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Original Article

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Does Topiramate Add-On Enhance the Response to the MATRIX Program in Individuals with Methamphetamine Use Disorder? A Double-Blinded Randomized Placebo-Controlled Trial

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Abstract

Background: Methamphetamine dependence significantly impacts individuals and society. Treating methamphetamine use disorder is challenging due to limited evidence on effective pharmacotherapies and their interaction with nonpharmacologic interventions. This study evaluated the efficacy of topiramate compared to placebo in treating methamphetamine use disorder among participants in a Matrix program.

Methods: Participants were recruited from the Addiction Center of Iran Psychiatric Hospital between January 2020 and June 2023 and randomly assigned to receive either topiramate or a placebo for 12 weeks, alongside Matrix program sessions. Blinding was maintained for participants, personnel, outcome assessors, and statisticians. Main outcomes included craving, desire to use, positive urine amphetamine toxicology rates, and depression severity. Craving was assessed using the Visual Analog Scale (VAS) and the Substance Craving Questionnaire–brief (SCQ-B). The desire to use was evaluated with the Addiction Severity Index (ASI), while depression severity was measured using the Beck Depression Inventory. Data analysis utilized IBM SPSS Statistics® 20.0, employing various statistical tests for comparison.

Results: Both groups exhibited improvement in craving as per VAS scores (p=0.007), with greater reduction in the topiramate group; however, no significant difference was found between groups (p=0.06). The negative urine toxicology rates showed no significant difference (Hazard ratio=1.15, 95% CI: 0.75, 1.78). Depression scores decreased in both groups without significant between-group differences (p=0.78).

Conclusion: The findings do not support the efficacy of topiramate in enhancing outcomes within a Matrix program for individuals with methamphetamine use disorder.

Keywords: Methamphetamine, Topiramate, Visual analog scale

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Introduction

Methamphetamine is a highly addictive and powerful central nervous system psychostimulant that induces a feeling of intense euphoria and well-being (1,2). Due to its strong pleasurable effects, methamphetamine is abused worldwide, and Methamphetamine Use Disorder (MUD) is a worldwide health problem (1). Methamphetamine activates the reward system of the brain and produces effects that are highly reinforcing, which can lead to abuse and dependence (2).

Stimulant use is associated with elevated mortality, increased incidence of HIV (Human Immunodeficiency Virus) and hepatitis C infection, poor mental health (suicidality, psychosis, depression, and violence), and increased risk of cardiovascular events (3). Long-term Methamphetamine exposure can induce neurotoxic effects through various pathways such as oxidative stress, mitochondrial functional impairment, endoplasmic reticulum stress, the activation of astrocytes and microglial cells, axonal transport barriers, autophagy, and apoptosis.

Methamphetamine use and harms are rising rapidly, and management of patients with MUD and problematic methamphetamine use is challenging, with no clearly established best approach (4). Treatments need to address various aspects of this complicated disorder including the psychological and social aspects, as well as the neurobiological adverse events of the disorder (4).

The Matrix Model is a 16-week intensive treatment program for drug addiction that was originally developed in response to the cocaine epidemic of the 1980s (5,6). It has been refined over the past 30 years to integrate cognitive behavioral therapy, contingency management, motivational interviewing, 12 steps facilitation, and other evidence-based treatments (7). The Methamphetamine Treatment Project (MTP) was the largest randomized clinical trial to examine different treatments for methamphetamine dependence. The project took place between 1999 and 2001 and was designed to examine the differences between the Matrix Model and Treatment As Usual (TAU). It was found that the participants in the Matrix Model were more likely to remain in treatment, were 27% more likely to complete treatment, and were 31% more likely to have meth-free urine screens than individuals who received usual treatments. Its efficacy has been replicated in many studies (6,8).

Although there is no FDA (Food and Drug Administration) -approved medication for MUD, several promising agents are targets of further research (5-7,9-11). Most pharmacological interventions for treating substance use disorders aim to modulate other non-dopamine reward systems in the brain, such as gamma-aminobutyric acid (GABA), serotonin, and opioid pathways. These agents decrease the amount of catecholamines available and therefore reduce the stimulating effect of methamphetamine (2,9,12-14). A systematic review of pharmacological interventions for methamphetamine dependence found that the most consistent positive effects have been observed with dopamine agonists, naltrexone, and topiramate (9).

Topiramate, a second-generation anticonvulsant agent is one of the medications that has shown promise in the treatment of stimulant use disorders (9,15-17). Its mechanism of action involves several pathways, including the gamma-aminobutyric acid (GABA) pathway and the glutamatergic pathway (5-7). Topiramate stimulates GABA-A receptor activity at brain non-benzodiazepine receptor sites and reduces glutamate activity at both AMPA and kainate receptors (11,13,18). These activities may potentially decrease the neurotoxicity of methamphetamine in the brain along with its shown effects in increasing abstinence rates, improving cognition, and reducing relapse rates (19,20). According to one study, the administration of 100-200 *mg* topiramate was associated with a small non-significant reduction in positive mood and reinforcement, and an increase in MA-induced stimulation. This suggests a beneficial role in decreasing MA-related reinforcement (21). Topiramate has also been reported to improve physiological processes involved in drug dependence and addiction behavior by modulating gene expression (22). Although some studies have approached this question, their results have been conflicting and authors have suggested that trials using larger doses and using real-life conditions including concomitant non-pharmacological

interventions may be necessary (9).

Therefore, we aimed to assess whether topiramate enhances the effectiveness of the Matrix model in terms of reducing cravings, depressive symptoms, and abstinence among patients with MUD.

Materials and Methods

Design

This study was a randomized controlled trial with a 1:1 allocation ratio. The intervention group received topiramate treatment for 12 weeks, while the comparison group received a placebo treatment. Both groups were enrolled in a Matrix program. The results presented herein are the findings of the first 12 weeks of the study. The results after the discontinuation will be published when the recruitment and data collection are completed.

Participants

The results of 30 patients who were recruited from the Addiction Center of Iran Psychiatric Hospital between January 2020 and June 2023 are reported in this study. For the primary outcome and a superiority hypothesis, the calculated sample size for the complete Randomized-Controlled Trial (RCT) was determined as 28 participants per group given a power of 90% ($\beta = 0.1$), $\alpha = 0.05$, $s = 0.3$, $d = 0.2$.

Inclusion and exclusion criteria

Inclusion criteria comprised a diagnosis of MUD based on DSM-5 (Diagnostic and Statistical Manual) criteria and aged 18-65 years with at least one urine sample during the screening period. Exclusion criteria included dependence on other illicit drugs (except methamphetamine, nicotine, and methadone), concomitant use of carbamazepine, phenytoin, or acetazolamide, history of significant psychiatric illness requiring continued medication use, pregnancy or breastfeeding, kidney stones or failure, failure to return for complete assessments, and intolerance to a daily Topiramate dose of at least 50 *mg*.

Study procedures

The Screening Phase

After obtaining the informed consent, the participants entered a screening phase for two weeks. During this period, the participants underwent a psychiatric diagnostic interview, clinical examination, ECG (Electrocardiography), electrolyte and liver enzyme level testing, complete blood count, urine pregnancy test (for women), and urine toxicology test.

The Matrix Model

All the individuals participated in a Matrix program. The program consists of relapse prevention groups, education groups, social support groups, individual counseling, and urine and breath testing delivered in a structured manner over a 16-week period. The treatment is a directive, non-confrontational approach that focuses on current issues and behavior change.

Randomization and Medications

An independent researcher randomly allocated eligible participants to treatment *vs.* placebo group by block randomization method with random block size (2,4,8) using Random Allocation Software version 1.0.0. The generated codes with the associated pills (topiramate or placebo) were inserted into opaque sealed envelopes. The participants were randomly assigned to receive either topiramate or a placebo for 12 weeks, along with participation in Matrix program sessions. Topiramate (Arya pharmaceutical company) was started with a dose of 25 *mg* and gradually increased to a dose of 300 *mg* over a period of 45 days, or to a maximum tolerated dose below 300 *mg*. The control group received a placebo with an identical appearance to topiramate and produced by the same company. After the study period, topiramate and placebo were gradually discontinued over four weeks, and follow-up visits continued on a monthly basis until two months after the end of the treatment.

Outcome Assessment

The outcomes which consisted of urine methamphetamine toxicology tests as a measure of abstinence, SCQ-brief (Substance craving questionnaire) and Visual Analogue Scale (VAS) for craving, and Beck's Depression Inventory (BDI) for the severity of depression were evaluated at baseline and in four-week intervals during the 12 weeks of the study. The groups

were also assessed at the beginning and on the 12th week for the severity of addiction-related impairments using the Addiction Severity Index (ASI).

Craving

The SCQ-Brief was utilized to assess craving behavior. This questionnaire comprises 10 questions that focus on factors associated with the desire to use, and the responses are measured on a 7-point visual scale ranging from "Strongly Disagree" to "Strongly Agree". The final score obtained from the average scores of the different items indicates the willingness to consume. The reliability for this 8-item scale was adequate (Cronbach's α=0.84; M=460.9, SD=167.4) (23).

VAS is a tool for describing the intensity of subjective feelings by individuals which is very easily understandable without needing any specific training or education. One place where it is commonly employed is reporting subjective substance craving in individuals with substance abuse, where it is valid and reliable (24).

The Addiction Severity Index

Both groups were evaluated in semi-structured interviews by a psychiatrist using the Addiction Severity Index (ASI)-composite score in the first and 12th weeks to assess for seven potential problem areas associated with substance abuse. These areas include medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. The ASI has been validated and deemed reliable with a Cronbach's alpha of for use in patients with substance use problems.

The most frequently used summary methods are the Interviewer Severity Rating (ISR) and the Composite Score (CS). The psychiatric composite score of the ASI has been shown to predict suicide and psychiatric care after inpatient residential treatment for Substance Use Disorders (SUDs) (25). It may also be used to assess whether the patient would benefit from another treatment. The ASI composite score is a widely used addiction assessment tool with strong scientific reliability and validity in various settings (25,26).

Ethical Approval

This research was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the participants, and the necessary arrangements were made to provide preventive and therapeutic facilities. The participants were informed that their information would not be disclosed.

Statistical Analysis

The data in the study were analyzed using several statistical methods. The IBM SPSS Statistics® 20.0 software was utilized for data analysis. The following statistical tests were used for data analysis:

The qualitative variables were compared between groups using the GEE model or the chi-square test. Repeated measure analysis was used for quantitative data. Fischer's exact test was used to compare nominal variables. Cox Regression method was utilized to compare the changes in relation to time between the two groups from the time of randomization to the end of the study. A two-sided p-value<0.05 was considered significant in all the tests.

Results

Participants' characteristics

In the current study, the participants consisted of 28 men (93%) and 2 women, with an average age of 36.33 years in the topiramate group and 32.6 years in the placebo group. The demographic characteristics and outcomes of the study at the study baseline are listed in table 1. The participants' characteristics and outcome measures were comparable in the two study groups at the beginning of the study.

70 individuals with methamphetamine abuse disorder were screened, 47 of which were randomized to enroll in this study. 17 of the participants were lost to follow up due mainly to COVID-19 infection and replacement of the attending psychologist of the study. However, the study groups have been comparable regarding each one's share of this number (Figure 1).

The Urine Toxicology

More patients in the placebo group had a negative

Table 1. Baseline characteristics of the study participants

Characteristics		Placebo group N=15 Number (percentage) Mean (standard deviation)	Topiramate group N=15 Mean (standard deviation) Number (percentage)
Age		32.60(8.56)	36.33(8.97)
Gender (male%)		15(100%)	13(86%)
Education	High school or below high school	3(20%)	6(40%)
	diploma	9(60%)	3(20%)
	Post-graduate and bachelor's degree	3(20%)	6(40%)
Age at the onset of abuse		24(7.01)	27.07(8.15)
VAS		3.13(3.39)	4.27(2.91)
Urine toxicology (positive rate)		10(66.7%)	12(80%)
Severity of depression (Beck Depression Inventory)		12.87(8.12)	10.60(6.87)
SCQ-Brief		22.46(7.01)	22.73(5.54)
ASI		0.22(0.07)	0.25(0.07)

Visual Analogue Scale--VAS

Stimulant Craving Questionnaire--SCQ

Table 2. Number of the patients in the study arms with negative urine toxicology for methamphetamines.

Urine toxicology measurement time-point	Number of the negative cases in the placebo group (n=15)	Number of the negative cases in the topiramate group (n=15)	P-value
Beginning of the study (0) (Before the intervention)	5	3	0.680
Week 1	4	6	0.700
Week 4	9	11	0.700
Week 8	10	10	1.000
Week 12	12	14	0.590

urine test at the beginning of the study. The proportion of individuals with negative urine toxicology test results was compared in the study arms throughout the study duration (Table 2). The overall change in the rate of negative urine toxicology was not significantly different between study arms [Hazard ratio=1.15 (95% CI: 0.75, 1.78)].

The VAS for Craving

At the beginning of the study, the average VAS score for craving was comparable between the two drug groups. The mean VAS score decreased significantly in both groups during the study (p-value=0.007). Also, the mean increase from baseline in VAS score of the topiramate group was larger than the increase in

Table 3. Comparison of the two study groups in terms of severity of addiction according to VAS at different times of the study

VAS measurement time-point	Placebo group Mean (95% confidence interval)	Topiramate group Mean (95% confidence interval)	p-value
Beginning of the study (0) (Before the intervention)	3.13 (1.48-4.77)	4.26 (2.62-5.91)	0.660
Week 1	3.06 (1.67-4.45)	3.86 (2.47-5.25)	0.920
Week 4	3.20 (1.82-4.57)	3.133 (1.75-4.51)	0.980
Week 8	3.26 (2.09-4.44)	1.867 (0.69-3.04)	0.183
Week 12	2.40 (1.29-3.50)	1.133 (0.03-2.23)	0.661

Table 4. Comparison of the effect of topiramate and placebo on the SCQ-BRIEF scale

SCQ-BRIEF Measurement time-point	Placebo group Mean (Standard deviation)	Topiramate group Mean (Standard deviation)
Beginning of the study (0) (Before the intervention)	22.46(7.01)	22.73(5.54)
Week 1	21.86(6.19)	21.20(6.24)
Week 4	21.20(7.59)	19.26(5.50)
Week 8	20.46(7.38)	19.13(6.01)
Week 12	18.60(3.73)	17.93(3.45)

Figure 2. Comparison of the effect of topiramate and placebo on the SCQ-BRIEF scale

Table 5. Substance use scores during the beginning and at end of the study in the topiramate and placebo groups

Measurement time-point	Placebo Mean (95%CI)	Topiramate Mean (95%CI)
First week after the start of the intervention	0.24(0.18,0.26)	0.25(0.21,0.29)
12th week after the start of the intervention	1.17(-0.35,2.7)	0.13(-1.4,1.6)

the placebo group. However, no significant difference was observed between the two groups in terms of VAS score changes in the general linear model (p-value =0.062, f-value =2.90) (Table 3).

The Severity of Depression

At the beginning of the study, the average depression score in the topiramate group was slightly lower than the placebo group. The depression scores had a trend towards decreasing in both groups during the study period (p-value<0.01, F=32.66). However, in the general linear models, no significant difference was observed between the drug groups in terms of the reduction in depression severity (p-value=0.782, F=0.07).

The SCQ-BRIEF scale

The study groups were comparable in terms of

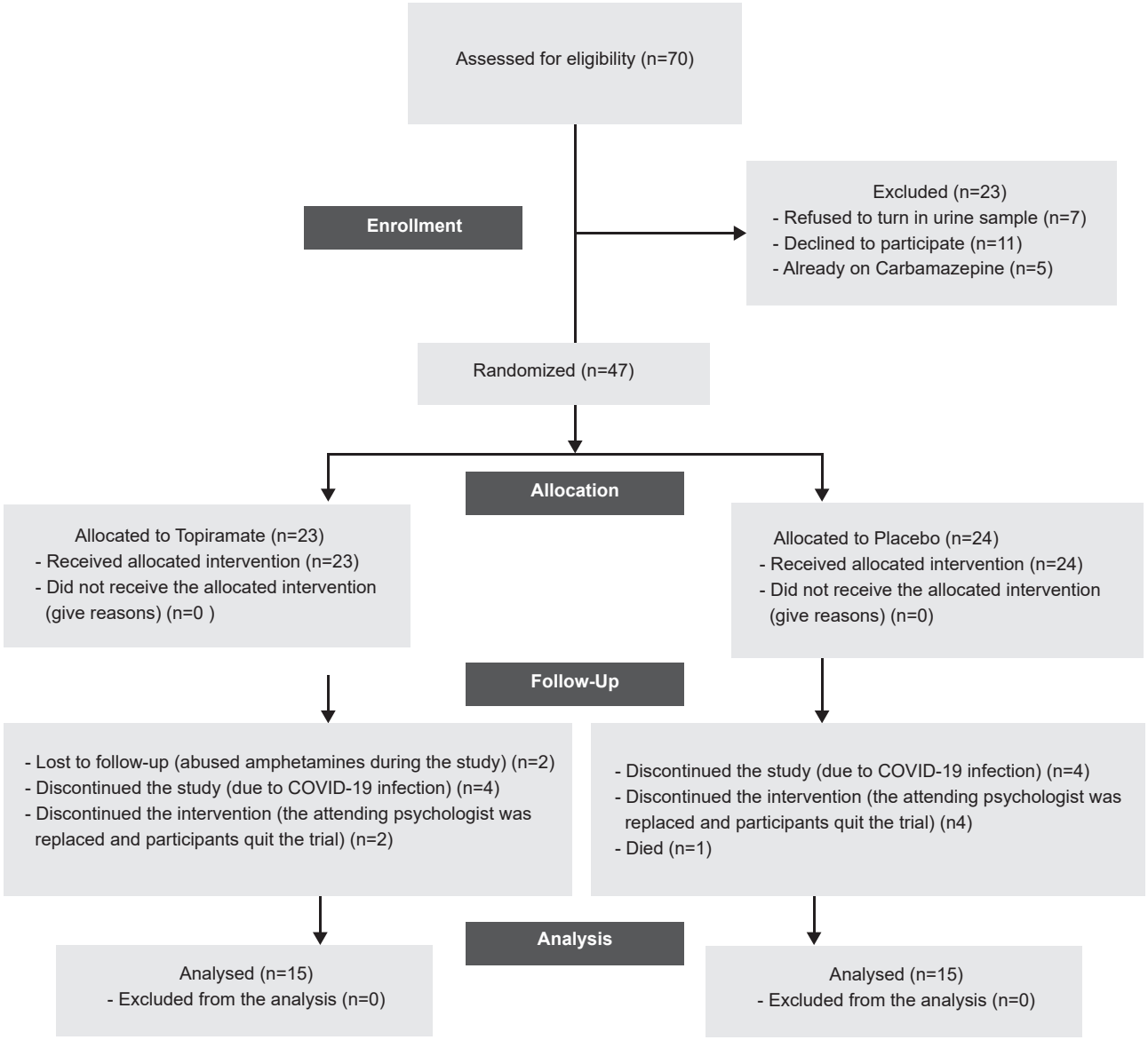

Figure 1. The CONSORT diagram shows the number of participants at each stage of the study and the reasons for incomplete follow-ups.

craving at the beginning of the study. During the study, the mean score decreased significantly compared to baseline in both groups (p-value=0.021, f-value=2.89). But the medication group showed no significant effect on this reduction (p-value=0.514, f-value=0.4) (Table 4, Figure 2).

The Substance Use Scale

As shown in the table 5, the groups were similar regarding their mean scores on substance use scale on week one. On the 12th week, the mean score decreased in the topiramate group, while it increased in the placebo group. However, this change in substance use score in the topiramate group was not significantly different from placebo [p-value=0.321, MD=1.10 (95% CI: -1.10, 3.25)].

The ASI Scale

The average ASI scores at the end of the study in the topiramate group was 1.66 (±0.53), and in the placebo group, it was 1.58(±0.51). The groups were not significantly different (p-value=0.952).

Discussion

It was found that although both groups showed significant improvement in the study outcomes,

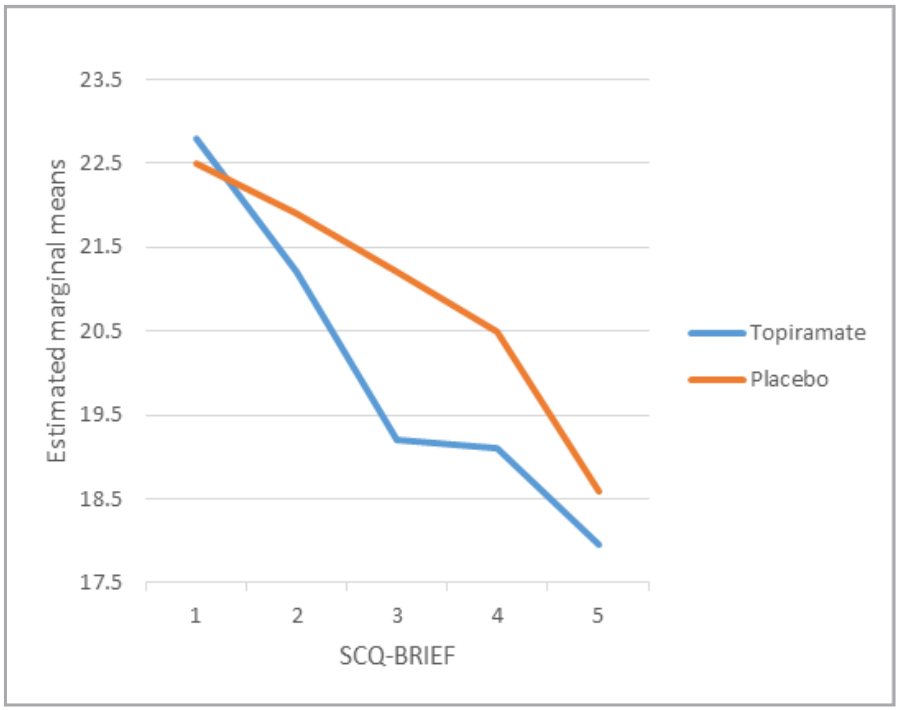

Figure 2. Comparison of the effect of topiramate and placebo on the SCQ-BRIEF scale.

individuals in the topiramate group revealed no significantly superior improvement to the placebo group. This means that topiramate showed no additional benefit to the effects of Matrix.

Topiramate is an antiepileptic and anticonvulsant drug commonly used for the treatment of migraine, alcohol dependence, borderline personality disorder, and post-traumatic stress disorder (27-29). Two potential mechanisms underlie the effects of topiramate in stimulant abuse. Topiramate plays a pivotal role by enhancing GABAergic function through a non-benzodiazepine site on the gamma-aminobutyric acid-A (GABAA) receptor, leading to the depression of cortico-mesolimbic dopaminergic activity (30). Studies in animal models have shown that the pharmacological augmentation of GABA concentration effectively inhibits cocaine self-administration (30). Simultaneously, topiramate antagonizes glutaminergic activity, primarily through its impact on kainate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (31). Experimental findings have demonstrated that blocking glutamate, mediated by the kainate receptor, reduces the reinstatement of drug-seeking behavior (32). Anticonvulsants with GABAergic properties, including topiramate, have shown some benefits in addressing cravings associated with various substances including alcohol (33), nicotine (34), and cocaine (35) use disorders, as well as in the treatment of eating disorders (36). The multifaceted action of topiramate, encompassing both GABAergic facilitation and glutaminergic antagonism, underscores its potential as a therapeutic agent in managing stimulant abuse.

The efficacy of topiramate is controversial for MUD. Two studies suggest that topiramate may be beneficial for the treatment of methamphetamine dependence and reducing relapse rates (15,16). In contrast, one other study indicates that it may enhance the positive subjective effects of methamphetamine and another study reported no difference (17).

Two RCTs assessed the efficacy of 200 *mg*/d topiramate in comparison with placebo in the treatment of methamphetamine dependence; One study used fixed 200 *mg* doses (16), whereas in the other one, flexible dosing was utilized with a maximum of 200 *mg*/d based on the patients' tolerability (17). While the latter study detected no between-group difference in their primary outcome using the intention-to-treat analysis, the former study revealed significant improvement in

all the study outcomes. In this study, variable doses were used based on the patients' tolerance with a maximum dose of 300 *mg*/d, and no additional effect was detected to the routine Matrix program in the topiramate group regarding the primary outcomes. This variation in dosage in contrast to excluding patients with intolerability in this study may have resulted in underestimation of the treatment effects. In other words, the study by Rezaei *et al* excluded the outcomes of the patients who discontinued the treatment due to the topiramate adverse effects from their analysis, whereas the maximum tolerable dose was used in the current study, and the treatment continued. In the Elkashef *et al* study and present study, the results of patients who tolerate suboptimal doses of topiramate were analyzed (16,17). Another important difference in the study by Perugi G *et al* was the exclusion of the participants with ADHD who may have different treatment response profiles compared to neurotypicals (37). This point may have also contributed to the larger and more consistent effect sizes across all their study outcomes.

Also, neither of the previous studies included a concomitant psychosocial intervention. Given the large effects reported for the effectiveness of the Matrix program (38-41), larger sample sizes might be required to detect the additional benefit from topiramate. Moreover, the sample size was smaller than both of these two studies yielding a lower power. Overall, the treatment choice for the patients with MUD is a complex decision and multiple studies suggest that the treatment should be tailored to the individual patients given their heterogeneity in treatment response (40,42,43). Moreover, current evidence suggests that some combinations of non-pharmacological interventions like the Matrix model with tailored medications may lead to superior outcomes compared to pharmacotherapy alone (9,41). The present study utilized a randomized placebo-controlled trial design in which the participants, personnel, outcome assessors, and statisticians were all blinded to the assigned treatments. These factors increase the internal validity of this study. We also implemented a multimodal treatment approach, which included the Matrix program as well as adjunctive treatment with topiramate at a dose tailored to the individual patients. This approach is more similar to the real-life treatment plans for addiction, making the study more applicable to clinical practice and improving its external validity. Additionally, the use of topiramate as an adjunctive treatment to accepted non-pharmacological interventions is a suggested and understudied approach, and our study provides important information about its potential benefits for individuals with MUD.

Limitations

There are limitations that should be considered when interpreting the results of this study. Firstly, there was a high rate of attrition, which could under- or overestimate the effects of topiramate based on the outcomes of the drop-outs. An intention-to-treat analysis would have partly solved this problem. However, the outcomes of the dropouts could not be assessed.

Although the optimal dosage of topiramate for treating MUD is not yet established, this study used a flexible dosing based on the patients' tolerability, thus we may not have used adequate doses of topiramate to achieve the desired effects in all the patients. On the other hand, while this flexibility can reduce the internal validity of this study, it can increase the external validity by resembling the actual clinical circumstances where tolerability to medication and dosing varies among the patients.

Importantly, the sample size of the current report was relatively small, with the data from only 30 participants. As such, the study may not have had enough statistical power to detect a significant difference, even if a clinically meaningful effect was present.

Although randomization decreases the effects of confounding factors, it may not completely balance the confounding factors in smaller studies. Ideally, we would assess and adjust for the predictors of topiramate response or predictors of successful abstinence, such as comorbidities like ADHD and personality disorders, which could affect the results. Lastly, the enrolled patients may not be representative of the general population with MUD, especially

women who were a small proportion of the patients in this study.

Future research could address the limitations of this study by improving participant retention rates and adherence to the treatment regimen, exploring a range of topiramate doses, increasing sample sizes, enrolling a more diverse population of the participants, and assessing and adjusting for potential predictors of topiramate response and successful abstinence. These measures could improve the generalizability and statistical power of future studies and identify potential subgroups of the patients who may benefit more from topiramate treatment. Studies with a factorial design for potential predictors of response to topiramate may also be helpful given the complex nature of methamphetamine dependence.

Conclusion

The results demonstrated no significant improvement with tolerability-adjusted doses of topiramate compared to placebo as adjunctive pharmacotherapy for individuals with MUD in a Matrix program. According to the current study, there is still no sufficient evidence on the effectiveness of topiramate in individuals with MUD in a Matrix program.

Acknowledgement

This project was approved by the Iran University of Medical Sciences Ethics Review Board under the reference numbers IR.IUMS.REC.1398.1031on 2020-01-13 and IR.IUMS.FMD.REC.1399.374. The Protocol was registered under the reference number IRCT20180929041167N1 in the Iranian Registry of Clinical Trials.

Conflict of Interest

There was no conflict of interest in this manuscript.

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