

## Abstract

**Objective:** The aim of the present study was to examine the effectiveness of Transcranial Direct-Current Simulation (tDCS) in drug use craving, depression, and anxiety in students with tramadol abuse. **Method:** An experimental single-subject research design was employed for the conduct of this study. All the students with tramadol abuse in Mohaghegh Ardabili University in the academic year of 2015-2016 constituted the statistical population of this study. For this purpose, three students were selected by convenience sampling method. For data collection purposes, Franken's Craving Questionnaire (2002) and Lewinda's Depression, Anxiety and Stress Scale (DASS-21) (1995) were used. Treatment sessions of transcranial direct-current simulation (tDCS) were held in ten 20-minute sessions in such a way that the anode electrode was placed on left dorsolateral prefrontal cortex (F3) and the cathode electrode was placed on the right dorsolateral prefrontal cortex (F4) and 2 milliamperes of direct electric current were passed through the participants' skulls for 20 minutes. **Results:** The results of this study indicated the effectiveness of this method in the reduction of craving and depression among tramadol abusers, but it could not have any significant effect on individuals' anxiety. **Conclusion:** According to the results, it appears that Transcranial Direct-Current Simulation (tDCS) can cause a reduction in depressive symptoms and craving in tramadol users. Hence, it is suggested that addiction therapists and psychotherapist in the domain of addiction use Transcranial Direct-Current Simulation (tDCS) as an intervention method towards the treatment of these patients.

**Keywords:** transcranial direct-current simulation (tDCS), dorsolateral prefrontal cortex, craving, anxiety, depression, tramadol

# On the Effectiveness of Transcranial Direct-Current Simulation (tDCS) in Craving, Depression, and Anxiety among Students with Tramadol Abuse: Preliminary Study

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## Introduction

From among the pseudo-opioid analgesics popular with young people and particularly students, one can refer to tramadol. University students are more likely to take this type of pill than other substances due to a number of reasons, including living in places without parental supervision such as dormitories, stresses arising from living in another city, academic anxiety, especially during exams, huge advertisements about the non-addictive effects of tramadol and its effect on the increase of attention and concentration, the low price and availability of this substance compared to other substances. This drug was first proposed in Germany in 1970 to relieve post-surgical pains and control chronic pains (Radbruch, Grond, & Lehmann, 1996). At present, substance abuse among young people in Iran has led to such a progressive development that tramadol abuse with 26.5% lies in the first rank among the other drugs according to the statistics released by Drug Control Headquarters (Fathi, Bashirian, Barati & Mehdi Hazaveh'ea, 2012). There are a number of reasons for this increase as follows: the ease of access and consumption, ignorance of the risks of abuse, parents and the government's obscurity regarding the negative consequences of taking tramadol, especially its addictive effect, and the lack of serious attention to design and implement preventive programs (Fathi et al., 2012). Craving, temptation, or eagerness for consumption are among the most complex issues that one faces when it comes to the treatment of addictive disorders. Tiffany, & Drobos (1991) defined drug use craving as a term that covers and entails a wide range of phenomena, including the expectation of amplifying effects and strong tendency to drugs. Hormes, & Rozin (2010) defined craving as follows: a very strong and urgent yearn for something so that it is impossible to focus on anything other than the subject matter. Various studies have shown that craving is known as the central phenomenon and the main cause for continued drug abuse, as well as cause of addiction relapse after therapeutic courses.

On the other hand, drug addiction is a chronic disease that is often accompanied by another psychiatric disease. Mood disorders and depression are among the most common first-axis disorders caused by addiction based on the fifth revised version of the Diagnostic-Statistical Manual of Mental Disorders. The prevalence of major depressive disorder in individuals is about 50-60% and the degree of depression is close to 10% (Ilegn, Jain, & Trafton, 2008). In addition to the reports pertaining to the high comorbidity of substance abuse with mood disorders and the high rates of depression and anxiety among drug users, research findings confirm the same neurological position of craving, depression, and anxiety in such a way that the Dorsolateral Prefrontal Cortex plays an important role in mood disorders and craving according to brain imaging (Da Silva et al., 2013). On the other hand, the available therapies and treatment methods for substance abuse which address disorders and consider the

individuals' mental status are limited and are weak in terms of the duration of long-term success (Vincent, Shoobridge, Ask, & Allsop, 1998).

Considering the new interventional strategies in the field of addiction, the development of noninvasive brain stimulation techniques, such as transcranial direct current stimulation (tDCS) has come up with acceptable results in terms of the reduction of craving, depression, and anxiety. This technique acts based on the use of direct and low electric current on the skull in order to make changes pertaining to polarity in cortical irritability. Anodic and cathodic stimulation subsequently leads to the increase and decrease of cortical irritability (Nitsche & Paulus, 2000). Fregni, Liguori, & Fecteau (2008) examined the effect of cortical stimulation of the prefrontal cortex with transcranial direct current stimulation on the reduction of cue-provoked smoking craving among cigarette smokers and found that the stimulation of the right or left dorsolateral prefrontal cortex by direct stimulation with electric current reduced drug use craving. Other studies have shown that the stimulation of the right or left dorsolateral prefrontal cortex leads to a reduction in depression (Da Silva et al., 2013) and anxiety (Edson, Jaisa, Felipe, Michael, Nitsched, & Ester, 2015).

Students' general health and mental health (as the elites in the community) are the main worries and concerns of planners and decision-makers; however, a small number of studies have been carried out in this area and there are a limited number of researchers who directly conduct therapeutic research among students. Moreover, it is known that the reduction of craving and the decline of mental symptoms that play a major role in the desire for substance use and addiction relapse are currently among the main challenges of other psychotherapy approaches since craving is the first important phenomenon in addiction relapse. Accordingly, the present study seeks to investigate the effectiveness of transcranial direct-current stimulation (tDCS) (the placement of anode on left dorsolateral prefrontal cortex (F3) and the cathode on the right dorsolateral prefrontal cortex (F4)) in craving, depression, and anxiety among students with tramadol abuse.

## **Method**

### **Population, sample, and sampling method**

An experimental single-subject research design was employed for the conduct of this study. Single-subject designs fall within the category of quasi-experimental research wherein changes in the dependent variable are measured in one subject. Since it is difficult to find a group of students using tramadol, the single-subject research design was selected for the conduct of this study. In these designs, the dependent variable is measured several times during the baseline stage and one or more stages of the treatment, that is, when the independent variable is presented. In this research, the ABA baseline was used. In the baseline stage, the levels of craving, depression, and anxiety were measured (step A). Then, the intervention stage included transcranial direct-current stimulation (step

B) and the re-evaluation of craving, depression, and anxiety in the post-test phase was performed (step A). Eventually, a follow-up was conducted after two weeks. The independent variable in this study was transcranial direct-current simulation; and the dependent variables included therapeutic changes arising from the use of this therapeutic approach into the rate of craving, depression, and anxiety. At the intervention stage, the participants received 10 sessions of brain stimulation from the skull. In this state, the anode electrode was placed on left dorsolateral prefrontal cortex (F3) and the cathode electrode was placed on the right dorsolateral prefrontal cortex (F4) and 2 milliamperes of direct electric current were passed through the participants' skulls for 20 minutes. The effectiveness of the intervention was assessed by comparing the participants' responding process in the baseline stages with the treatment and continuation of responses in the follow-up phase.

All the students with tramadol abuse in Mohaghegh Ardabili University in the academic year of 2015-2016 constituted the statistical population of this study. Considering the available population and the intervention nature of this research, and also due to the inclusion of certain conditions and time constraints, as well as the conditions for the satisfaction of the inclusion criteria and exclusion criteria, three participants were selected as the sample units. The inclusion criteria were being university student, the lack of comorbidity with major psychiatric disorders, no history of brain injury or stroke, and willingness in participation in the research. On the other hand, the exclusion criteria were the history of epilepsy, brain surgery, tumor, head impact resulting in anesthesia, head trauma or seizure in the individual or family, the presence of shunt and physical instruments in the body and snail planting, the history of bipolar disorder or psychotic symptoms of drug dependence (other than tramadol), presence of heart pacemakers, metal, and prosthesis, and implantation.

### **Instruments**

1. Demographic information: The demographic information, including age, level of education, occupation, duration of tramadol use, history of medication, and marital status was gathered through closed and open questions.

2. Desire for Drug Questionnaire: This questionnaire consists of 14 questions and has been developed by Franken, Hendriks, & Van den Brink (2002). It has been derived from the Desire for Alcohol Questionnaire, which is used for heroin dependents. However, it was later used to measure the desire for the use of other substances due to its feature of measuring the overall craving. This instrument examines the current craving and includes three subscales, namely desire and intention, negative reinforcement, and control. The questionnaire is scored based on a 7-point Likert scale (strongly opposite to strongly agree). In other words, the response to each item is rated from 1 to 7. Franken et al. (2002) calculated the reliability of this scale by Cronbach's alpha and obtained the value of 0.85 for the whole scale; in addition, they reported the coefficient values of 0.77, 0.80,

and 0.75 for the subscales, i.e. desire and intention, negative reinforcement, and control, respectively. Mousayi, Mousavi, & Kafi (2012) reported the Cronbach's alpha coefficients of 0.96 for opium users, 0.95 for crack users, 0.90 for methamphetamine users, 0.94 for heroin inhaler, and 0.98 for heroin injectors.

3. Lewinda's Depression, Anxiety and Stress Scale (DASS-21): This questionnaire was developed by Lewinda (1995) and has 21 items, which are answered on a Likert scale from never (0) and low (1) to high (2) and very much (3). The items numbered 1, 6, 8, 11, 12, 14, and 18 assess stress; the items numbered 2, 4, 7, 9, 15, 19; and the items numbered 3, 5, 10, 13, 16, 17, and 21 assess depression. A large number of studies have been carried out to validate this questionnaire. Cronbach's alpha coefficients on a 717-participant sample were obtained equal to 0.71, 0.73, and 0.81 for depression, anxiety, and stress. In terms of the convergent validity of the scale, the correlation coefficients of Beck Depression scores with the depression, stress, and anxiety scores of this questionnaire were obtained equal to 0.66, 0.49, and 0.67, respectively, which were significant (Sahebi, Sadaat Salari & Asghari, 2005).

### **Procedure**

The initial design of transcranial direct-current simulation dates back to over 100 years ago. A number of primary experiments had been carried out using this technique on animal and human specimens before the 19th century. In 1804, Adeline embarked on a research project on transcranial direct-current simulation and the results indicated that this method would be effective in the improvement of depressed people's mood. In the 1960s, a person named Albert managed to demonstrate that this method could affect brain function by altering the stimulation of the cerebral cortex. He also discovered that positive and negative stimuli have different effects on cortical irritability. Although these findings were important for the use of transcranial direct-current simulation, pharmacotherapy showed itself as a more effective treatment method since limited research was carried out again on transcranial direct-current simulation. This argument continued until the present time, and this method regained its importance as much as the new techniques of brain stimulation and new brain imaging techniques after the increase in the interests in doing studies on brain functions and therapeutic applications (Janicak, Davis, Gibbons, Ericksen, Chang, & Gallagher, 1985). In this research, the participants first filled out the questionnaires to determine the pre-test score. In the next stage, transcranial direct-current simulation was performed for 10 consecutive days upon the skulls where the anode electrode had been placed on left dorsolateral prefrontal cortex (F3) and the cathode electrode was placed on the right dorsolateral prefrontal cortex (F4) and 2 milliamperes of direct electric current were passed through the participants' skulls for 20 minutes. After the end of the intervention, the research variables were re-evaluated. Moreover, one month after the completion of re-intervention, the variables were evaluated in the follow-up stage.

## Results

Considering the single-subject research design, the indexes of the change trend, recovery slope and percentage were used for data analysis in each patient and the trend of changes in scores during the sessions was shown separately on the graphs. The ups and downs of the dependent variable are the basis for the judgment on the rate of change. In addition to this criterion, the clinical significance was also used for data analysis. The following formula was used to objectify the degree of recovery.

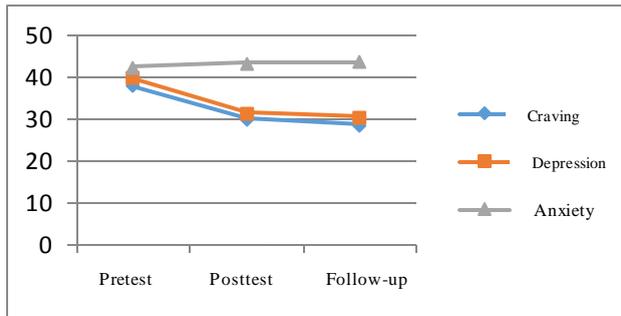
$$\text{Recovery percentage} = \frac{\text{Posttest score} - \text{pretest score}}{\text{Posttest score}}$$

The first participant was 21 years old and was an engineering student with a history of three-year tramadol use (a daily dose of 600 milligrams). The second participant was 22 years old and a student of Humanities with a history of two-year tramadol use (a daily dose of 800 milligrams) and, finally, the third participant was 20 years old and a student of basic sciences with a history of two-and-a-half-year tramadol use (a daily dose of 1000 milligrams). The descriptive statistics of the research variables are presented in Table 1 for each participant and test stage.

**Table 1: Descriptive statistics of the research variables for each participant and test stage**

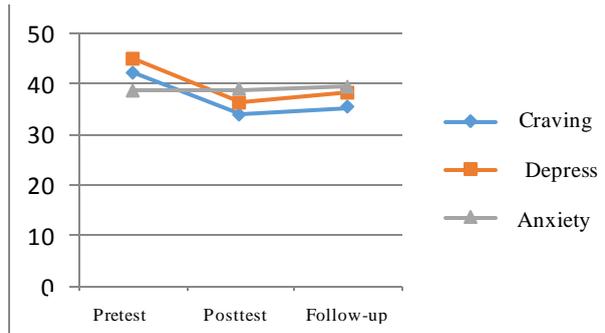
| Variable   | Participants | Mean    |          |           | SD      |          |           | Recovery percentage | Effect size |
|------------|--------------|---------|----------|-----------|---------|----------|-----------|---------------------|-------------|
|            |              | Pretest | Posttest | Follow-up | Pretest | Posttest | Follow-up |                     |             |
| Craving    | First        | 37.83   | 30       | 28.56     | 7.42    | 5.64     | 4.72      | 0.26                | 1.14        |
|            | Second       | 42.26   | 34       | 35.21     | 10.26   | 6.78     | 5.34      | 0.24                | 1.09        |
|            | Third        | 45.67   | 37.46    | 40.92     | 13.56   | 7.59     | 6.68      | 0.22                | 1.02        |
| Depression | First        | 39.67   | 31.25    | 30.45     | 10.23   | 7.46     | 6.78      | 0.26                | 1.16        |
|            | Second       | 44.89   | 36.26    | 38.23     | 12.47   | 9.64     | 7.68      | 0.24                | 1.07        |
|            | Third        | 48.52   | 38.46    | 39.39     | 13.56   | 11.27    | 9.44      | 0.25                | 1.12        |
| Anxiety    | First        | 42.25   | 43.34    | 43.39     | 12.41   | 12.44    | 13.21     | 0                   | 0           |
|            | Second       | 38.56   | 38.78    | 39.42     | 10.45   | 11.23    | 11.79     | 0                   | 0           |
|            | Third        | 37.24   | 35.77    | 33.26     | 9.45    | 8.35     | 7.79      | 0.24                | 1.06        |

The results of Table 2 show that craving and depression have been clinically reduced in all three participants as the percentage of recovery and the effect size indicate these changes. However, anxiety has been reduced only in the third participant and the method has not had any effect on anxiety in the first and second participants. The obtained effect sizes indicate the effect of transcranial direct-current simulation, and the obtained effect sizes are considered to be large according to Cohen's categorization.



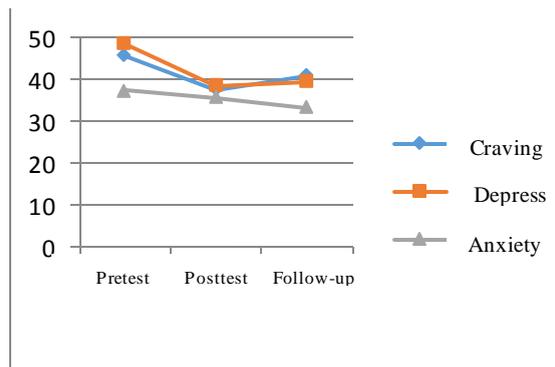
**Fig. 1: Scores changes in the first participant in terms of craving, depression, and anxiety**

According to figure 1, there is a significant reduction in craving and depression, but there is no significant change in the anxiety variable.



**Fig. 2: Scores changes in the second participant in terms of craving, depression, and anxiety**

According to figure 2, there is a significant reduction in craving and depression, but there is no significant change in the anxiety variable.



**Fig. 3: Scores changes in the third participant in terms of craving, depression, and anxiety**

According to figure 1, there is a significant reduction in craving, depression, and anxiety.

### **Discussion and Conclusion**

The research finding reported by Fregni (2008) and Boggio (2008) are consistent with that of the confirmed hypothesis regarding the effect of the anodic stimulation on left dorsolateral prefrontal cortex and the cathodic stimulation on the right dorsolateral prefrontal cortex. The results of these studies showed that the simultaneous anodic and cathodic stimulation of F3 and F4 reduces craving for cigarette smoking and craving for alcohol consumption. Although the results of the anodic F3 and the cathodic F4 arrangement were more suitable, the placement of the electrodes exactly on the opposite mode was also effective. The significant effect of transcranial direct current stimulation on the reduction of craving in the prefrontal cortex confirms the important role of the dorsolateral prefrontal cortex in craving. In addition, the results of this part of the study are consistent with those of the research conducted by Hajloo, Poursmaeali, Alizadeh Goradel & Molaei (2015) who confirmed the simultaneous stimulation of the anodic F3 and cathodic F3 in daily and social smoking craving. In a study conducted by Politi, Fauci, Santoro, & Smeraldi (2008) on 36 cocaine users, it was revealed that 10 sessions of the left dorsolateral prefrontal cortex stimulation brought about a decrease in cocaine craving. Boggio et al. (2008) administered one session of stimulation in the left and right prefrontal cortex on 13 alcohol users, and reported a temporary decline in craving on both sides. Amiaz, Levy, Vainiger, Grunhaus, & Zangen (2009) conducted the left dorsolateral prefrontal cortex stimulation on 48 nicotine users during 10 sessions and reported a decrease in craving. In another study, Fregni et al. (2008) reported the temporary reduction of craving in both sides of the hemisphere after one session of stimulation in the left and right prefrontal cortex on 24 nicotine users.

Based on the previously-done studies and the present study, it can be argued that the increasing or decreasing stimulation of the left or right prefrontal cortex can interfere with the balance of activity in the two hemispheres. The left and right dorsolateral prefrontal cortex stimulation can normalize the states of drug use craving. A number of the cerebral cortex centers that are active in drug use craving in humans, as well as the limbic and prefrontal structures have become activated by stimulation. These areas of the brain were broadly related to the left hemisphere of the brain. Moreover, the activation of the anterior cingulate cortex has been seen during the experience of substance craving (Garavan, et al., 2000). To explain this finding, one can argue that transcranial direct current stimulation has been used frequently in the withdrawal of using tramadol, alcohol, and opiates (Kaluss, Sexton, Loo, & Ebmeier, 2014). Stimulants in the reward system directly increase the level of extracellular dopamine through the release of dopamine or prevention of its reabsorption at the pre-synaptic terminus, but some substances (such as nicotine, alcohol, and cannabis) affect the neurons

containing Gamma-aminobutyric acid or glutamate and, thereby, boosts dopaminergic transmission in the reward system's circuit. These are the events that are observed during the use of transcranial direct current stimulation through the skulls. Additionally, the regulation of dopamine release in the nucleus accumbens is carried out by the prefrontal cortex and, thereby, the response to the stimulating stimuli will be controlled (Feltenstein, & See, 2008).

Many studies have been carried out on animals and have shown that anodic stimulation increases the neuronal firing and cathodic stimulation leads to the opposite results (Bindman, Lippold, & Redfearn, 1964). Therefore, based on these pieces of evidence, it is assumed that the increase in both the activity of the right prefrontal region and in the left prefrontal region leads to a decrease in craving (Fregni, Liguori, Fecteau, Nische, Pascual-Leone, & Boggio, 2008). Dorsolateral pre-frontal cortex is one of the important regions of the prefrontal cortex, which is responsible for recognizing and designating actions, assessing the future outcomes of the current behavior and the predictive outcomes, and social control. Therefore, a possible mechanism that the stimulation of this area leads to a decrease in craving is that this stimulation increases social control; in other words, it increases the participants' ability to suppress their inclinations. Another explanation is that the prefrontal cortex group stimulation also stimulates the dopaminergic pathways. In particular, it is assumed that the diffusion of mesolimbic dopamine into striatum leads to the regulation of the substance received through the mediation of motivational processes. The dopaminergic modulation through cortical stimulation by this method has been confirmed in the study conducted by Nitsche, Lampe, Antal, Lietanz, Lang, Tergau (2006).

The results of this study also indicated that transcranial direct current stimulation has reduced depression in the three tramadol users. This finding is in line with other findings in this regard. Rigonatti et al. (2008) did a study on the effectiveness of transcranial direct current stimulation on depression and showed that the anodic stimulation of the prefrontal cortex in depressed subjects reduced the depressive symptoms where this reduction was equivalent to the effect of a 6-week fluoxetine. In seven studies conducted on the effectiveness of transcranial direct current stimulation in the reduction of depression, the significant effect of this method on the treatment of depression was proved (Vigod et al., 2014). Depression disorder is usually associated with activity changes and cortical stimulation, especially in prefrontal areas. Recent studies on the change of prefrontal cortex and establishment of a trade-off between the prefrontal cortex activities of the left and right hemispheres have proved the significant effects of transcranial direct current stimulation on the reduction of depressive disorder symptoms (Arul-Anandam & Loo, 2009). Transcranial direct current stimulation is a promising non-pharmacological intervention for the treatment of depression disorders. In a study conducted by Boggio et al. (2006), it has been shown that the dorsolateral prefrontal cortex stimulation

through transcranial direct current is associated with a mood change towards positive emotional states. Depression disorder is usually associated with activity changes and cortical stimulation, especially in prefrontal areas. Recent studies on the change of prefrontal cortex in the left and right hemispheres have revealed the significant effects of transcranial direct current stimulation on the reduction of depressive disorder symptoms (Boggio et al., 2006). The result of this study is consistent with that of the research conducted by Brunoni et al. regarding the enhancement of the cognitive function and pain relief by transcranial direct current stimulation. The anodic stimulation of the left dorsolateral prefrontal cortex (the region responsible for the treatment of depression) has led to the promotion of performance across a number of cognitive-behavioral tasks, the utilization of higher levels of cognitive functions, such as working memory, verbal influence, and programming ability (Brunoni et al., 2012).

However, the results on the effect of transcranial direct current stimulation on anxiety reduction in tramadol users showed that the anxiety scores in the post-test did not decrease significantly compared to the pre-test in all three participants. This finding is inconsistent with other research findings in this area. For example, in a review of previous studies, Pallanti & Bernardi (2009) concluded that the brain magnetic stimulation above the dorsolateral prefrontal cortex is useful in the treatment of anxiety disorders. Moreover, Edson et al. (2015) suggested the effectiveness of transcranial direct current stimulation in the reduction of anxiety in substance users. To explain this finding and the inconsistency, one can refer to the nature of the current research samples. Indeed, the tramadol users during the treatment process experience a higher incidence of insomnia, body pain, trembling, and other symptoms as a result of decreased craving. These symptoms naturally increase anxiety or at least do not decrease anxiety during the treatment.

In the end, it can be concluded that the results of the present study indicate that the right and left dorsolateral prefrontal cortex stimulation reduce the degree of craving and depression in tramadol users. Since a limited number of studies have been done on the effect of transcranial direct current stimulation on the reduction of craving in tramadol users, the results of this study can be used by experts and practitioners in the field of addiction treatment as a non-invasive method in the completion of therapeutic and treatment processes. This research suffered from some limitations, such as the self-report scale for data collection on tramadol craving, depression, and anxiety as well as the single-subject research design and the limited sample size, which make the generalizability of results a difficult task. According to the results and evidence of this study, it is recommended that this method be used by psychologists and psychiatrists in psychiatric clinics and psychiatric services and addiction treatment clinics as an intervention and prevention method.

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