Combination Therapy and Opioids: Effectiveness of Transcranial Direct-Current Stimulation (tDCS) and Emotion Regulation Training in Reducing Current Drug Craving

Behzad Rigi KOOTEH[a], Behrooz DOLATSHAHI[b], Masoud NOSRATABADI[c], Nour Mohammad BAKHSHANI[d], Abed MAHDAVI[e], Mousa Chakeri HAKAMI[a]

[a]Department of Clinical Psychology, Faculty of Behavioral Science, University of Social Welfare and Rehabilitation Science, Tehran, Iran

[b]Substance Abuse and Dependence Research Center, Department of Clinical Psychology, University of Social Welfare and Rehabilitation Science, Tehran, Iran

[c]University of Social Welfare and Rehabilitation Science, Paarand Specialized Center for Human Enhancement, Tehran, Iran

[d]Children and Adolescents' Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

[e]Department of Psychology and Educational Sciences, University of Tehran, Tehran, Iran

✦

—*ABSTRACT*—

Background: Background and objectives: Craving is the main symptom of addiction that is accompanied by dependence and relapse. The present study was aimed to compare the effectiveness of combined Transcranial Direct-Current Stimulation (tDCS) and emotion regulation training with that of separate tDCS and emotion regulation training in reducing current drug craving and thoughts and fantasies about drug use.

Methods and instruments: This was a quasi-experimental study with a pretest-posttest design and three intervention groups. The statistical population included all patients dependent on opioids in medium-term residential drug rehabilitation centers in Zahedan, Iran, in 2018-2019. From eight randomly selected centers, a total of 54 patients were selected based on inclusion and exclusion criteria, and randomly divided into three intervention groups. Data were gathered using the Personal Drug Use Questionnaire, Desires for Drug Questionnaire (DDQ), and Drug Use Thoughts, Fantasies, and Temptations Questionnaire. All analyses were performed using SPSS-16.

Address for correspondence:
Behrooz Dolatshahi, Assistant Professor
University of Social Welfare and Rehabilitation Science, Tehran, Iran
Tel.: +989122890655

Results: The Kruskal-Wallis test indicated significant differences between the three intervention groups in current drug craving and thoughts and fantasies about drug use (P ≤.001). In addition, examination of the mean rank showed that t significant decrease was higher for the combined tDCS and emotion regulation training group.

Conclusion: Addiction is very similar to other chronic disorders. Therefore, combined (integrated) therapies can have a very important role in treating addiction, especially in relapse prevention.

Keywords: tDCS, emotion regulation, craving, opioids.

INTRODUCTION

Craving is the main symptom of addiction and an important diagnostic factor in the definition of drug abuse disorder in the Diagnostic and Statistical Manual of Mental Disorders (1). Craving as a construct refers to continuing to use drugs despite the negative consequences (2, 3).

Based on the important role of craving in addiction relapse, it has been the focus of different previous studies. Emotion regulation and the related techniques had a significant role in psychological interventions aimed at reducing drug craving (2, 4-6).

Poor emotion regulation is regarded as an important factor in drug relapse (7-9). Therefore, emotion regulation training can lead to higher use of reappraisal in overcoming drug abuse that is more effective than the negative emotion regulation strategies, *i.e.*, acceptance or suppression (2).

Through improving the ability to handle negative and positive emotions, emotion regulation training can control most of the triggers of drug craving and reduce relapse (6). As a result, emotion regulation training leads to the modification of maladaptive emotion regulation strategies and negative emotions, and can provide an opportunity for direct or indirect reduction of drug cravings through the effective management of emotions (5).

Recently, some studies have focused on the effectiveness of Transcranial Direct-Current Stimulation (tDCS) in reducing cravings through changing the activity of the prefrontal cortex (10, 11). tDCS is a technique in which a continued and low electric current is delivered to the scalp. It is a non-invasive method for brain stimulation that is useful in modulation of cortical arousal and directing the human behavior and perception (12). tDCS, in fact, leads to reduction in drug cravings through inducing changes in dopaminergic neurotransmission in the brain and reducing cortical arousal (13). In addition, tDCS reduces drug craving through influencing the DLPFC area of the prefrontal cortex (14).

Although emotion regulation training and tDCS both can significantly reduce drug craving, research shows that addiction is very similar to other chronic disorders, and that it is very difficult to change the behaviors that force a patient to use drugs; therefore, combination therapy is considered an important method for relapse prevention in drug abuse (6). At the same time, although the anodal stimulation of the DLPFC area using the tDCS reduces craving, this reduction is only temporary, which can be due to a lack of insight or attentional biases toward symptoms of craving or may even increase the symptoms of craving (15).

Combination therapy for addiction can increase flexibility in the clients, improve their emotion regulation skills, and prevent relapses. Combining tDCS with other psychotherapies can lead to better therapeutic effects. In fact, the interactive effect of tDCS and cognitive intervention can improve the overall therapeutic results (16, 17).

Combination therapy can influence the specific symptoms of addiction. This is due to different combinations of therapies that improve the therapeutic effects through different mechanisms (18, 19).

Therefore, the goal of the present study is to answer the following question: is combined tDCS and emotion regulation training is more effective than each of these therapies separately in reducing current drug carving and thoughts and fantasies about drug use in opioid-dependent patients? ❑

METHODS

According to the study objective, "Examination of the Effectiveness of Combined Transcranial Direct-Current Stimulation (tDCS) and Emotion Regulation Training in Reducing Current Drug Craving and Thoughts and Fantasies about Drug Use in Patients Dependent on Opioids", a quasi-experimental design with pretest-posttest and three intervention groups was selected. The statistical population included all opioid-dependent patients in medium-term residential drug rehabilitation centers in Zahedan, Iran, in 2018-2019, who were treated in a two-month program. Among eight rehabilitation centers, eight centers were randomly selected. Then, A total of 54 patients were selected form these centers, using a purposeful sampling me-

Sessions	Contents
Session 1	Importance of stress, painful emotions and negative moods, and their role in creating a vicious cycle. Introduction of ART skills: 1) Emotional relaxation; 2) Breathing exercises for relaxation; 3) Non-judgmental awareness; 4) Acceptance and tolerance; 5) Compassionate self-support; 6) Analysis of emotions
Session 2	How to create emotion – Importance of brain structure in emotion – Benefits of emotions – Identification of emotion regulation strategies
Session 3	Review of the vicious cycle of activation of amygdala and muscle tension, and then activation of amygdala and respiratory tension. Getting rid of these vicious cycles through muscle and breathing relaxation trainings
Session 4	The vicious cycle of the brain under the name of negative thoughts and activation of amygdala – Role of thought suppression in intensification of negative thoughts – Techniques for experiencing emotions without judging or labeling them – Non-judgmental awareness
Session 5	Review of the chain of skills in relaxation – Non-judgmental awareness – Role of avoidance in the activation of amygdale
Session 6	1) Acceptance and tolerance as a goal; 2) Group members' reasons for acceptance and tolerance; 3) Observation of emotions as one's partner; 4) Resilience in different situations; 5) Temporary nature of emotions
Session 7	Review of emotional reframing – Review of each of the following emotions: stress, anger, fear, guilt, sorrow, hopelessness, and depression – Value of each emotion – The good times-bad times technique to improve client's resilience
Session 8	Review of the two essential parts of compensate self-support, *i.e.*, self-worth and involving with positive emotions – Practicing self-compassion. These practices were repeated at the end of the session.

TABLE 1. Summary of the contents of cognitive regulation training sessions based on Berking's model (2014)

thod and based on the inclusion and exclusion criteria, and randomly divided into three intervention groups. Each group consisted of 18 patients dependent on opioids. In the first group, subjects received eight sessions of combined tDCS and emotion regulation training; the emotion regulation training was based on the Berking's model (2014). In the second group, patients received eight sessions of tDCS. In the third group, subjects received eight sessions of emotion regulation training based on the Berking's model (2014). Overall, 10 subjects left during the course of study.

The tDCS was applied using a battery-powered electrical stimulator and a pair of electrodes (5×7 cm) at 2-mA intensity. In order to target the DLPFC, the anodal electrode was placed on the F4 region and the cathodal electrode was placed on the F3 region (determined based on the 10-20 System of Electrode Placement). The stimulation was provided for 45 minutes with a 30s rise and fall time with Neurostim2. Devices were provided by Medina Teb company (www.medinateb.com).

The desires for drug questionnaire (DDQ) has been designed to assess current drug craving. It was first designed to assess heroin dependence, but it was later used to assess dependence on other drugs too. The DDQ items are rated on a seven-point Likert-type scale ranging from 1 (totally disagree) to 7 (totally agree). Franken et al. reported a Cronbach's alpha of .85 for the total questionnaire, and alphas of .77, .80, and .75 for its subscales, respectively (20). In the present study, an alpha of .73 was found for the total questionnaire.

The drug use thoughts, fantasies, and temptations questionnaire was developed by Fadardi, Barerfan, and Ziaei in 2008 (21). It has 20 items designed to assess thoughts, fantasies, and temptations about drugs, which are rated on a six-point Likert-type scale ranging from 0 (totally true) to 5 (totally untrue). The questionnaire reliability using the Cronbach's alpha coefficient has been found to be .94. The questionnaire validity was assessed by correlating it with the situational confidence questionnaire (SCQ) developed by Annis and Graham (r=.53, p=.001) (22), the Mental Desire Scale (r=.48, p=.001), and the Positive and Negative Affect Schedule (PANAS) developed by Watson, Clark, and Tellegen in 1988 (23); the direction and magnitude of correlations indicated the questionnaire validity (21). In the present study, a Cronbach's alpha of .80 was found for the total questionnaire.

At the beginning of the study, the informed consent for completing the instruments and participating in the scheduled sessions was obtained from all participants. ❑

RESULTS

The mean age of participants was 29.93 years (SD=4.96). The youngest participant was 20 years old and the oldest 40. In terms of marital status, 18 (41.9%) participants were married and 25 (41.9%) single. In terms of education, 31 (72.1%) participants had a high school diploma, seven (16.3%) an associate degree, and five (11.6%) a bachelor's degree. In terms of the type of abused opioid, seven (16.3%) participants used hashish, 18 (41.9%) opium, 2 (4.7%) hero-

Variable	Skewness		Kurtosis	
	Statistic	Standard error	Statistic	Standard error
Age	0.035	0.36	-0.32	0.71
Marital status	-0.34	0.36	-1.97	0.71
Education	1.51	0.36	0.88	0.71
Abused opioid	0.39	0.36	-1.35	0.71
Method of use	0.74	0.36	-1.16	0.71
Reason for use	0.34	0.36	-1.05	0.71
Current craving	0.43	0.36	-0.090	-0.71
Craving thoughts	0.027	0.36	0.11	0.71

TABLE 2. Skewness and kurtosis values for the study variables

Group	Pretest			Posttest		
	N	Mean	SD	N	Mean	SD
Combined tDCS and emotion regulation training	15	53.40	9.54	15	28.53	6.11
tDCS	14	47.21	10.72	14	42.71	14.43
Emotion regulation training	14	46.64	10.96	14	36.42	13.51
Total	43	49.18	10.62	43	35.72	12.97

TABLE 3. Means and standard deviations of pretest and posttest scores for current drug craving in the three groups (combined therapy, tDCS, and emotion regulation training)

Group	Pretest			Posttest		
	Number	Mean	SD	Number	Mean	SD
Combined tDCS and emotion regulation training	15	61.26	18.87	15	35.46	14.79
tDCS	14	59.85	13.21	14	48.14	15.26
Emotion regulation training	14	65.64	15.95	14	46.71	12.03
Total	43	63.23	16.06	43	43.25	14.95

TABLE 4. Means and standard deviations of thoughts and fantasies about drug use at pretest and posttest for the three study groups (the combined tDCS and emotion regulation training group, tDCS group, and emotion regulation training group)

in, 7 (16.3%) shire, and 9 (20.9%) a combination of opioids. In terms of method of use, 25 (58.1%) participants smoked the drug, three (7%) injected it, eight (18.6%) took the drug orally, and seven (16.3%) used a combination of methods. In terms of the reason for drug use, 15 (34.9%) participants mentioned curiosity, five (11.6%) fatigue, 13 (30.2%) recreation, five (11.6%) life problems, and five (11.6%) psychological problems.

Skewness and kurtosis were calculated to assess the normality of data distribution, and results are summarized in Table 2.

According to results provided in Table 2, the skewness and kurtosis values for all variables range from -2 to +2, indicating a normal distribution of data.

The means and standard deviations of pretest and posttest scores for current drug craving and thoughts and fantasies about drug use in opioid-dependent patients are presented in Table 3.

According to the results presented in Table 3, the pretest mean score of current drug craving is 53.40 (SD=9.54), 47.21 (SD=10.72), and 46.64 (SD=10.96) for the combined tDCS and emotion regulation training group, tDCS group, and emotion regulation training group, respectively,

while the posttest mean score of current drug craving is 28.53 (SD=6.11), 42.71 (SD=14.43), and 36.42 (SD=13.51) for each of the three groups, respectively. Therefore, the combined tDCS and emotion regulation training group had a higher decrease in the mean posttest score of current drug craving than the two other groups.

Table 4 shows the means and standard deviations of thoughts and fantasies about drug use at pretest and posttest for opioid-dependent patients.

According to the results presented in Table 4, the pretest mean score of thoughts and fantasies about drug use is 61.26 (SD=18.87), 59.85 (SD=13.21), and 65.64 (SD=15.95) for the combined tDCS and emotion regulation training group, tDCS group, and emotion regulation training group, respectively, while the posttest

Box's M	12.67
F	1.96
DF1	6
DF2	3.870
Sig.	.068

TABLE 5. Results of Box's M test for homogeneity of variance-covariance matrices

Variable	Groups	Number	Mean rank
Current drug craving	Combined tDCS and emotion regulation training	15	14.57
	tDCS	14	29.11
	Emotion regulation training	14	22.86
	Total	43	
Thoughts and fantasies about drug use	Combined tDCS and emotion regulation training	15	15.47
	tDCS	14	26.36
	Emotion regulation training	14	24.64
	Total	43	

TABLE 6. Mean ranks of current drug craving and thoughts and fantasies about drug use scores for the three groups

mean score of thoughts and fantasies about drug use is 35.46 (SD=14.79), 48.14 (SD=15.26), and 46.71 (SD=12.03) for each of the three groups, respectively. Therefore, the combined tDCS and emotion regulation training group had a higher decrease in the mean posttest score of thoughts and fantasies about drug use than the two other groups.

Given that a pretest-posttest design was used, and that we aimed to compare the means of several groups influenced by the independent variable and control the effects of intervening variables, we needed to use covariance analysis. Before conducting the multivariate covariance analysis, the assumption of homogeneity of variance and covariance should be tested. This assumption was tested using the Box's M test. Results are presented in Table 5.

As shown in Table 5, the Box's M test is significant (P ≥.05), indicating that the equal variances assumption is violated; therefore, we used a nonparametric test (the Kruskal–Wallis test) instead of multivariate covariance. Results are presented in Tables 6 and 7.

Table 6 shows the mean ranks of current drug craving and thoughts and fantasies about drug use scores for the three groups. The highest mean rank of current drug craving is for the tDCS group, and the lowest mean rank for the combined group.

According to the results presented in Table 7, significant differences were found between the three groups in current drug craving (Chi square = 9.82, p ≤ .001, df = 2) and thoughts and fantasies about drug use (Chi square = 6.37, p ≤ .001, df = 2). In addition, comparison of the mean ranks shows that the significant decrease is higher for the combined tDCS and emotion regulation training group than the two other groups. ❏

Variable	Statistic	
	Chi-Square	9.82
Current drug craving	Df	2
	Sig.	.007
Thoughts and fantasies about drug use	Chi-Square	6.37
	Df	2
	Sig.	.041

TABLE 7. Results of the Kruskal–Wallis test in terms of the effectiveness of combined therapy, tDCS, and emotion regulation training in reducing drug use thoughts and fantasies

DISCUSSION AND CONCLUSION

The goal of the present study was to examine the effectiveness of a combined Transcranial Direct-Current Stimulation (tDCS) and emotion regulation training intervention in reducing current drug craving and thoughts and fantasies about drug use among patients dependent on

opioids. The results showed that combined tDCS and emotion regulation training was more effective than each intervention separately in reducing current drug craving and thoughts and fantasies about drug use. This finding is in line with those of Powers et al (2018), Brunoni et al (2014), Ditye et al (2012) ((17-19), and Bajbouj *et al* (2017) (24).

McElrath and Joseph (2009) emphasized that today addiction was an important health issue, and the current treatments for it, including detoxification or psychological and pharmacological therapies, were hardly leading to stable results due to strong cravings related to drug use; therefore, this problem required integrated therapies (25). In addition, Brunoni et al concluded, in 2014, that combining different therapies could influence specific symptoms of addiction. They also maintained that the therapeutic effects of combination therapy were due to different mechanisms that improved overall therapeutic results (18). Moreover, Ditye et al maintained that, by combining different therapies, more sessions could be designed for patients, which could increase the chance of having long-term therapeutic effects (19).

Combination therapy through combining psychological and neuroscience interventions can significantly improve emotion regulation skills and flexibility of drug-dependent patients. In addition, this therapeutic path can lead to a greater recovery and fewer relapses in patients with substance abuse disorder (26).

Combination therapy approach to treating addiction considers it as a biological and behavioral disorder. On the other hand, experience has revealed that addiction results from an interaction between biological predisposition, life experiences, and environmental factors (27).

In addition, the biopsychosocial model of addiction more clearly shows the importance of combination therapy. This model indicates that biological, psychological, and sociocultural factors have a role in drug abuse, and therefore, they should be all considered in prevention and treatment approaches. This model was introduced as a response to the individual-biological model of addiction. In the traditional model of addiction, that was more supported by medical scientists, addiction was often regarded as a re-current disease with a biological and genetic etiology (28).

Complementary or integrated therapies for addiction increase therapy cost-effectiveness, making it more likely that patients continue the treatment and learn the networking skills necessary for long-term recovery (25). However, one-dimensional therapies often cannot treat addiction adequately, and many experts in this domain support the integration of different therapeutic elements to treat addiction. ❏

CONCLUSION

Combination therapy for addiction can improve interdisciplinary cooperation, so that integrated therapies could be designed for addiction using knowledge from different domains of treating addiction, and this was, craving could be reduced in patients more effectively. The present study provided a new model for treating addiction that emphasized the importance of the biopsychosocial model. In our study, the chance of relapse in opioid-dependent patients was reduced through diminishing their cravings by using a combined therapy. This combination of therapies could help to address food cravings or cravings for other abused drugs. The current study had some limitations, including the fact that the sample comprised only male subjects and there was no follow-up period, which could influence results in the long term. ❏

REFERENCES

1. **American Psychiatric Association.** Diagnostic and statistical manual of mental disorders: DSM-5, 5th ed, 2013.
2. **Szasz P, Szentagota IA, Hofmann S.** Effects of emotion regulation strategies on smoking craving, attentional bias, and task persistence. *Behaviour Research and Therapy* 2012;50:333-340.
3. **Baker TB, Piper ME, McCarthy DE, et al.** Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychological Review* 2004;1:33-51.
4. **Beadman M, Das RK, Freeman TP, et al.** A comparison of emotion regulation strategies in response to cravingcognitions: Effects on smoking behavior, craving and affect in dependent smokers. *Behavior Research and Therapy* 2015;69:29-39.
5. **Kober K.** Emotion regulation in Substance Use Disorders. In: J. J. Gross (Ed), *Handbook of emotion regulation, 2nd ed*, New York, NY: Guilford, 2014, pp 428-446.
6. **Ahmadi Gh, Sohrabi F, Borjali A, et al.** Effectiveness of emotion regulation training on mindfulness and craving in soldiers with opioid use disorder. *Journal of military Psychology* 2015;22:5-21.
7. **Aldao A, Nolen-Hoeksema S, Schweizer S.** Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clin Psychol Rev* 2010;2:217-237.
8. **Garnefski N, Kraaij V, Spinhoven P.** Negative life events, cognitive emotion regulation and emotional problems. *Personality and Individual Differences* 2001;8:1311-1327.
9. **Gross JJ.** The emerging field of emotion regulation: An integrative review. *Review of General Psychology* 1998;2:271-299.
10. **Kroczek AM, Häußinger FB, Rohe V, et al.** Effects of transcranial direct current stimulation on craving, heart-rate variability and prefrontal hemodynamics during smoking cue exposure. *Drug and Alcohol Dependence* 2016;168:123-127.
11. **Conti CL, Moscon JA, Fregni F, et al.** Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction. *Int J Neuropsychopharmacol* 2014;9:1465-1475.
12. **Zaghi S, Acar M, Hultgren B, et al.** Noninvasive brain stimulation with low intensity electrical currents. *The Neuroscientist* 2009;11:289-307.
13. **Yalcin BM, Unal M, Pirdal H, Karaban TM.** Effect of an anger management and stress control program on smoking cessation: A randomized controlled trial. *Journal of American Board Family Medicine* 2014;5:645-660.
14. **Mook Choi K, Scott D, Lim S.** The modulating effects of brain stimulation on emotion regulation and decision-making. *Neuropsychiatric Electrophysiology* 2016;4:2-24.
15. **Shahbabaie A, Golesorkhi1 M, Zamanian B, et al.** State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. *International Journal of Neuro psychopharmacology* 2014;17:1591-1598.
16. **McHugh RK, Hearon B, Otto MW.** Cognitive-Behavioral Therapy for Substance Use Disorders. *Psychiatr Clin North Am* 2011;3:511-525.
17. **Powers A, et al.** Effects of Combining a Brief Cognitive Intervention with Transcranial Direct Current Stimulation on Pain Tolerance: A Randomized Controlled Pilot Study. *Pain Medicine* 2018;4:677-685.
18. **Brunoni A, et al.** Differential improvement in depressive Symptoms for DCS alone and combined with Pharmacotherapy: an exploratory analysis from The Sertraline vs. Electrical Current Therapy for Treating Depression Clinical Study. *International Journal of Neuropsychopharmacology* 2014;17:53-61.
19. **Ditye T, Jacobson l, Walsh V, Lavidor M.** Modulating behavioral inhibition by tDCS combined with cognitive training. *Exp Brain Res* 2012;219:363-368.
20. **Franken IHA, Hendricks VM, Van den Brink W.** Initial validation of two opiate craving questionnaires the Obsessive Compulsives Drug Use Scale and Desires for Drug Questionnaire. *Addiction Behaviors* 2002;27:675-685.
21. **Fadardi JS, Ziaee SS, Barerfan Z.** The Persian Post-Detoxification Craving and Temptation Scale. Unpublished Manual, Mashhad, 2008.
22. **Annis HM, Graham JM.** Situational Confidence Questionnaire: User'sGuide. Unpublished manuscript, Addiction Research Foundation, Toronto, Ontario, 1988.
23. **Watson D, Clark LA, Tellegen A.** Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol.* 1988;6:1063-1070.
24. **Bajbouj M, Aust S, Spies J, et al.** Psychotherapy Plus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder-study design and methodology of a multicenter double-blind randomized placebo-controlled trial. *European Archives of Psychiatry and Clinical Neuroscience* 2018:1-12.
25. **McElrath K, Joseph H.** Medication-Assisted Treatment (MAT) for Opioid Addiction: Introduction to the Special Issue. *Substance Use & Misuse* 2018;2:177-180.
26. **Hoseiny H, Jadidi M, Habiballah Nataj L, Saberi-Zafarghandi MB.** The Effect of Methadone-Maintenance Therapy with and Without Interactive Treatment on Improving Emotion-Regulation Strategies and Resilience among Opiate-Dependent Clients. *Int J High Risk Behav Addict* 2015;1:1-7.
27. **Stocker S.** Drug Addiction Treatment Conference Emphasizes Combining Therapies, 1998. https://archives.drugabuse.gov/news-events/ /nida-notes/1998/07/drug-addiction-treatment-conference-emphasizes-combining-therapies. NIH (National Institute On Drug Abuse).
28. **Borrell-Carrió F, Suchman A, Epstein R.** The Biopsychosocial Model 25 Years Later: Principles, Practice, and Scientific Inquiry. *Ann Fam Med* 2004;6:576-582.