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Protocol Effects of Transcranial Direct Current Stimulation on craving in Opioid use disorder: Protocol for a pilot randomized controlled trial

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Abstract:

Opioid use disorder (OUD) is a chronic relapsing condition which is characterized by problematic pattern of opioid use despite of physical, mental and social distress. It is important individual and public health problem worldwide, especially in USA due to increased non-medical use of prescription opioids. Medication assisted treatment (MAT) is a gold standard for treatment of OUD which includes pharmacological treatment combined with psychosocial therapies. Though these treatments are effective, there are barriers for successful outcomes. Transcranial direct current stimulation (tDCS) is a safe, simple and effective technique to modulate neuronal excitability. It has been used to reduce craving in substance use disorder (SUD). tDCS may be used in opioid use disorder to reduce craving and drug use. We are proposing pilot, randomized, double blind, placebo-controlled trial protocol to assess effects of anodal tDCS over left dorsolateral prefrontal cortex (DLPFC), in OUD. We will randomize 80 subjects in parallel group design to either active or sham group. Five stimulation sessions of 2 mA for 20 minutes, will be provided. Primary outcome is cue induced craving score on VAS of 0 -10. Measures of feasibility, safety and effectiveness will be assessed at baseline and at different time points over 6 weeks. Aim of this trial is to assess feasibility of tDCS to reduce cue induced craving in OUD and to provide data for future fully powered trials, if trend of effectiveness observed.

Keywords: *tDCS, Opioid use disorder, Dorsolateral prefrontal cortex, Craving*

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INTRODUCTION

Opioid use disorder (OUD) continues to be an important public and individual health problem and significant source of mortality and morbidity in USA and all over the world (Toce et al., 2018). According to national institute of drug abuse, every day more than 115 people in USA die after overdosing on opioids. Approximately 21 -29% of patients prescribed opioids for chronic pain misuse them and 8-12% develop an opioid use disorder (NIDA, 2018). Like any other addiction, opioid addiction is a compulsive seeking behavior to rewarding stimuli and associated with abnormal dopaminergic activity in the mesocortico-limbic circuitry, resulting in altered cortical neurotransmission and excitability (Kosten and George, 2002).

Current available treatments for OUD include pharmacological and psychosocial therapies (Medication assisted treatment/MAT), with well evidenced benefits. . It includes FDA approved medicines like Methadone, Buprenorphine and Naltrexone combined with behavioral therapies and counseling. However pharmacological treatments have limits and barriers to successful outcomes like frequent dosing, attendance to collect medicines, difficulty to achieve optimal dosing, regulations for physicians to prescribe, misuse, diversion, accidental exposure and stigma for the treatment (Gilman, et al., 2018). These medications are approved to use in conjunction with psychosocial therapies, but there are limited evidences about the efficacy of psychosocial treatments in conjunction with medications (Dugosh et al., 2016). Neuromodulation techniques like transcranial

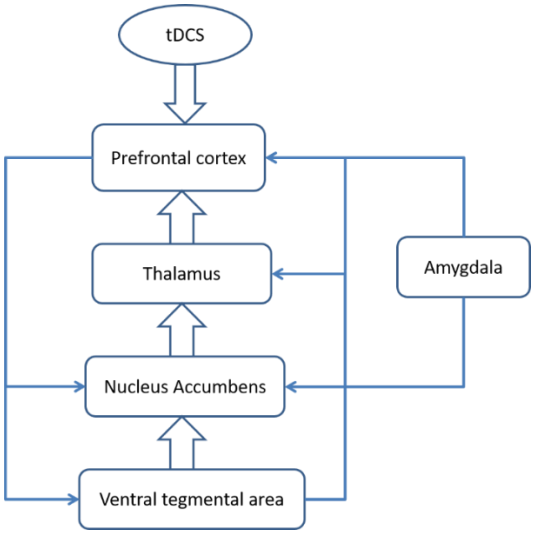
direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have been studied for substance use disorder. Recent systematic review in 2017 found preliminary evidence of tDCS being effective for reduction of cravings for substance use disorder (Lupi et al., 2017).

Transcranial direct current stimulation is a novel and safe technique which uses weak direct electric current through surface electrodes over scalp. Anodal stimulation increases, and cathodal stimulation decreases neuronal excitability. Prefrontal cortex can be the most suitable target for opioid use disorder. Dorsolateral prefrontal cortex is main component in neural substrate of craving for various psychoactive substances (Hartwell et al., 2011). Neurocircuitry involved in rewarding effect of addiction involves dopaminergic mesocortico-limbic system and its projections from the ventral tegmental area (VTA) to the *nucleus accumbens* (NAC) and to the prefrontal cortex (PFC) (Koob and Volkow, 2016). Secondly, structural imaging studies have shown reduced PFC grey matter density or thickness in addiction populations (up to 20% loss). Also, there is an evidence from PET studies of lower striatal dopamine receptor D2 availability in addicted individuals and which is associated with reduced metabolic activity in orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) (Goldstein and Volkow, 2002). Prefrontal cortex is densely attached to other cortical and subcortical regions and networks. Evidence shows that addiction behaviors, that is seeking and consumption of addictive substance involves neurobiological alternations in brain networks related to reward, stress and executive control (Koob and Volkow, 2016). On the other hand, neuromodulation techniques like transcranial direct current stimulation, specifically over PFC showed promising results for modulating cognitive control for emotional process (Chrysikou et al., 2013).

DLPFC stimulation may improve cognitive component of executive function, subsequently reducing craving and probable relapse in drug addiction (Lapenta et al., 2018). In summary, as DLPFC receives direct inputs from meso-cortical dopaminergic pathways originating from VTA and its projections to thalamus, basal ganglia and hippocampus, it could be most easily accessible and relevant target for addiction disorders, affecting dopaminenegic pathways and subsequently craving. Figure 1A shows mesocortico-limbic pathways and interconnections between the different neural regions. Anodal tDCS at left DLPFC can modulate the dopaminergic pathways and can affect cue induced cravings in OUD.

Craving is an important risk factor for relapse in substance use disorder and higher craving is related to higher relapse rates. Most of the studies regarding substance use disorder assesses cue induced craving as outcome measure (Amiaz et al., 2009; Rose et al., 2011; Li et al., 2013; Dinur-Klein et al., 2014). Many studies showed reduction of cravings and consumption of drug as well after DLPFC tDCS (Boggio et al., 2009; da Silva et al., 2013; Gorin et al., 2014). As previous neuroimaging and clinical studies showed modulation of cravings with DLPFC stimulation, we hypothesize that stimulation of this area will modulate opioid cravings.

(A)



(B)

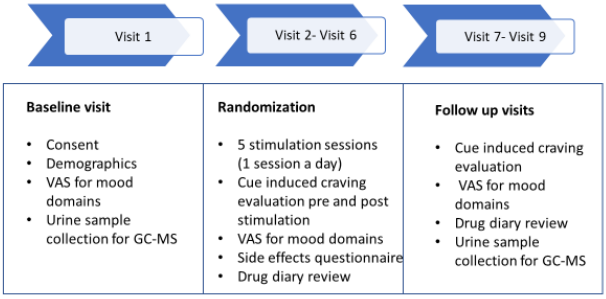


Fig. 1. (A): Mesocortico-limbic dopaminergic pathways and neural interconnections involved in addiction and craving of opioid use disorder. Anodal tDCS at left dorsolateral prefrontal cortex can modulate above pathways and affect cue induced cravings in OUD. (B) Flow of study visits and description of procedures during the visits.

Possible mechanisms of effect of DLPFC-tDCS on craving could be: (1) Decrease in risk taking behavior and impulsivity by improving top down cognitive control. (2)

Decrease in attentional bias. (3) Reduction of craving by acting on mesocortico-limbic dopaminergic pathways and by changing synaptic plasticity in reward system. (4) Stimulation of prefrontal cortex may indirectly stimulate subcortical regions related to motivation and decision making, via connections.(5) Interconnections between DLPFC and ventral tegmental area (VTA) may increase excretion of dopamine from VTA to ventral striatum which is mainly involved in reward processing.(6)Stimulation of DLPFC may stimulate glutamate containing cortico fugal fibers which have endings on dopamine containing terminals in ventral striatum, leading to increased excretion of dopamine. Neurostimulation of DLPFC may also enhance cognitive functioning and cognitive control and may help to prevent relapse.

To our knowledge, till date there is no randomized clinical trial reported to assess the effects of tDCS on opioid use disorder or addiction, therefore, we propose a pilot, randomized, double blind, sham controlled trial protocol to assess feasibility and effectiveness of tDCS for opioid use disorder.

METHODS

Trial Design

The aim of the study is to design a pilot trial protocol and provide data for future fully powered clinical trials, if trend of effectiveness is observed. Participants will be randomized in 1:1 parallel design, to either active or sham group.

Eligibility Criteria

Inclusion Criteria: 18 years and older, both male and female, diagnosed with moderate or severe opioid use disorder according to DSM-5 criteria for opioid use disorder (American psychiatric association, 2013), ability to provide written informed consent and has not been treated for any substance use.

Exclusion Criteria: Neuropsychiatric disorder like severe depression (score on beck depression inventory >30), epilepsy or history of seizures, unstable medical condition like uncontrolled hypertension or diabetes, major illness like cancer, contraindications to electrical stimulation like brain metal implant and massive brain lesion, pregnancy, taking medications like carbamazepine, under treatment for any substance use disorder and refusal to provide consent for participation.

Recruitment

We will recruit 80 non-treated participants from general advertisements and via flyers posted in public places and newspapers. The information of trial will also be posted on internet. As this scenario is very common, subjects with any other addiction concurrent with OUD like alcohol or smoking can also participate (S.A.a.M.H.S.A, 2005). We will ask subjects to keep the diary to note the name, dose and time of drug taken throughout the study. To assess the eligibility, potential participants will complete the online questionnaire and screened participants will be contacted by research coordinator to schedule the baseline visit. All participants will sign the written informed consent at baseline visit.

Sample Size Calculation

Recent meta-analysis investigating the effects of single session versus multi session of noninvasive brain stimulation on craving and consumption in drug addiction and eating disorders, found effect size of 0.68(Medium) (Song et al., 2018). We used G*Power 3.1.9.4 for sample size calculation, with t-test-difference between two independent means and assumption of significance level 0.05, power 0.8 and effect size of 0.68. Sample size resulted is 35 subjects per group. Assuming approximately 15 % drop out, we finalized 40 subjects per group (Total sample size 80).

Randomization

An independent investigator will prepare computer generated randomization sequence and keep each allocation in sealed, opaque, sequentially numbered envelops and envelops will be kept in a secured closet. The stimulator will open the envelop just before the stimulation, after confirming the eligibility. Participants will be randomized with 1:1 parallel group design to either active or placebo group.

Blinding

Participants and outcome assessors are blinded to the group assignment. Only the investigators providing stimulation are unblinded. tDCS set up is similar for both active and sham group. The staff involved in preparing randomization list will have the authority to break blinding in case of clinical need or any emergency. The participants will remain blinded until the last visit of the study or in case of adverse events which needs unblinding.

Intervention

Participants will be randomized to either active or sham tDCS. There would be 5 consecutive stimulation sessions, daily over one week. Each session will last for 20 minutes with the current intensity of 2 mA. tDCS device of Soterix

Medical Inc. will be used for stimulation. It has the adjustment for sham mode in which there is ramp up and ramp down period of 30 seconds in the beginning and at the end of stimulation, however, in between there is no current flowing. Thus, the sham group subjects will feel cutaneous sensations similar to active group. This is reliable method of sham tDCS wherein tDCS less than 3 minutes will not lead to lasting effect on cortical excitability (Gandiga et al., 2006).

tDCS will be delivered through two 5cm×7cm electrode sponges for a surface area of 35 cm^2 with anode placed over left dorsolateral pre-frontal cortex (F3) according to 10-20 international EEG system and cathode over right supra orbital area. Following every tDCS session, tDCS side effects questionnaire will be asked. All investigators including stimulators will be properly trained and certified by the study PI.

Cue Induced Craving Score Evaluation

For evaluation of cue induced craving, the subjects will be asked to watch the presentation on computer screen, which includes the images of crushed pills, pill bottles, powders, rolled up paper, syringes and intravenous injections. These cues have been used to elicit craving in opioid dependent subjects (McHugh et al., 2016). This presentation will be showed for 10 minutes and then the subjects will be asked to score their craving on the visual analogue scale of 0 to 100, where 0 means not at all and 100 means very likely to use opioid drug. The stimulation as per group allocation will start after 10 minutes of craving evaluation. After the stimulation, after removing electrodes, we will replay the same video presentation for 10 minutes and will ask the subjects to score craving again on VAS of 0-100.

Study Timeline and Procedures

There are 8 visits throughout the study as outlined in the Figure 1B and detailed below:

Visit 1: Baseline visit

1.1 Written informed consent.

1.2 Following data will be collected by the study investigator:

Demographic data: Age, gender, race, ethnicity, level of education, opioid use duration, type of drug (heroin, other prescription opioids), other substance use. Any co existing psychiatric co morbidity (We will use M.I.N.I. psychiatric interview (version 7.0.2 for DSM-5) for evaluation of psychiatric co morbidity) (Sheehan et al., 1998).

1.3 VAS for mood domains 0 to 10 (including sleepiness, depression, anxiety and stress) 0 means not at all and 10 means very likely.

1.4 Collection of urine sample (30 ml) for Gas chromatography with mass spectrometry testing to measure drug used.

Visit 2: Randomization and first session of stimulation

At this visit subjects will get randomized to either active or sham group. Then they will be showed the cue presentation video (mentioned above) for 5 minutes and then will be asked to rate craving on VAS from 0 to 10. After 10 minutes, the subjects will receive stimulation as per randomization, for 20 minutes. After removing electrodes subjects will be asked to rate craving on VAS. VAS for mood domains and tDCS side effects questionnaire will also be asked.

Visit 3 to Visit 6: Stimulation visits

During these visits, similar procedure from visit 2 will be repeated (except randomization).

Visit 7 to Visit 8:

These are post stimulation follow up visits after 1 week, 2 weeks and 4 weeks. During these visits the subjects will be showed the same cues and asked to rate craving score on VAS and VAS for mood domains will be asked. The amount and dose of drugs will be reviewed in a diary. At every follow up visit urine sample of 30 ml will be collected, to quantify drug use with Gas chromatography and mass spectrometry. To assess opioid withdrawal symptoms (if any), we will use Clinical Opioid Withdrawal Scale (COWS). This is a quick, 11 items, and validated scale to quantify the opioid withdrawal symptoms. The sum of the 11 items' score will be done and categorized as follows- Score: 5- 12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal (Wesson and W. Ling, 2003).

Primary and Secondary Outcomes

We will use cue induced craving score as primary outcome. The subjects will rate the craving on visual analogue scale (VAS) of 0 to 10, where 0 means not at all and 10 means very likely to use opioid drugs. Secondary outcomes are as follows: (1) Amount of drug use (2) Subgroup analysis for the group with concurrent substance use and without concurrent substance use (like alcohol, smoking etc.). (3) VAS for mood domains including sleepiness, depression, anxiety and stress. (4) tDCS side effects questionnaire.

Statistical Analysis Plan

All data will be compiled and analyzed using SPSS software version 24. Demographic data and amount of drug reviewed from diary will be presented as descriptive statistics with means and standard deviation or median and inter quartile range. Cue induced craving score (primary outcome) at different time points will be analyzed using repeated measures ANOVA. For secondary outcomes subgroup analysis will be done for the subjects having concurrent substance use and without concurrent substance use. Adverse effect questionnaire and mood domain will be analyzed by using chi square test. Amount of drug used measured by urine drug test will be analyzed with repeated measure ANOVA. COWS (Clinical Opiate Withdrawal Scale) scores will be analyzed using ANOVA. Significance level will be set at α=0.05. All data will be analyzed after every participant finishes all the study visits. No interim analysis will be done considering short interval of the study.

Study Modification or Discontinuation

tDCS is a safe intervention when the safety guidelines are followed. Common side effects include tingling, itching, headache, burning sensations, local erythema and mild discomfort. If there are any severe side effects observed, the study will be interrupted, and medical treatment will be provided to the subject in the research facility by the licensed physician. Emergency unblinding will be done in case of clinical need. All side effects will be reported to PI and IRB (Institutional Review Board).

Data Management

We will collect all the data in paper and electronic form. Thus, privacy and confidentiality of the data will be maintained. The binders with the data will be kept in the secure closet which can be accessed only by PI and authorized study staff. The data in electronic form will be kept in password secured computer. Subjects will be given contact information of PI and co investigators and assured about the confidentiality of the data collected.

Missing Data

Considering the short interval of the study, we do not anticipate high dropout rate. However, if there is missing data, we will use last observation carried forward method to deal with it.

DISCUSSION

According to World health organization, worldwide there were 27 million people who suffered from opioid use disorder in 2016. Mortality rate among opioid addict is 6 to 20 times greater than general population, even after 10 years of follow up (Hser et al., 2018). At social level OUD leads to loss of productivity, increase in crime rate and violence, neglect of children, increased health care cost, homelessness, unemployment and financial problems. Opioids are category of drugs which travels through bloodstream and attach to the specialized proteins called mu opioid receptors on the surfaces of opiate sensitive neurons. This triggers the mesolimbic dopaminergic pathways and signals other parts of brain including ventral tegmental area (VAT) which causes release of chemical dopamine in nucleus accumbens. This process causes feeling of pleasure. The feedback from pre-frontal cortex appears to be compromised in drug addict people, which can contribute to drug misuse. Opioids includes heroin, some prescription opioids like oxycodone, hydrocodone, morphine and semisynthetic opioids like Fentanyl.

OUD is commonly treated with medication assisted treatment (MAT) which includes pharmacotherapy combined with appropriate counselling or behavioral therapy. FDA has approved 3 medications for the treatment of opioid use disorder to prevent relapse and stabilization or maintenance therapy: Methadone (agonist) buprenorphine (partial agonist) and Naltrexone (antagonist) that affect opioid receptors. Though available treatments for OUD are effective, treatment uptake, response and adherence is not optimal (NIH, 2018). According to world health organization report in 2018, only less than 10% people who need the OUD treatment receives it (WHO, 2018). Prescriptions of medicines for OUD did not keep pace with the diagnoses. As Opioid crisis is ongoing public health issue and existing treatments are not ideal for everyone, finding new and innovative treatments and technologies to treat OUD is critical (Volkow and Collins, 2017). In this scenario, noninvasive brain stimulation techniques like transcranial magnetic stimulation and transcranial direct current stimulation can be the useful tools, either used individually or in combination with MAT. Recent evidences suggest potential use of these techniques to successfully treat substance use disorder including heroin.

Craving is an important therapeutic target in treatment of addiction. It is a core feature of substance use disorder. Craving has been recently added to DSM-5 criteria (American psychiatric association) of SUDs which shows its importance in diagnosis and treatment of SUD. Evidence suggests association between craving and opioid use which supports craving being an important factor while treating OUD. The results from the study assessing craving and subsequent opioid use found

greater degree of craving associated with higher likelihood of using opioids (Tsui et al., 2014). We are using cue induced craving score as a primary outcome. Long abstinent (1 year) heroin dependent subjects showed higher cue reactivity and it can be argued that these subjects are vulnerable to drug use if exposed to drug cues in natural settings even after long time of recovery (Franken et al., 1999).Therefore it would be helpful to treat cue induced craving, which can affect positively on drug use and probably on relapse. Anodal tDCS of pre-frontal cortex proposed in this protocol can be safe and efficacious to treat opioid use disorder in non-treated subjects. tDCS has potential to be used as an adjunct to pharmacological or psychosocial therapy for OUD if found effective in this trial. This pilot, placebo controlled RCT will help us to assess feasibility and effectiveness of tDCS to reduce cue induced cravings and drug use in OUD.

As the interval of the study is short, long term effects of tDCS cannot be assessed. Also, the types of drugs used by subjects can be different and drug diary records are subjective and self-reported. Although to verify these self-reports, we are using urine test to measure amount of drug used, it has the limitation of short detection window period of opioid drugs (1-4 days). Though Subjects are recruited by using broad based strategies, only untreated subjects are included which may lead to selection bias. However, this is necessary to avoid confounding if we include subjects with any other concurrent treatments. The strengths of the study are the fact that we are targeting DLPFC, which is supposed to be the most suitable target in substance use and involved in craving and also, we are using repeated sessions of tDCS. We will provide open label, active, free tDCS sessions for the subjects in sham group, if they are willing after completion of the study.

Impact of the Study

This pilot trial will assess the feasibility and effectiveness of tDCS to reduce craving and drug use in opioid use disorder and can provide valuable data to run future fully powered phase I or phase II trials, if trend of effectiveness is observed. As tDCS is safe, novel and inexpensive technique, this study may help to explore potential of this neuromodulation method to treat opioid use disorder.

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Conflict of interest and financial disclosure

The authors have no personal or financial conflicts of interest to declare. No funding was received for this research proposal.

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