Original Article

Effect of add-on valproate on craving in methamphetamine depended patients: A randomized trial

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Abstract

Background: Methamphetamine dependence lead to the compulsive use, loss of control, and social and occupational dysfunctions. This study aimed to compare the effect of valproate in reducing the craving in methamphetamine dependents.

Materials and Methods: This is a randomized, double-blind, controlled clinical trial on 40 men of 18–40 years old referred to Noor Hospital during December 2012–September 2013 in Isfahan, Iran. The subjects participated in matrix program and randomly were divided into two groups of valproate and placebo. A 4-months program of intervention with valproate or placebo was arranged for each group. The rate of craving to methamphetamine and positive methamphetamine urine tests were evaluated in both groups every 2 weeks using cocaine craving questionnaire-brief (CCQ-Brief) and urine test. After the 4 months (active treatment with valproate and placebo), the drug was tapered and discontinued within 10 days, and patients were introduced to self-help groups and monitored regularly on a weekly basis over another 3 months. Collected data were analyzed with SPSS 20 using analysis of covariance repeated measure, Chi-square, and *t*-test.

Results: CCQ score of the intervention group was significantly less than the placebo group ($P < 0.001$), except on weeks 1, 3, and 28. The ratio of a positive urine test for methamphetamine in the intervention group was significantly lower than the control group in all screenings except weeks 3 and 28.

Conclusion: Adding valproate to matrix program in the treatment of methamphetamine dependence showed significant effect on the reduction of the craving to methamphetamine.

Key Words: Matrix program, methamphetamine, valproate

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INTRODUCTION

Amphetamine or phenyl-isopropylamine was made as a drug in Germany in 1886 for the 1st time. First cases of the amphetamine abuse were reported in 1936, and the first epidemic of amphetamine abuse was observed in Japan after the Second World War and subsequently was spread in other countries and in 80th in Western countries.[1]

The evidence have shown that methamphetamine abuse has widely increased in Iran in recent years, and currently, methamphetamine is second drug of

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abusing in this country and the age of consumers declined from 25–29 years on 2000 to 10–19 in recent years.[2-5]

Methamphetamine dependence is a recurrent and chronic disorder leading to loss of behavioral control, social, and occupational dysfunctions.[6,7] Stopping the use of methamphetamine in dependent persons leads to the irregular brain reward system and forming the withdrawal signs as dysphoria, depression, anxiety, mood swings, and sleep and concentration disturbances and these problems cause to reuse and recur.[1,8,9] Although methamphetamine dependence has been considered as a health and social problem since many years ago, but the study on pharmacological treatments are at the early stages[10,11] and psychosocial treatments are included main part of treatment.[12]

The main current treatment of methamphetamine dependence is matrix method which is a combination of cognitive, behavioral, and psychological approaches improving the strategies of the substance re-consumption which is not suitable for the patients with cognitive disorders, paranoid ideation, and other psychotic symptoms or mood swings.[12,13] There is no Food and Drug Administration approved pharmacological treatment to methamphetamine dependence heretofore.[14]

Behavioral sensitization induced by substances is related to psychopathology, neurotoxicity, drug dependency, and craving and controlling of the behavioral sensitization reduce subsequent craving to the substances.[15-17] A survey conducted on mice shown that manipulation of central GABAergic system reduce the behavioral sensitization via reducing dopamine turn over in the mesolimbic system.[18] Other studies shown that strengthening of GABAergic neurotransmitter system blocks the extracellular dopamine increases induced by methamphetamine, leading to undermine the reward system and behavioral sensitization of this substance.[19-21]

Valproate is a GABAergic drug via inhibition of gamma-aminobutyric acid (GABA) transaminase and stimulation of manufacturing and releasing of GABA.[22-24] In a survey conducted on mice has shown that the prescription of the multiple doses of valproate reduce the behavioral sensitization due to methamphetamine consumption in a dose dependent manner.[25]

This study designed to study the possible effect of valproate in the reduction of craving to methamphetamine in human samples.

MATERIALS AND METHODS

This study was a randomized controlled double-blind clinical trial, including 54 methamphetamine dependent males of 18–40 years who had referred to addiction treatment center of Noor Hospital in Isfahan, Iran for treating and attending matrix sessions from January 2012 to October 2013 using a simple random sampling method. All of them with a sever mood disorder, serious suicide thoughts, psychosis, unstable medical condition, intolerable or life-threatening complications of Valproat (such as obesity, liver problems, and hepatitis), another substance abuse during the study excluded from study.

We used a simple random sampling method for selecting participants from the patients who met the inclusion criteria and had a desire to participate in the study The 54 selected individuals were allocated into two groups of either intervention or placebo using a random allocation method.

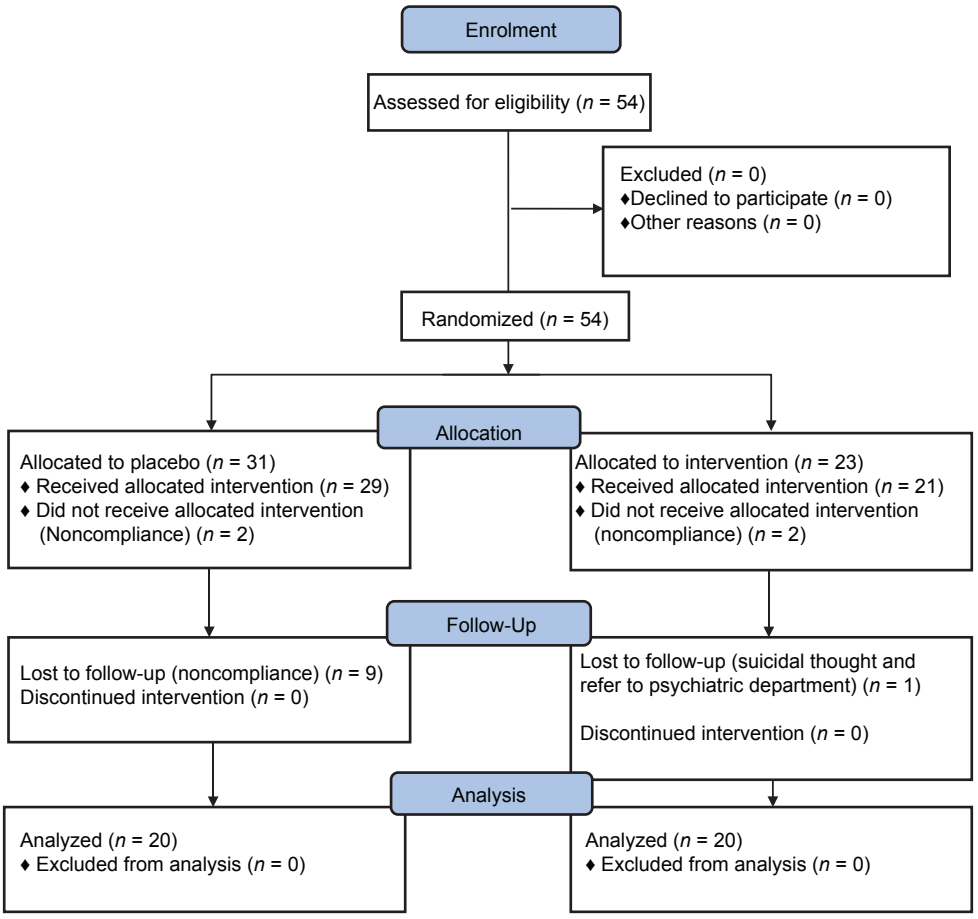
Consort Flow Diagram 1 shows the details of excluded and dropout persons.

After taking the oral and written informed consent. A toxicology test for 10 substances and liver function tests (alanine transaminase and aspartate transaminase) were done and the cocaine craving questionnaire-brief (CCQ-Brief) was completed (there is no specific questionnaire for methamphetamine, and the craving pattern of methamphetamine is similar to cocaine).[26,27] This 10-item questionnaire is a brief form of the 45-item CCQ questionnaire, which was prepared by Sussner *et al*. in 2006. Its reliability is confirmed by Cronbach's alpha score 0.90.[28]

To validate the Persian copy of CCQ-Brief, the questionnaire was translated into Persian by two psychiatrists, and then two other psychiatrists who were fluent in English and Persian Language, translated it into English. Text translated by the translator was evaluated for a final decision by three psychiatrists.

All of the patients were enrolled in the matrix program as a routine treatment program at this center. They were randomly assigned into two groups and given either valproate or a placebo. We arranged a 16-week intervention program with valproate or a placebo for each group.

A psychiatry resident visited the patients every 2 weeks to assess the frequency of methamphetamine use during the previous 2 weeks: A physical examination was done, drug side effects were assessed, a urine test



Flow Diagram 1: Consort 2010 flow diagram

for methamphetamine was taken, and the CCQ-Brief was filled out. Physical examinations and drug side effects were evaluated using a checklist. Patients were advised to visit or make a phone call as soon as possible in unbearable side effects.

In intervention group, valproate was started with the dose of 250 mg and within 10 days it increased to the dose of 1000 mg, and the same dose was taken over 16 weeks. On a daily basis and before the beginning of matrix program session the drug was delivered to patients by trained personnel, and on holidays, the drug was delivered to the patient with the sum amount of the days that was impossible for him to visit; also he was trained how to consume it at home.

In the control group, the placebo with the same pharmaceutical form of valproate, which had been developed by the school of pharmacy at Isfahan University of Medical Sciences, was administered in a same manner of valproate.

After the 4-months program (active treatment with valproate and placebo), the drug was tapered and discontinued within 10 days, and patients were introduced to self-help groups and monitored regularly on a weekly basis over another 3 months.

After 16th week, patients were introduced to self-help groups and monitored regularly every 2 weeks basis over another 3 months, and we had no drop out of patients.

Comparisons and assessments of impacts were conducted through analysis of covariance with repeated measure (ANCOVA repeated measure). All analyses were performed by SPSS 18 Software (SPSS, Chicago, Illinois, USA) (with 0.05 significance level in all tests).

RESULTS

Fifty-four methamphetamine-dependent males of 18–40 years participated in this study; Table 1 shows the demographic variables of the studied sample. The results of Chi-square and *t*-test, respectively, for comparing qualitative and quantitative variables in both groups showed that in terms of demographic variables, there is no significant difference between the two groups ($P > 0.05$).

Descriptive indices of CCQ-Brief score with separation of groups were calculated during the study, and the values in both groups were compared via *t*-test [Table 2]. The results revealed that the average in all measurements, except weeks 1 (baseline), 3 and 28, were significantly less than placebo group ($P < 0.001$).

ANCOVA repeated measurement was used for assessing changes of CCQ-Brief over time and also evaluating the effects of the intervention [Table 3]. There were significant changes over time ($P < 0.001$). The effect of the intervention on these changes was significant too ($P < 0.001$).

Figure 1 shows the schematic changes of CCQ-Brief score during study and follow-up times.

In 16th week, the intervention stopped, and patients were introduced to self-help groups and regularly monitored on a weekly basis over another 12 weeks.

A paired *t*-test was used for comparing changes at any measurement relative to different weeks. For example, the average of CCQ-Brief score in the 1st week is significantly different from all stages of measurements in the study ($P < 0.001$) except week 28 ($P = 0.075$).

The ratio of positive methamphetamine urine tests in both groups were compared using Chi-square test on a weekly basis [Table 4]. The results showed that the ratio of positive tests in both groups in all weeks except weeks 3 and 28 were significantly different.

In the baseline measurement, all of the patients in both groups had positive methamphetamine urine tests.

Table 5 shows the frequency of drug complications in both groups during all stages of measurements in study.

Table 1: Results of Chi-square and *t*-test, respectively, for qualitative and quantitative comparison of demographic variables in two groups

Demographic variables	Placebo group	Intervention group (valproate)	*P*
Marital status (%)			
Single	16 (51.6)	11 (47.8)	0.783
Married	15 (48.4)	12 (52.2)	
Job (%)			
No job	13 (41.9)	7 (30.4)	0.387
Employee	18 (58.1)	16 (69.6)	
Education (%)			
<Diploma	13 (41.9)	5 (21.7)	0.056
Diploma-bachelor	15 (48.4)	18 (78.3)	
>Bachelor	3 (9.7)	0 (0.0)	
Age (year)			
n	31	23	0.090
Mean (SD)	29.6 (5.5)	32.1 (4.9)	
Addiction duration (month)			
n	31	23	0.345
Mean (SD)	49.6 (24.8)	55.8 (22.0)	
The longest previous purity time (day)			
n	31	23	0.746
Mean (SD)	43.5 (64.7)	50.0 (81.8)	

SD: Standard deviation

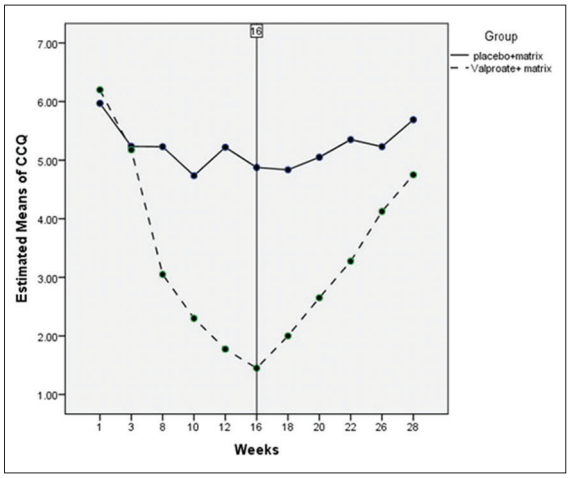


Figure 1: Trend of cocaine craving questionnaire-brief score during study and follow-up times in two groups. In 16th week the intervention stopped and follow-up time started

Table 2: *T*-test results for comparing CCQ-Brief scores in intervention and placebo group at the times of measurement

CCQ	Placebo group		Intervention group (valproate)		*P*
	n	Mean (SD)	*n*	Mean (SD)	
Base line	31	6.1 (0.89)	23	6.0 (1.1)	0.976
Week 3	29	5.3 (1.1)	21	5.2 (1.3)	0.791
Week 8	26	5.2 (0.7)	20	3.1 (1.3)	<0.001
Week 10	24	4.8 (1.5)	20	2.3 (1.0)	<0.001
Week 12	21	5.2 (1.0)	20	1.8 (0.7)	<0.001
Week 16	20	4.9 (1.5)	20	1.5 (0.6)	<0.001
Week 18	20	4.8 (1.2)	20	2.0 (0.9)	<0.001
Week 20	20	5.0 (1.3)	20	2.7 (1.2)	<0.001
Week 22	20	5.4 (0.9)	20	3.3 (1.0)	<0.001
Week 26	20	5.2 (1.3)	20	4.1 (1.7)	0.023
Week 28	20	5.7 (1.0)	20	4.8 (2.1)	0.083

SD: Standard deviation, CCQ-Brief: Cocaine craving questionnaire-brief

Table 3: The results of ANCOVA repeated measure regarding changes of CCQ-Brief over time in intervention and control groups

Changes of CCQ-Brief	*F*-test	df	*P*
Time effect	39.1	10 and 29	<0.001
Group effect	52.5	1 and 38	<0.001
Interaction	17.1	10 and 29	<0.001

df: Degree of freedom, CCQ-Brief: Cocaine craving questionnaire-brief, ANCOVA: Analysis of covariance

DISCUSSION

In this clinical trial, it is investigated the effect of adding valproate on current treatment of methamphetamine consumption in a human sample. The results had shown that adding valproate to matrix program in the treatment of methamphetamine dependence had a significant effect on the reduction of the craving to methamphetamine consumption over the treatment time. These results are different with results of some clinical studies[29-36] but are similar to obtained results on the mice.[25] In the previous studies, antidepressants (such as fluoxetine, sertraline, paroxetine, imipramine, and mirtazapine),[29-33] GABAergic drugs (such as gabapentin and baclofen),[34] dopamine receptor antagonists (such as haloperidol and risperidone),[35] and HT3 receptor antagonists (ondansetron)[36] failed to show the benefits compared to the placebo in reducing the desire to consume. In few studies, it is proven naltrexone,[37,38] bupropion,[39,40] and Modafinil effects[41,42] in reducing the desire to consume methamphetamine.

The average propensity to methamphetamine consumption based on CCQ-Brief and the ratio of positive urine tests of amphetamine in the intervention group from 6 to 26 weeks was significantly lower than the control group, but the difference returned to non-significant level at 28th week. This indicates that maintenance treatment with valproate may be essential to reduce the relapsing rate. In placebo group, there were a reduction in average CCQ-Brief Score during treatment with placebo, but the differences were not meaningful along the study.

The probable mechanism of valproate in decreasing of craving to methamphetamine may be related to GABA. GABA neurons decrease dopamine transmission in the nucleus accumbens and ventral tegmental mesolimbic regions in preclinical models, possibly decreasing the reinforcing effects of psychostimulants and providing the theoretical basis for trials of GABA agonists with METH-abusing patients.[10] Recently, two open-labels trials with gamma-vinyl GABA and placebo-controlled trials with GABAergic medications baclofen topiramate and tiagabine found evidence for efficacy in treating cocaine dependence. Regarding the similarity of the mechanism of action of methamphetamine to cocaine,[43] GABAergic neurotransmitter system can be considered as the main focus of attention regarding the decreasing of craving to methamphetamine with valproate consumption.

No serious complication such as the liver failure, pancreatitis, and encephalopathy were not observed

Table 4: The results of Chi-square in comparing the ratio of positive methamphetamine urine tests in both groups

Urine test times	Urine test results	Placebo group (%)	Intervention group (valproate) (%)	*P*
Week 3	Positive	17 (58.6)	12 (57.1)	0.917
	Negative	12 (41.4)	9 (42.9)	
Week 8	Positive	16 (64.0)	2 (10.0)	<0.001
	Negative	9 (36.0)	18 (90.0)	
Week 10	Positive	14 (58.3)	1 (5.0)	<0.001
	Negative	10 (41.7)	19 (95.0)	
Week 12	Positive	13 (61.9)	0 (0)	<0.001
	Negative	8 (38.1)	20 (100)	
Week 16	Positive	14 (70.0)	0 (0)	<0.001
	Negative	6 (30.0)	20 (100)	
Week 18	Positive	11 (55.0)	0 (0)	<0.001
	Negative	9 (45.0)	20 (100)	
Week 20	Positive	10 (50.0)	3 (15.0)	0.018
	Negative	10 (50.0)	17 (85.0)	
Week 22	Positive	14 (70.0)	4 (20.0)	0.001
	Negative	6 (30.0)	16 (80.0)	
Week 26	Positive	16 (80.0)	8 (40.0)	0.010
	Negative	4 (20.0)	12 (60.0)	
Week 28	Positive	16 (80.0)	13 (65.0)	0.288
	Negative	4 (20.0)	7 (35.0)	

Table 5: Frequency of drug complications in both groups during the study

Drug complications checking times	Placebo group			Intervention group (valproate)		
	n	Complication	Frequency (%)	*n*	Complication	Frequency (%)
Week 3	29	Headache	3.5	21	Dyspepsia	9.5
					Drowsiness	4.8
Week 8	25	Headache	4	20	Tremors	5
Week 10	23	-	-	20	Tremors	5
					Weight gain	15
Week 12	21	Headache	4.8	20	Weight gain	15
Week 16	20	-	-	20	Tremors	5
Week 18	20	-	-	20	-	-
Week 20	20	-	-	20	-	-
Week 22	20	-	-	20	-	-
Week 26	20	-	-	20	-	-
Week 28	20	-	-	20	-	-

in the intervention group, and only a few minor side effects such as dyspepsia, somnolence, tremor, and weight gain were observed but in regard to few samples size and short time of trial, this findings do not ruled out the probability of known side effects of valproate.

Regarding the high prevalence and increasing trend of methamphetamine abuse and dependence and its abundant physical, psychological, economic, and social complications and regarding the limitations of the matrix method as a standard and accepted treatment for some consumers, our findings may be represents adding of valproate to matrix program as a hopeful treatment option for reducing the craving to methamphetamine. Repeating of the same studies with larger sample size and longer duration of time is needed to confirm the results.

Limitations

Small sample size, short duration of trial, and limiting to male sex of the samples are the main limitations for generalization of findings of this study.

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Conflicts of interest

There are no conflicts of interest.

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