tDCS group compared to the sham group; however, in most studies, no significant changes were observed in the relapse rate.

All the trials were conducted in eastern or south-western Asia (Iran, India, and China). Among the seven studies in the review, five included only male subjects, limiting the generalizability of the trial results. All trials had some limitations, such as a small sample size, which might be related to the nature of the studies. Loss of follow-up data was another standard limitation, making it difficult to judge the long-term side effects of tDCS. Although tDCS has

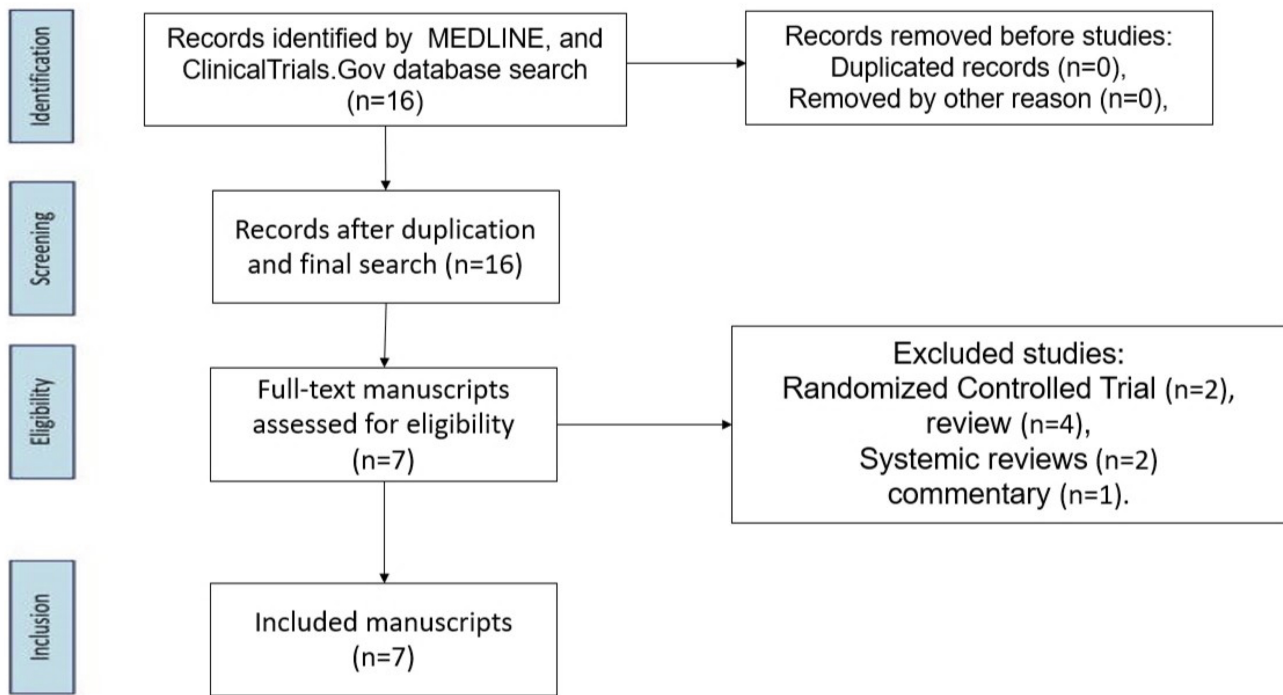


Figure 1: Scheme of articles selection.

been evaluated in a few studies, it has provided promising results sufficient to hypothesize its future impacts as part of OUD treatment (Martinotti, G. et al. 2018). Further, a few meta-analyses have revealed a medium-sized effect of active tDCS stimulation in decreasing substance dependence regardless of the substance type (Chen, J. et al., 2020).

The clinically relevant effects of long-lasting treatment using tDCS need to be studied. To date, only the acute effects of stimulation have been explored. [21]. Additionally, the mechanism of action of tDCS still needs to be fully elucidated. Therefore, its future clinical applications are yet to be determined.

The broader implications of tDCS could be augmented by conducting future trials by adding appropriate pharmacological agents or behavioral tasks that facilitate synaptic plasticity (Brunoni AR et al. 2012).

In the future, the long-term effects of the treatment and the methodology of measuring cravings should be explored further with standardized measures and not self-reported drawings. These results could also be applied to treating other addictive disorders.

Conclusions

In conclusion, most studies present limitations, such as geographical localizations focused on Asiatic countries, the low aggregate number of study subjects, and the short study duration. Hence the external validity is low. However, this is the first step to new studies with broader implications.

Author Contributions

Conceptualization: all authors; methodology: Victor Anculle-Arauco, Mohammed S. Alnafisah, Nassima Allouche Colak; formal analysis: Alexandra Frealdo Dumont Alves.; investigation: Sorivel Sosa, Emilia Petrikova; resources: Karen Czischke. Ángel L. Rodríguez Lockward; data curation: all authors.; writing: original draft preparation: all authors; writing-review and editing: all authors.; project administration: Victor Anculle-Arauco. All authors read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Article #	Reference	Condition	Country	Study design	Sample	Measure	Treatment and Follow-up	Control group	Main Finding
1	Kumar et al., 2022	Early Abstinence Among Patients With OUD on Buprenorphine-Naloxone	India	Pilot randomized, double-blind, sham-controlled parallel-group study	Total N= 28 (males) Active:N= 14 Sham: N= 14	Clinical Opiate Withdrawal Scale (COWS), the Desire for Drug Questionnaire (DDQ), the Obsessive-Compulsive Drug Use Scale (OCDUS), and glutamate-glutamine and GABA at DLPFC via proton magnetic resonance spectroscopy	Active and sham HD-tDCS stimulation, twice daily for consecutive 5 days and 7 days of follow-up.	Sham high-definition transcranial direct current stimulation (HD-tDCS) group	Active HD-tDCS group showed comparable changes in craving and withdrawal, and glutamate-glutamine and GABA at DLPFC compared with sham HD-tDCS.
2	Eskandari et al, 2021	OUD	Iran	Randomized sham-controlled double blinded trial, with three parallel arms	Total N=31(males) Group left anode/right cathode tDCS: N=10 right anode/left cathode tDCS Group:N=11 Sham tDCS Group N=10	Desires for Drug Questionnaire (DDQ), IL-6 and TNF- α expression levels by ELISA kits and impulsivity by Barratt Impulsiveness Scale version 11 (BIS-11)	Active tDCS (2 mA, 20 min) applied over their dorsolateral prefrontal cortex (DLPFC) for 10 consecutive days and 10 days of follow-up.	Sham transcranial direct current stimulation (tDCS)	tDCS is a promising technique for modifying brain dysfunctions and is likely to be a therapeutic tool in specific populations characterized by high levels of impulsivity.
3	Eskandari et al, 2019	OUD in methadone treatment for at least 2 weeks	Iran	Randomized controlled trial with three parallel arms	Total: N= 30(males) Group A L- dorsolateral prefrontal cortex (DLPFC) anodal left/cathodal right: N=10 Group B R- DLPFC anodal right/cathodal left: N=10 Group C, Sham-tDCS: N=10	Desires for Drug Questionnaire (DDQ), Depression Anxiety Stress Scale (DASS-21)	tDCS was applied in each group for 10 days, 20-minute sessions and 10 days of follow-up period.	Sham transcranial direct current stimulation (tDCS)	Administering tDCS over the cortex increases the level of BDNF and decreases the psychological symptoms such as depression, anxiety, stress, and craving for drugs.
4	Kooteh et al, 2020	OUD treated in a two- month program	Iran	Parallel groups, three arms randomized controlled trial	Total N=54(males) First group, subjects received eight sessions of combined tDCS and emotion regulation training: N=18 Second group, subjects received eight sessions of tDCS: N=18 Third Group, subjects received eight sessions of emotion regulation: N=18	Desires for drug questionnaire (DDQ)	Sessions of combined tDCS and the Berking's model (2014) emotion regulation training. There was no follow-up period.	tDCS, emotion regulation training	Combined tDCS and emotion regulation training was more effective than each intervention separately in reducing current drug craving, thoughts and fantasies about drug use.
5	Taremanian et al, 2019	OUD on stable methadone treatment for at least one month	Iran	Randomized clinical trial with three parallel arms	Total:N=60(male) Group 1 Active tDCS combined with methadone treatment: N=20 Group 2 Sham tDCS combined with methadone treatment: N=20 Group 3 Methadone treatment: N= 20	Desire for Drug Questionnaire(DDQ), Obsessive-Compulsive Drug Use Scale, Beck Depression Inventory II (BDI-II), Beck Anxiety Inventory (BAI)	An average daily dosage of methadone 90 mg plus 1 tDCS session for 20 minutes per day in 10 consecutive and 10 days of follow-up period.	Sham tDCS with methadone maintenance treatment	Methadone integrate with tDCS technique can lead to a more significant decrease in opium craving as well as depression and anxiety symptoms.
6	Wang et al, 2016	OUD	China	Sham controlled, single blinded, Randomized Controlled Trial	Total: N=20 (male) Group 1, real tDCS: N=10 Group 2, sham tDCS: N=10	VAS craving score	One tDCS session for 5 minutes.	Sham tDCS stimulation	One session of tDCS over bilateral FPT area significantly reduced subjective craving score induced by heroin cues in heroin addicted subjects.
7	Garg et al, 2019	OUD in standard treatment	India	Case control study	Total:N=20(males) Group 1. tDCS along with treatment as usual during detoxification: N=10 Group 2. Treatment as usual during detoxification: N=10	VAS craving score	Two sessions of tDCS, 20 minutes long per day, during 2 weeks and two weeks of follow-up.	10 subjects in an usual treatment	There was no significant difference, between both the groups in craving scores at the baseline as well as at the end of 20 tDCS sessions.

Table 1: Studies included in the review.

Article	Reference	Risk of bias					Reporting of results
		Randomization process	Blinding	Deviations from intervention	Missing data	Measurement of outcomes, sensitivity analysis	
1	Kumar et al., 2022	No concerns - two groups with block randomization.	No concerns - double blinded study.	Some concerns - not mentioned, due to the study setup probably no.	Some concerns - not mentioned, due to the study setup probably no.	No concerns - statistics good etabled.	No concerns - data form all the participants were reported.
2	Eskandari et al, 2021	Low risk of bias - three groups randomized through sealed envelope randomization system.	No concerns - double blinded study.	Some concerns - not mentioned, due to the study setup probably no.	Some concerns - not mentioned, due to the study setup probably no.	Low risk of bias - double blinded study.	Some concerns - all results described in the methods were showed and did not seemed to be chosen.
3	Eskandari et al, 2019	High risk of bias - there is no information about concealment of the allocation sequence.	High risk of bias - there is no information about blinding.	High risk of bias - there is no information about deviations.	High risk of bias - there is no information about missing data.	High risk of bias - there is no information about blinding so it may have influence the outcome.	Some concerns - all mean results described but we do not know about any missing data.
4	Kooteh et al, 2020	High risk of bias - there is no information about concealment of the allocation sequence.	High risk of bias - there is no information about blinding.	High risk of bias - there is no information about deviations.	High risk of bias - there is no information about missing data.	High risk of bias - there is no information about blinding so it may have influence the outcome.	Some concerns - all mean results described but we do not know about any missing data.
5	Taremian et al, 2019	High risk of bias - there is no information about concealment of the allocation sequence.	Low risk of bias - assessor were blinded.	Some concerns - not mentioned, due to the study setup probably no.	Some concerns - not mentioned, due to the study setup probably no.	No concerns - statistics good etabled.	Some concerns - results from all groups were expressed with means and deviations and p-values.
6	Wang et al, 2016	High risk of bias - there is no information about concealment of the allocation sequence.	Some concerns – participants were blinded.	Some concerns - not mentioned.	Some concerns - not mentioned.	High risk - the measure outcomes are weak.	Low risk - results were analyzed according a pre-specified plan.
7	Garg et al, 2019	High risk of bias - there is no information about concealment of the allocation sequence.	Some concerns - people delivering the interventions were aware of intervention groups.	Some concerns - not mentioned about deviation.	Some concerns - not mentioned.	Low risk - the method of measuring the outcome was not inappropriate.	Low risk - results were analyzed according a pre-specified plan.

Table 2: Risk of bias based on the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) (Sterne et al., 2019).

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