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Original Article

The Effectiveness of Topiramate in the Treatment of Amphetamine and Methamphetamine Use Disorder: A Randomized Controlled Trial

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Abstract

Objective: Limited studies have yet evaluated the effectiveness of topiramate in the treatment of amphetamine and methamphetamine addiction. Therefore, the aim of this study was to investigate the effectiveness of topiramate in the treatment of patients with this disorder.
Methods: In this randomized, double-blind, placebo-controlled clinical trial, 52 patients with amphetamine and methamphetamine use disorder, within the age range of 16-60 years, were randomly divided into an intervention group (n = 26) and a placebo group (n = 26). The intervention group was treated with topiramate tablets with a starting dose of 50 mg, which was gradually increased to the target dose of 200 mg. The control group was treated with placebo. The duration of drug intervention in this clinical trial was 12 weeks, and all participants were evaluated before the intervention and 2, 4, 6, 8, 10, and 12 weeks after beginning the intervention. The Beck Depression Inventory, drug use temptation questionnaire, urine test, and side effects questionnaire were used as outcome measures to assess the patients. The data were analyzed using chi-square, independent t-test, and analysis of variance with repeated measurements.
Results: There was no significant difference between the intervention and placebo groups in depression at the beginning of the treatment and at the 4^{th}, 8^{th}, and 12^{th} weeks after the intervention ($P > 0.05$). The urine test also showed no significant difference between the two groups at any of the evaluation stages ($P > 0.05$). Although there was no significant difference between the two groups in the drug use temptation results at the beginning and the 2^{nd}, 4^{th} and 6^{th} weeks ($P > 0.05$), the level of drug temptation in the intervention group was significantly lower than the placebo group in the 8^{th}, 10^{th}, and 12^{th} weeks ($P < 0.05$).
Conclusion: Topiramate can be effective in reducing the desire to use amphetamine and methamphetamine. However, further studies are needed to confirm these results.

Key words: *Amphetamine; Drug Use Disorder; Methamphetamine; Randomized Controlled Trial; Topiramate*

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Addiction is a chronic and progressive brain disease that has deep psychological, social, economic, and physical effects. Drug abuse is increasing especially among the young generation (1). Based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), substance abuse disorder is characterized by cognitive, behavioral, and physiological symptoms, such that people continue to use substance despite significant problems associated with its misuse. In addition, the DSM-5 suggests that substance abuse disorder creates an infrastructural change in the brain circuits that may persist after the drug addiction (2). Currently, there are at least 1,300 types of stimulants, among which amphetamine compounds and their products being the most consumed in the world (3, 4). Amphetamines and methamphetamines are industrial substances and both groups have similar structures and functions. These materials are particularly important because of the side effects caused by their misuse (5, 6).

Amphetamine derivatives were initially used for the treatment of nasal congestion and asthma. However, after the discovery of their hallucinogenic effects, the trafficking and abuse of these substances spread rapidly all over the world, such that now amphetamine and its derivatives including methamphetamine is the second most trafficked drug after cannabis (7). Amphetamines and methamphetamines have a common mechanism, both causing the release of monoamine neurotransmitters, including dopamine, serotonin, norepinephrine (8). It has been proven that methamphetamine affects the neuronal network related to depression, and there is evidence based on the medullary effect of the serotonin system on the stimulating effects of methamphetamine (9). Chronic use of methamphetamine often results in severe mental disorder or methamphetamine-related psychosis similar to schizophrenia (7). The cognitive impairment caused by methamphetamine is its neurotoxicity, which leads to psychotic disorders, depression, and suicidal behavior (10). Some of the withdrawal symptoms of these drugs include depressed mood, anhedonia, excitability, anxiety, fatigue, drowsiness, reduced attention, and increased violence (7). Addiction to amphetamine and methamphetamine is associated with serious health problems such as cardiac arrhythmia, stroke, high blood pressure, hyperthermia, and central nervous system dysfunction which reflects changes in the function and effectiveness of neurotransmitters such as dopamine, serotonin, and glutamate (11). Unfortunately, no effective treatment for dependence on stimulants has been identified to date (12, 13).

Despite the progress that has been made in the treatment of amphetamines and methamphetamines, the relapse to uncontrollable use is one of the existing problems that has caused this situation to remain a problem (5). In order to treat the use of stimulants, drug treatment is one of the methods of choice in treating this category of patients; however, the available medications in this field are not completely effective, and treatment failures can occur in this treatment method (5, 7). One of the drugs that is probably effective in the treatment of amphetamine and methamphetamine use disorder is topiramate. After promising findings in a proof-of-concept study of topiramate in alcoholics (14), as well as a randomized, placebo-controlled, multi-center trial of topiramate for alcohol dependence (15), topiramate was considered a suitable candidate for the treatment of stimulant abuse. In a placebo-controlled pilot study, topiramate effectively reduced cocaine use after receiving a full dose of topiramate for eight weeks (16). In another randomized controlled trial, topiramate was effective as an anticonvulsant with GABAergic properties. Topiramate has been shown to be effective in the treatment of craving for alcohol (14), nicotine (17), cocaine (16), and eating disorders (18). However, its potential to facilitate abstinence from methamphetamine is less clear. A study conducted on rats using conditioned place preference model for methamphetamines did not show any effect of topiramate (19), but other models of substance-seeking behavior have not been investigated. However, in one clinical case, topiramate treatment proved successful in promoting abstinence in a user of 3,4-methylenedioxymethamphetamine, and its euphoria was blocked (20).

Stimulant use disorder contributes to a significant burden of disease worldwide, yet evidence-based treatment options are limited. So far, limited studies have evaluated the efficacy of this drug in the treatment of amphetamine and methamphetamine addiction. Given the high prevalence of addiction to amphetamines and methamphetamines and the importance of paying attention to the treatment methods used for this category of patients, this study aimed to investigate the effectiveness of topiramate in the treatment of patients with this disorder.

Materials and Methods

This study was a randomized, double-blind, placebo-controlled clinical trial. The research was confirmed by the Medical Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code: IR.AJUMS.REC.HGOLESTAN.1400.015), and this trial was registered in the Iranian Registry of Clinical Trials with the code of IRCT20160417027437N.

Participants

The study participants were selected from the people who were referred to the addiction clinic of Golestan Hospital (Ahvaz, Iran) in 2022. These individuals were diagnosed with amphetamine and methamphetamine use disorder by a psychiatrist based on the diagnostic criteria of the DSM-5. The inclusion criteria were as follows: being within the age range of 16-60 years, singing the inform consent form, not using drugs other than amphetamine and methamphetamine, having no history of major psychiatric disorders (e.g., schizophrenia, autism, and bipolar disorder), exhibiting no thoughts of self-harm or harm to

others, having no underlying medical diseases, having no history of receiving psychiatric drugs in the past three months, having no history of allergy to topiramate, not using medications that interact with topiramate (such as other carbonic anhydrase inhibitors, anticonvulsants), and not being pregnant or breastfeeding. In addition, the exclusion criteria were non-completion of the research method and non-compliance with medication.

Based on the purpose of the research and considering a power of 90% ($\beta = 0.1$), $\alpha = 0.05$, $s = 0.3$, $d = 0.2$ (21), the sample size was calculated to be 60 subjects. Therefore, 60 patients with amphetamine and methamphetamine use disorder were enrolled in this trial based on the above-mentioned criteria and were randomly divided into either the intervention or placebo group. It should be noted that the main reasons for exclusion were the participants' inability to meet the study requirements, dependence on other psychoactive substances in addition to amphetamine and methamphetamine (e.g., nicotine or marijuana), history of significant psychiatric or other medical problems, and failure to return for full screening assessments. After explaining the research to the patients and obtaining written informed consent from each participant, random allocation was performed based on the random block permutation method, so that both the therapist and the patient were blinded to the intervention conditions. Among these 60 people, four subjects from each group did not complete the research procedure, and the final analysis was conducted on 52 participants (26 patients in each group).

Trial procedure

The intervention group was treated with topiramate tablets with a starting dose of 50 mg per day, and the medication dose was increased weekly by 50 mg to the target dose of 200 mg. On the other hand, the control group was treated with a placebo with the same shape, smell, taste and usage method as topiramate. It is important to note that both the project manager and the patients were unaware of which group received the drug or the placebo. The duration of drug intervention in this clinical trial was 12 weeks and all participants were evaluated before the intervention and at 2, 4, 6, 8, 10 and 12 weeks after beginning the intervention. Indeed, the participants were evaluated with drug temptation scores at the beginning of treatment and every two weeks, as well as amphetamine and methamphetamine urine tests. Further, all participants were assessed with the Beck Depression Inventory at the beginning of treatment and at the 4th, 8th and 12th weeks. In this study, the side effects questionnaire was also employed to evaluate the side effects caused by the use of topiramate in the 2^{nd}, 4^{th}, 6^{th}, 10^{th}, and 12^{th} weeks.

Tools

Beck Depression Inventory: The second edition of the Beck Depression Inventory, measuring 21 symptoms of depression, are included in this tool, and the respondents were asked to rate the severity of these symptoms on a scale from 0 to 3. In Iran, this questionnaire was administered to a sample of 94 Iranians, and the results indicated an alpha coefficient of 0.91, a correlation coefficient of 0.89 between binomials, and a retest coefficient of 0.94 after one week (22).

Drug use temptation questionnaire: This is a questionnaire to measure the temptation to use drugs after quitting, which consists of 20 items that are used to measure the frequency of thoughts and fantasies related to drugs and the intensity of the temptation to use drugs. The scoring of the questionnaire is in the form of a 6-point Likert scale (completely true = 5 and not true at all = 0). The validity and reliability of this tool has been confirmed in the Iranian population (23).

Statistical analysis

The normality of the data was checked using the Kolmogorov-Smirnov test. Independent t test, chi-square test, and analysis of variance test with repeated measurements were used to analyze the data. All the tests were done using SPSS software version 25. A significance level of 0.05 was considered.

Results

In this research, 52 patients with an age range of 16-60 years (M ± SD: 31.79 ± 9.10 years) participated and were divided into two groups including the intervention group and the placebo group, each having 26 participants (n = 26). These two groups were compared. Figure 1 shows the stages of enrollment, allocation, follow-up and final analysis of patients in the study. Notably, no significant difference was found between the groups in terms of drop-outs (P = 0.98).

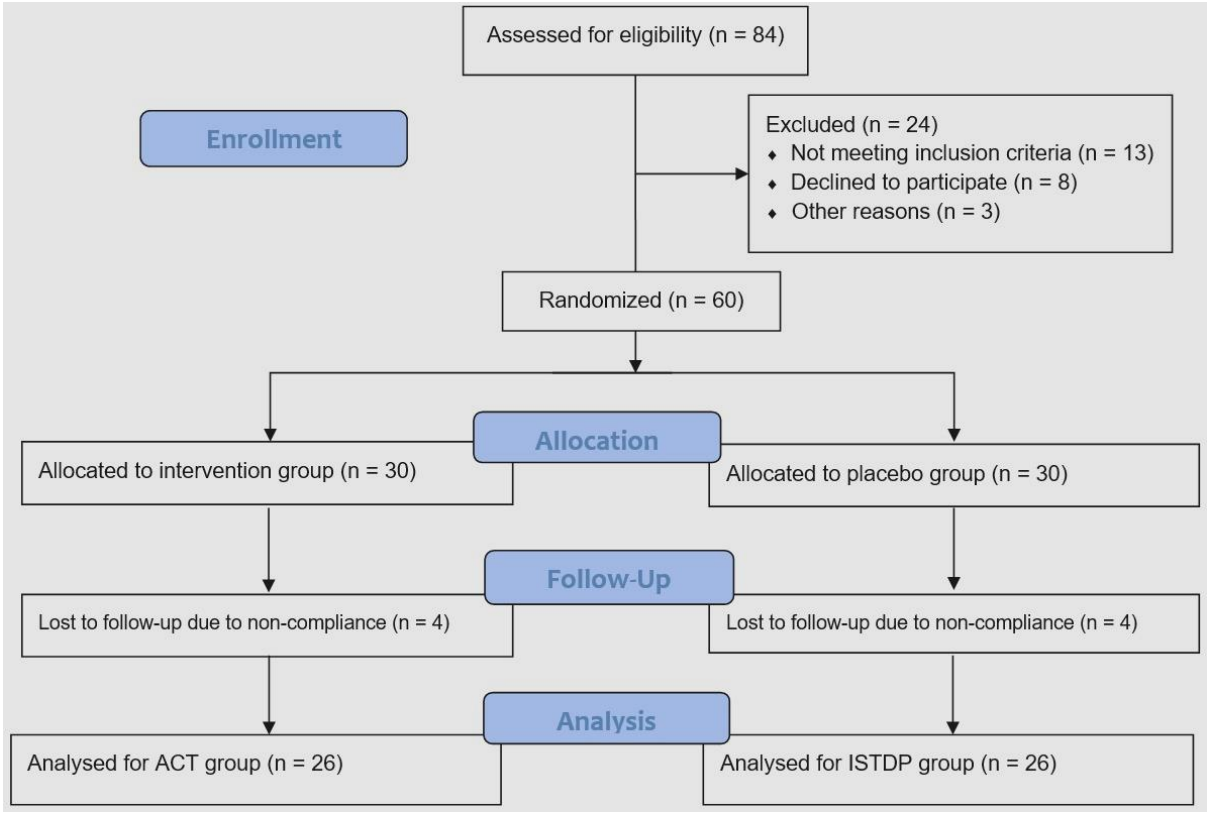

Figure 1. Consort Flow Diagram for a Randomized Controlled Trial to Assess the Effects of Topiramate in Patients with Amphetamine and Methamphetamine Use Disorder

Based on Table 1, the chi-square test was used to measure the significance of the difference between the groups in terms of education variables, substance abuse history, previous history of minor psychiatric illness, employment status, and gender. The results indicated that there were no significant differences between the groups in terms of these demographic data ($P > 0.05$). The independent t-test showed that there was no significant difference between the two groups in terms of age and duration of use ($P > 0.05$). Before using this test, the assumption of normality was confirmed with the Kolmogorov-Smirnov test, and the homogeneity of variances was confirmed using Levine's test.

Table 1. Demographics Characteristics of Patients with Amphetamine and Methamphetamine Use Disorder Participated in the Research

Variable		Intervention group (n = 26)	Placebo group (n = 26)	Total	P-value
Gender: n (%)	Male	23 (88.5)	22 (11.5)	45 (86.5)	0.68[+]
	Female	3 (84.6)	4 (15.4)	7 (13.5)	
Age (year), mean ± SD		31.54 ± 10.45	32.04 ± 7.72	31.79 ± 9.10	0.74[#]
Employment: n (%)	Employment	8(30.8)	7(26.9)	15(28.8)	0.76[+]
	Unemployed	18(69.2)	19(73.1)	37(71.2)	
Education: n (%)	Diploma and sub-diploma	16(61.5)	15(57.7)	31(59.6)	0.94[+]
	Bachelor	5(19.2)	5(19.2)	10(19.2)	
	Master	4(15.4)	4(15.4)	8(15.4)	
	Doctorate	1(3.8)	2(7.7)	3(5.8)	
History of minor psychiatric illness	Yes	8(30.8)	7(26.9)	15(28.8)	0.76[+]
	No	18(69.2)	19(73.1)	37(71.2)	
Duration of use (year), mean ± SD		5.30(4.14)	6.37(3.21)	6.02(3.3)	0.30[#]

[+]Chi-Square Test; [#]Independent T-Test

The mean ± SD scores of the Beck Depression Inventory for two groups are depicted in Table 2. As shown, no significant difference was found between the two groups at baseline (t = 0.34, P = 0.73). Repeated measures ANOVA showed no significant difference between the two protocols as indicated by the effect of group and time (F = 0.61, P = 0.45). Post hoc comparisons revealed that there was no statistically significant difference in depression between the intervention and control groups (P > 0.05) based on the Beck Depression Inventory scores at the beginning of treatment and 4th, 8th, and 12th weeks after treatment.

Table 2. Post Hoc Comparisons of Depression Results Based on the Beck Depression Inventory in Two Groups at the Beginning of Visit and 4th, 8th, and 12th Weeks After Treatment

Assessment time	Intervention group (n = 26)	Placebo group (n = 26)	P-value	t
At the beginning	24.69 ± 7.12	24.10 ± 5.24	0.73	0.34
4th week	24.18 ± 7.05	24.15 ± 4.89	0.98	0.01
8th week	21.55 ± 6.31	22.08 ± 7.11	0.77	0.28
12th week	20.26 ± 6.04	21.15 ± 6.64	0.61	0.50

The results were shown as mean ± standard deviation.

The mean ± SD scores of Drug Use Temptation Questionnaire for two groups are depicted in Table 3. As shown, no significant difference was found between the two groups at baseline (t = 0.10, P = 0.91). However, repeated measures ANOVA showed that there were significant effects for group (F = 4.28, P = 0.04), time (F = 5.81, P = 0.02), and group × time interaction (F = 44.16, P < 0.01). In the intervention group, post hoc comparisons revealed a significant decrease in the drug use temptation scores in the 12th week. In contrast, in the placebo group, post hoc comparisons revealed a significant increase in drug use temptation scores beginning from the 8th week. The mean change from baseline to the 12th week was significant between the intervention (-5.04 ± 1.10) and placebo (19.54 ± 5.23) groups (mean difference = 24.58, t = 5.78, P < 0.01, Cohen's d = 6.50). Furthermore, there was no statistically significant difference between the two groups at the beginning and weeks 2, 4 and 6 (P > 0.05). However, in the 8th, 10th, and 12th weeks, the intensity of temptation to use drugs according to the drug use temptation questionnaire in the intervention group was significantly milder than the placebo group (P < 0.05) (Table 3).

Table 3. Post Hoc Comparisons of Drug Use Temptation Results in Two Groups at the Beginning of Visit and in the 2nd, 4th, 6th, 8th, 10th, and 12th Weeks

Assessment time	Intervention group (n = 26)	Placebo group (n = 26)	P-value	t
At the beginning	47.11 ± 8.70	46.85 ± 9.24	0.91	0.10
2nd week	47.97 ± 8.27	47.01 ± 8.95	0.68	0.40
4th week	49.52 ± 10.23	49.02 ± 9.58	0.85	0.18
6th week	49.06 ± 9.89	48.94 ± 9.47	0.96	0.04
8th week	45.31 ± 8.91	61.58 ± 12.98	< 0.01	5.26
10th week	44.63 ± 7.75	64.22 ± 13.16	< 0.01	6.54
12th week	42.07 ± 7.43	66.39 ± 13.44	< 0.01	8.07

The results were shown as mean ± standard deviation.

According to Table 4, no statistically significant difference (P > 0.05) between the intervention and placebo groups were observed in the results of the urine test at the beginning of visit and at 2nd, 4th, 6th, 8th, 10th, and 12th weeks after treatment.

Table 4. Comparison of Urine Test Results Using Chi-Square Test in Two Groups at First Visit and 2nd, 4th, 6th, 8th, 10th, and 12th Weeks

Variable		Intervention group (n = 26)	Placebo group (n = 26)	Total	P-value
At the beginning n (%)	Positive	23 (88.5)	21 (88.5)	44 (84.6)	0.97
	Negative	3 (1.5)	5 (9.5)	8 (15.4)	
2nd weeks: n (%)	Positive	23 (88.5)	19 (73.1)	42 (88.8)	0.95
	Negative	3 (1.5)	7 (26.9)	10 (19.2)	
4th weeks: n (%)	Positive	21 (80.5)	19 (73.1)	40 (76.9)	0.97
	Negative	5 (9.5)	7 (26.9)	12 (23.1)	
6th weeks: n (%)	Positive	23 (88.5)	20 (76.9)	43 (82.7)	0.96
	Negative	3 (1.5)	6 (23.1)	9 (17.3)	
8th weeks: n (%)	Positive	22 (84.6)	19 (73.1)	41 (78.8)	0.96
	Negative	4 (15.4)	7 (26.9)	11 (21.2)	
10th weeks: n (%)	Positive	22 (84.6)	18 (69.2)	40 (76.9)	0.95
	Negative	4 (15.4)	8 (30.8)	12 (23.1)	
12th weeks: n (%)	Positive	23 (88.5)	19 (73.1)	42 (80.8)	0.95
	Negative	3 (1.5)	7 (26.9)	10 (19.2)	

As shown in Table 5, the most common observed complication was dizziness, and the frequency distribution of possible complications did not have a statistically significant difference between the two groups ($P > 0.05$).

Table 5. Comparison of Potential Side Effects in Two Groups

Side effect	Intervention group (n = 26)	Placebo group (n = 26)	P-value
No Side effects, n (%)	4 (15.4)	1 (3.8)	
Headache, n (%)	3 (11.5)	2 (7.7)	
Weight Loss, n (%)	2 (7.7)	4 (15.4)	
Anorexia, n (%)	1 (3.8)	0 (0.0)	
Strabismus, n (%)	2 (7.7)	3 (11.5)	
Paresthesia, n (%)	1 (3.8)	2 (7.7)	
Speech Problem, n (%)	1 (3.8)	1 (3.8)	0.919
Psychomotor Disorder, n (%)	3 (11.5)	1 (3.8)	
Drowsiness, n (%)	2 (7.7)	2 (7.7)	
Nausea, n (%)	1 (3.8)	2 (7.7)	
Aggression, n (%)	1 (3.8)	1 (3.8)	
Fatigue, n (%)	1 (3.8)	1 (3.8)	
Dizziness, n (%)	4 (15.4)	6 (26.1)	

Discussion

In this research, we attempted to assess the therapeutic effects of topiramate on individuals with amphetamine and methamphetamine use disorder through a randomized controlled trial. The results showed that there was no significant difference between the intervention and placebo group regarding depressive symptoms at the beginning of treatment and at the 4th, 8th, and 12th weeks. Furthermore, the urine test has no significant difference in any of the evaluation stages including the first visit, 2nd, 4th, 6th, 8th, 10th, and 12th weeks. Drug use temptation results at the beginning of the study and at the 2nd, 4th, and 6th weeks were not significantly different between the two groups. However, in the 8th, 10th, and 12th weeks, the intensity of temptation for drugs in the intervention group was significantly milder than the placebo group. In addition, no serious side effects were observed in any of the groups. Topiramate demonstrated effectiveness in reducing methamphetamine and amphetamine use temptation in people who had abstained at the beginning of the trial. Given that these findings were observed in a subset of the total cohort, topiramate could be considered for relapse prevention rather than simply targeting methamphetamine and amphetamine use in current users. Therefore, the use of topiramate in preventing temptation in people who have stopped using methamphetamine and amphetamine should be further investigated.

The effect of topiramate, a mild carbonic anhydrase inhibitor, on the metabolism and excretion of methamphetamine should be taken into account when interpreting urinalysis results. Urinary filtration of methamphetamine is increased by acidification of urine and inhibited by alkalization. However, carbonic anhydrase inhibition simultaneously makes the blood acidic and the urine alkaline. An increase in urinary pH is anticipated to decrease methamphetamine excretion and increase methamphetamine blood levels. On the other hand, a decrease in plasma pH is likely to accelerate the metabolism of methamphetamine. Therefore, the unusual pharmacokinetic effect of topiramate on methamphetamine has important implications for chronic treatment. In fact, while users consume less methamphetamine, urine samples may underestimate the extent of this reduction (24).

To date, no drug has been approved as an effective treatment for methamphetamine and amphetamine dependence. Nonetheless, topiramate has attracted considerable attention as a treatment for alcohol and stimulant dependence (25). Topiramate was first designed as an anticonvulsant drug, and then it was found that it can be useful in the treatment of a variety of mental disorders and neurological complications, including migraine prevention (26), weight reduction (27), bulimia (28), binge eating (18), and alcohol dependence disorder (25). In addition, recently its effectiveness in the treatment of stimulant substance use disorder has been discussed (29). Considering the need for expanding the previous clinical trials and the findings related to the mechanisms of topiramate action, we were prompted to conduct this study.

Topiramate reduces the dopaminergic activity of the corticolimbic system by facilitating the γ-Aminobutyric acid (GABA)ergic action on the non-benzodiazepine part of GABA-A receptors (30). It also diminishes substance-seeking behaviors by an antagonistic effect on the activity of Glutamatergic receptors (31). It has been hypothesized that anticonvulsants may help treat stimulant use disorder by enhancing inhibitory GABA neurotransmission, thereby preventing the dopamine increase induced by cocaine use (29). Conflicting evidence regarding the effectiveness of anticonvulsants for the treatment of stimulant use disorder has been reported in the literature (32-34). In a systematic review and meta-analysis, Chan *et al*. evaluated the use of anticonvulsants to treat methamphetamine or amphetamine use disorder and reported no significant effects on abstinence or treatment retention outcomes (35). Another study involving 140 methamphetamine users showed that topiramate reduced the average weekly methamphetamine urine test as well as the severity of dependence in the study participants between 6 and 12 weeks; however, topiramate could not increase abstinence from methamphetamine (32). This result is in contrast with the studies conducted in the treatment of cocaine dependence compared to placebo (36), which indicated a significant positive effect of topiramate (300mg/day). While topiramate failed to increase the duration of abstinence in participants, those participants with negative urinalysis exhibited a longer duration of abstinence (32). Although the structure of the present research has similarities with the aforementioned research, the structural nature of cocaine and its difference in absorption with methamphetamine and amphetamine make comparison difficult. Singh *et al*. conducted a systematic review and meta-analysis that included five randomized peer-reviewed trials evaluating the use of topiramate in participants with cocaine dependence or cocaine use disorder. The study reported no significant difference for durability between the group treated with topiramate and the control group (29).

A meta-analysis study also found that the effectiveness of topiramate for cocaine dependence lacks clinical evidence and is not useful for first-line treatment and deserves to be used as an adjunctive therapy (37). However, a clinical trial found that a 10-week administration of topiramate in increasing doses was effective in reducing cravings in methamphetamine users (24).

Limitation

The use of self-report assessment for sensitive issues often leads to presenting a favorable social image by participants. Thus, self-reporting is associated with potential bias. The present study did not have a follow-up phase for assessing the long-term effectiveness of the treatment. Furthermore, in this study, the moderate therapeutic effect of topiramate was observed only on the temptation to use the drug. Therefore, conducting a

controlled trial with a larger sample size, testing higher doses, is needed to reach more definitive conclusions. There are several limitations to this study. First, one of the important limitations is the small number of samples and the short time of the study. Additionally, the method used to determine the effective dose of drugs can also be one of the limitations. Furthermore, the research did not consider the evaluation of family and social supports in the patients, despite the great impact of this factor on the treatment and recovery process. In fact, it should be noted that this confounding factor existed in both groups. It is recommended that future studies be conducted with larger sample sizes and in a longer period of time than the present one. The effect of different doses of topiramate on patients with amphetamine and methamphetamine addiction can be evaluated. Additionally, in future studies, it is suggested to investigate the effectiveness of other drugs along with topiramate and its different doses. It is also possible to check the effectiveness of topiramate on other substances.

Conclusion

So far, few studies have investigated the effectiveness of topiramate in the treatment of amphetamine and methamphetamine addiction. However,the results of the present study showed that topiramate can be effective in reducing the desire to consume stimulants and is useful in improving treatment results in drug users. Therefore, this drug can be used in the management of patients with amphetamine and methamphetamine use disorder, aiding in controlling their craving and improving their dependence symptoms. However, further studies with appropriate designs, large sample sizes, more objective outcome measures, and longer follow-ups are needed to draw definitive conclusions in this regard.

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Conflict of Interest

None.

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