

Original Article

Atomoxetine Efficacy in Methamphetamine Dependence during Methadone Maintenance Therapy

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Abstract

Background: Co-occurring methamphetamine (METH) use during methadone maintenance therapy (MMT) is a highly prevalent and progressive problem in Iran. There are no registered pharmacological treatments for treating METH use disorder. The present study investigates the potential efficacy of atomoxetine in the treatment of these patients.

Methods: In a double-blind, controlled clinical trial, 86 METH-dependents on MMT randomly received either atomoxetine (40 mg/d) or placebo. We measured the craving scores with visual analog scale (VAS) on a weekly basis, and evaluated depression, anxiety and stress with the Depression Anxiety Stress Scales (DASS) on a monthly basis. Measurements were made in each weekly visit with urinary METH drug test.

Results: Atomoxetine significantly reduced METH craving ($P < 0.001$). Negative METH urine test increased significantly in the drug group compared to the placebo group ($P = 0.007$). While initially the METH urine test was positive for all patients, 56% (25/45) in the atomoxetine group and 26% (11/41) in the placebo group had negative METH urine tests after 8 weeks. DASS were decreased in both groups with a greater reduction in the atomoxetine group [depression ($P = 0.028$), anxiety ($P = 0.038$), and stress ($P = 0.031$)]. Only mild side effects were observed.

Conclusion: This study confirms the safety and clinical tolerance of atomoxetine, and its appropriate efficacy in suppressing METH craving and possible potential effects on its treatment.

Keywords: Atomoxetine, Dependence, Methadone, Methamphetamine

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Introduction

Methamphetamine (METH) is one of the most widely abused drugs in the entire world. METH is a psychostimulant drug and its dependence leads to serious psychiatric, behavioral, and physical problems.¹ In the last decade, critical worries have been raised about the growing METH abuse in patients who are on methadone maintenance therapy (MMT) in Iran.² The combination of opiates and stimulants are administered by many substance-abusing individuals to produce the desired subjective effects and reduce their side effects.³ The main reasons mentioned by MMT participants for stimulant abuse during therapy include getting high, for depression, self-medication and feeling good.^{2,4}

Considering this progressive problem in Iran and the reasons listed for METH use among methadone maintenance patients, we decided to evaluate a drug intervention for this population. At present, the only

approved treatment for METH dependence is the matrix model (a combination of psychological, behavioral and cognitive approach)^{5,6}; to date, no standard medical treatment has been found for METH abusers to reduce relapses and improve the condition of the patients.^{7,8} Craving and drug-seeking behaviors constitute two important factors in substance dependence as well as the most important causes of relapse. Relapse is one of the important characteristics of substance dependence which is caused by continued addiction. Deep changes in brain circuits due to chronic and severe drug abuse lead to severe craving for drug. Thus, reducing these factors is a major step in treatment of addiction.⁹ Increasing release of dopamine, especially in the nucleus accumbens, seems to be linked to the augmenting effects of amphetamines.¹⁰ Brauer and De Wit showed the non-dopaminergic contributions to the subjective effects of amphetamines in a clinical trial study. In their study, a dopamine receptor

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antagonist did not alter dextroamphetamine-induced euphoria in healthy volunteers.¹¹ Also, according to the findings of Rothman et al, it seems that the subjective effects of amphetamines in humans are related to the release of norepinephrine, not dopamine.¹² Another study showed the acute effects of amphetamines with further contribution related to the activation of the noradrenergic system.¹³ Atomoxetine is commonly used to treat attention deficit hyperactivity disorder due to its cognitive enhancement property, and it has been efficacious and well-tolerated in long-term treatment.^{14,15} Atomoxetine regulates norepinephrine, as a selective norepinephrine inhibitor, by increasing norepinephrine reuptake in the presynaptic region of the nerve endings and thereby increases the extracellular levels of dopamine and norepinephrine in the prefrontal cortex but not the striatum.¹⁶ Since the mechanism of amphetamine function is to increase the levels of norepinephrine and dopamine in the brain, it may be concluded that atomoxetine therapy can help to determine the contribution of norepinephrine to the human amphetamine responses.

The current study was designed to investigate the effects of atomoxetine on reducing METH craving and its dependence treatment among subjects undergoing methadone maintenance treatment.

Patients and Methods

This is a double-blind placebo-controlled randomized clinical trial registered in the Iranian Registry of Clinical Trials (identifier: IRCT2016041627413N1, <http://www.irct.ir>). In this investigation, the efficacy of atomoxetine was evaluated in terms of reducing METH craving and its abuse treatment during MMT.

Between January 2016 and June 2017, volunteers were selected from METH abusers in MMT centers in Kashan, Iran. The patients included those who had been treated with methadone for a long time. Then, METHs were used to reduce methadone complications, but after a while they were addicted to METHs during their MMT. The patients were divided into atomoxetine and placebo groups by trained staff who had no contact with the patients. Simple randomization was done using tables of random numbers. The procedure was explained to each patient before starting the study and written consent was obtained. The medical and psychiatric information, history of substance abuse, demographic data and social status of individuals were assessed through structured clinical interviews previously designed by the Iranian National Center for Addiction Studies (INCAS).¹⁷

The inclusion criteria included men aged 18 to 50 years who were treated with methadone maintenance in official MMT centers according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria. They were treatment-seeking volunteers. The DSM-IV-TR criterion for METH

dependence was defined as self-reported METH abuse two or more days per week in the last month. Also, urinalysis at the beginning of the study had to be positive for methadone and METH and negative for other drugs and alcohol.

Exclusion criteria were: 1) current abuse of alcohol or drugs than methadone, METH and nicotine; 2) narrow angle glaucoma; 3) pheochromocytoma; 4) suicide attempts or even suicidal ideation; 5) untreated viral or bacterial infections or other unstable medical conditions; 6) history of myocardial infarction, cerebrovascular accident, congestive heart failure or other major cardiovascular disorders; 7) elevated liver function tests; 8) history of schizophrenia, major depression, bipolar disorder, or other psychiatric disorders, and taking a mood stabilizer, antipsychotic or antidepressant drugs; 9) using drugs which have major interactions with atomoxetine (for example congestive mono amine oxidase inhibitor and paroxetine); and 10) common medical contraindications for atomoxetine.

Nine volunteers in the treatment group and 16 in the placebo group did not complete the course of treatment due to various reasons such as imprisonment, immigration, and unwillingness to continue the treatment. Overall, 86 patients were investigated consisting of 45 in the treatment group and 41 in the placebo group (Figure 1). They were assigned to the atomoxetine and placebo groups using simple randomization.

Procedures and Variable Assessment

The study was completed over a course of 8 weeks. Individuals in the atomoxetine group received 40 mg/d of atomoxetine capsules (Tadbir Kalaye Jam Co, Iran), and subjects in the placebo group received placebo capsules that were completely similar to those of atomoxetine in shape, color and size. The patients' urine specimens were examined for the presence of cocaine, amphetamine, METH, tetrahydrocannabinol, methadone, medroxyprogesterone, phencyclidine, barbiturate, benzodiazepine and tricyclic antidepressant at the beginning of the research and on every weekly visit. METH craving was evaluated using a visual analog scale (VAS)¹⁸ and the Desire for Drug Questionnaire (DDQ)¹⁹ on a weekly basis. Furthermore, METH craving and depression, anxiety and stress assessment was performed for all patients on a monthly basis using the Leeds Dependence Questionnaire (LDQ)²⁰ and the Depression Anxiety Stress Scales (DASS),²¹ respectively. DDQ is a questionnaire which was designed by Franken and his team. This questionnaire is derived from the Desire for Alcohol Questionnaire (DAQ) which is used for heroin dependents to evaluate heroin craving at the moment. Nevertheless, due to its ability regarding overall measurement of substances, it has been used for craving assessment of other substances later. This questionnaire is based on a seven-step Likert-scale scored

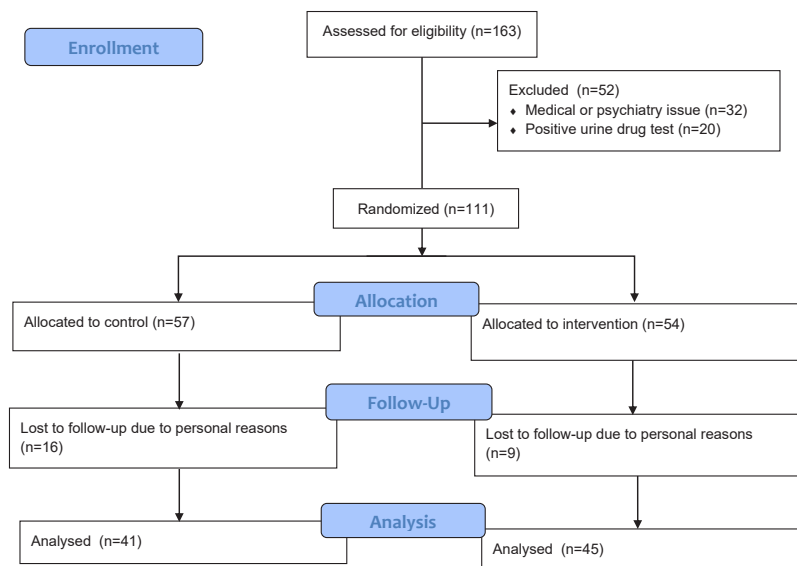


Figure 1. Flow Diagram of Patient Recruitment.

from one to seven (where 1 is “Strongly Disagree” and 7 is “Strongly Agree”). In a study by Franken et al, the total Cronbach’s alpha was reported to be 0.85 for general credit questionnaire. In addition, according to Abharian et al in 2016, this score was reported to be 0.75 for general credit questionnaire in Persian-speaking abusers.²²

VAS is an international valid instrument for subjective self-report, which is graded from 0 to 10 that shows the personal sense by pointing to degree of craving. Many studies have been conducted on the validity and reliability of the VAS and all of them have confirmed its validity and reliability.²³⁻²⁵ Data obtained from VAS can be converted parametrically to an interval-scale level.²¹ The advantage of VAS is that it is shown to be true for other entirely different subjective phenomenon such as mood, pain, and emotions.²⁶

The LDQ is a 10-item questionnaire based on a four-point Likert scale. This questionnaire was designed to measure the degree of dependency from mild to severe. It is used to evaluate the dependency of different substances. Cronbach’s alpha was reported to be 0.94 and test-retest reliability was 0.95.^{19,20} Habibi et al showed that the LDQ Cronbach’s alpha in Iranian population was 0.90.²⁷

DASS is a 42-item self-reported test for measuring depression, anxiety and stress. Since shorter questionnaires are preferred in some testing conditions, the 21-item DASS questionnaire is generally used. Cronbach’s alpha was 0.966 for total score, 0.947 for the depression scale, 0.897 for the anxiety scale and 0.933 for the stress scale.²⁸

Sahebi et al reported that DASS general, validity and reliability coefficients in Iranian population were significant with $P < 0.001$. The correlation between the DASS and the Beck Depression Inventory subscales, the Zung Anxiety inventory and the Perceived Stress Inventory were 0.70, 0.67 and 0.49 respectively and the correlations

were significant.²⁹

Statistical Analysis

Data analysis was performed using SPSS version 20.0. Before performing t test, we used the Kolmogorov-Smirnov test to evaluate the normality of the data. Our measures had normal distribution ($P > 0.05$). The demographic, clinical and psychological variables were compared between atomoxetine and placebo groups using the chi-square test and independent t test. Also, repeated measure ANOVA was used for investigation of the weekly variations. The data were presented as means and standard deviations and P values less than 0.05 were considered significant.

Results

Baseline Demographics

Eighty-six individuals completed this trial. At the beginning of the study, they had normal-range values of aspartate aminotransferase and alanine aminotransferase, normal electrocardiography, and their physical examination did not reveal any problems. No significant difference was seen between the two groups regarding their mean age and other demographic data including educational and marital status (Table 1). Also, there was no significant difference between the two groups in the duration of METH abuse and history of other important substance abuse (Table 2).

Primary Outcome: Results of Urine Tests

In both groups, all METH urine tests were positive in the beginning of the trial. Over the next weeks, positive urine tests were gradually reduced in both groups, but the reduction was greater in the atomoxetine group compared to the placebo group. Fifty-six percent (25/45) in the atomoxetine group and 26% (11/41) in the placebo group

Table 1. Demographic Data of Participants

Characteristics	Atomoxetine Group (n = 45)	Placebo Group (n = 41)	P Value
Age	32.6 ± 7.9	36.4 ± 33.5	0.540
Marital status			0.301
Permanent marriage	19 (42.2%)	24 (58%)	
Single/never married	18 (40%)	9 (22%)	
Separated but not divorced	5 (11.1%)	4 (10%)	
Divorced	3 (6.6%)	4 (10%)	
Educational status			0.672
Illiterate	0 (0%)	0 (0%)	
Elementary	8 (17.7%)	9 (22%)	
Primary	10 (22.2%)	5 (12%)	
High school	13 (28.8%)	18 (44%)	
College	12 (26.6%)	9 (22%)	
Bachelor of science (BSc)	2 (4.4%)	0 (0%)	

Table 2. History of Substance Abuse in Participants

Mean (SD)	Atomoxetine Group	Placebo Group	P Value
Age of first heroin use	22.2 (4.4)	21.2 (4.9)	0.35
Duration of METH use	3.6 (1.9)	3.2 (1.7)	0.31
Days of METH use in the last month	19.4 (6.5)	18.0 (5.7)	0.29
Duration of methadone use	6.7 (2.1)	6.8 (2.1)	0.81

SD, standard deviation; METH, methamphetamine.

had negative METH urine tests in the last week ($P = 0.007$) (Table 3).

Although in the repeated measures ANOVA test, P value was more than 0.05 in most cases, indicating that there was no meaningful difference between the two groups during the times, in the final weeks of the study, the comparison between the two groups showed a significant difference (Table 3).

The Atomoxetine Effects on Atomoxetine Craving and Dependence

Atomoxetine significantly improved craving and dependency on METH as shown by VAS, DDQ and LDQ results. The craving and dependence on METH gradually decreased in both groups, but in the final weeks, the reduction was significantly greater in the atomoxetine group compared to the placebo group (Figure 2A-C).

Table 3. Means (Standard Deviation) of Methamphetamine Positive Urine Test

Variable	Group	B (SD)	W1 (SD)	W2 (SD)	W3 (SD)	W4 (SD)	W5 (SD)	W6 (SD)	W7 (SD)	W8 (SD)	B-W8 (SD)
MPUT	A	100	93	96	84	80	69	51	40	44	56
	P	100	93	90	83	85	73	80	68	73	27
	P value ^a	1.000	0.907	0.340	0.851	0.518	0.667	0.004	0.008	0.007	—
	P value ^b					0.050					—

MPUT, methamphetamine positive urine tests; A, Atomoxetine group; P, Placebo group; SD, Standard deviation; B, Baseline; W, Week; B - W8, Difference between baseline and week 8.

^a P value of t test; ^b P value of repeated measures ANOVA.

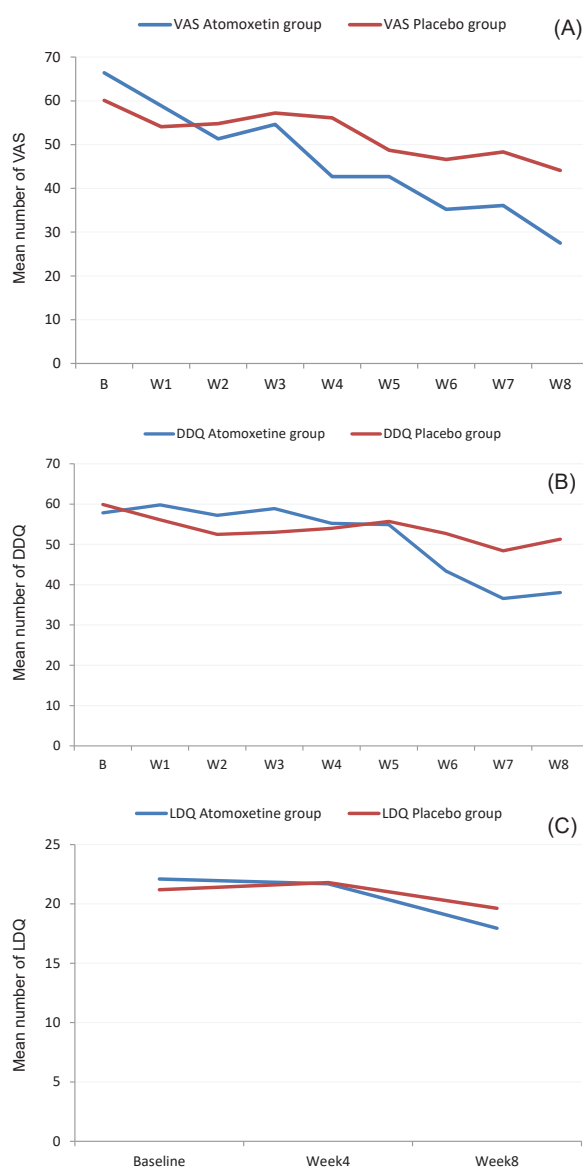


Figure 2. Craving Changes in (A) the Visual Analog Scale, (B) the Desire for Drug Questionnaire and (C) the Leeds Dependence Questionnaire.

The Atomoxetine Effects on Depression, Anxiety and Stress Scores

Using DASS, it was found that the mean scores of depression, anxiety and stress were significantly reduced compared with the placebo group and the greatest difference between the atomoxetine and placebo groups

was observed in the last weeks (Table 4).

Tolerability and Side Effects

In each weekly visit, the participants were asked about the side effects of the capsules and finally, the data were analyzed. The reported side effects (including nausea, dry mouth, loss of appetite, insomnia, constipation, abdominal pain, mild headache, and dizziness) were not significant ($P = 0.267$) and the participants did not report any serious side effects (Table 5).

The side effects were mild and self-limiting. According to the findings, atomoxetine was safe and well-tolerated by METH-dependent individuals during METH maintenance therapy.

Discussion

The current study compared the efficacy of atomoxetine and placebo in reducing METH craving and the side effects in METH dependent patients. The results showed that atomoxetine was effective in reducing METH craving. Atomoxetine was safe and well-tolerated by treatment-seeking METH-dependent subjects. No unexpected side effects were reported. In general, there were mild and self-limiting side effects that often occurred in the beginning of treatment. The study revealed that in treatment of stimulant dependence, noradrenergic agents, including atomoxetine may increase the effects of behavioral interventions, especially because they have a cognitive enhancement property. However, in most previous studies on cocaine, the results do not support the use of atomoxetine in the treatment of cocaine abuse.²⁹ Walsh et al showed that use of cocaine was not changed by atomoxetine in cocaine-dependent individuals.³⁰ In cocaine-dependent individuals, atomoxetine reduced the drug-related cues.³⁰ According to Elise et al, atomoxetine had a modest effect on cognitive enhancement and mood.³² Atomoxetine may have good tolerability and potential for abuse in cocaine-dependent individuals who are in the early stages of abstinence.³² Given the similarities between the stimulants, it seems that atomoxetine has similar effects on cocaine and METH abusers. The differences between them were important due to the greater contribution of norepinephrine to the effects of amphetamine on cocaine.³² In METH, the norepinephrine transporter is 5 to 9 times more potent than dopamine transporter, whereas in cocaine, they have equal potential.³⁴ Previous studies have shown that synaptic levels of norepinephrine will increase with therapeutic drugs that inhibit norepinephrine transporters.²⁶ It also seems that atomoxetine is more effective in the treatment of METH-dependent individuals than cocaine.³⁴

The studies on the effects of atomoxetine in reducing METH craving among MMT patients are rare, limiting the possibility of comparing our findings. Atomoxetine was found to be tolerable and safe in the present study which is consistent with the findings of Passamonti et al.³¹

Table 4. Mean (Standard Deviation) of LDQ, Depression, Anxiety and Stress

Variable	Group	B (SD)	W4 (SD)	W8 (SD)	B- W8 (SD)
Depression	A	22.4 (7.2)	20.1 (5.3)	17.1 (6.4)	5.2 (6.6)
	P	20.2 (4.6)	18.9 (4.3)	18.0 (4.5)	2.2 (5.4)
	<i>P</i> value ^a	0.112	0.262	0.499	0.028
	<i>P</i> value ^b		0.369		—
Anxiety	A	18.9 (5.3)	18.5 (5.0)	14.6 (6.2)	4.3 (5.8)
	P	19.7 (3.8)	18.3 (4.3)	17.8 (3.6)	1.9 (4.6)
	<i>P</i> value ^a	0.450	0.796	0.006	0.039
	<i>P</i> value ^b		0.167		—
Stress	A	21.3 (6.5)	19.8 (4.8)	15.8 (5.9)	5.4 (6.5)
	P	21.2 (4.4)	19.2 (4.7)	18.4 (5.0)	2.7 (4.3)
	<i>P</i> value ^a	0.943	0.591	0.035	0.031
	<i>P</i> value ^b		0.182		—

A, Atomoxetine group; P, Placebo group; SD, Standard deviation; B, Baseline; W, Week; B - W8, difference between baseline and week 8.

^a *P* value of *t* test; ^b *P* value of repeated measures ANOVA.

Table 5. Frequency of Side Effects in Atomoxetine and Placebo Groups

Side Effects	Atomoxetine Group (n = 45)	Placebo Group (n = 41)
Nausea	11 (24.4)	6 (14.6)
Mild headache	4 (8.8)	5 (12.1)
Dry mouth	9 (20)	2 (4.8)
Loss of appetite	7 (15.5)	4 (9.7)
Insomnia	6 (13.3)	8 (19)
Constipation	3 (6.6)	5 (12.1)
Abdominal pain	3 (6.6)	5 (12.1)
Dizziness	3 (6.6)	1 (2.4)

All variables are presented as number (%).

The study showed no significant difference in the number of people reporting side effects in the atomoxetine and placebo groups. In addition, the findings of Schottenfeld et al are consistent with our results, showing clinical tolerability and safety as well as the potential efficacy of atomoxetine in treating amphetamine-type stimulants (ATS-use disorders in ATS-dependent individuals during buprenorphine maintenance treatment). The proportion of ATS-negative urine tests was higher in atomoxetine-compared to placebo-treated participants and depressive symptoms were reduced from baseline in both groups ($P < 0.02$), with a greater reduction observed in the atomoxetine- than the placebo-treated group ($P < 0.02$).³⁶ Furthermore, it was revealed that atomoxetine significantly decreased the DASS in the atomoxetine group compared to the placebo group. The small sample size and short study period are limitations of present study. In addition, all participants were male because of the limited number of drug-dependent women in Iran. Finally, further studies are recommended with larger sample sizes, longer study periods and higher doses to evaluate the long-term and higher dose clinical effects of atomoxetine treatment. Functional magnetic resonance imaging can be used to explore the mechanisms of brain atomoxetine in reducing METH craving and this will be a very exciting field of research.

In conclusion, our study demonstrated the efficacy of atomoxetine in suppressing METH craving and its potential effects on the treatment of METH dependence, as well as confirming the safety and clinical tolerance of atomoxetine.

Authors' Contribution

AR designed, supervised and wrote the manuscript. Data gathering was accomplished by MF and AR. Data analysis and statistical methods were accomplished by PHA, AR and ARM, with critical feedback and consultation by HRB, PHA and GA.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This is an original work, and was approved by the Committee on Medical Ethics of Kashan University of Medical Sciences (KAUMS) and the Declaration of Helsinki was followed (Ethic No. IR.KAUMS.REC.1396.123).

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