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Research Paper: Effects of Atomoxetine for Cognitive Function in Methamphetamine-dependent Patients: A Randomized Controlled Trial

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ABSTRACT

Background: A substantial body of evidence indicates that methamphetamine abuse can lead to persistent and severe cognitive dysfunction. Preclinical studies and early pilot clinical investigations suggested that atomoxetine, a cognitive enhancer, may improve cognitive dysfunction. The present study evaluated whether atomoxetine would affect cognitive dysfunction in methamphetamine-dependent patients.

Methods: Participants with methamphetamine dependence (N=86) under Methadone Maintenance Therapy (MMT) were enrolled in a double-blind, placebo-controlled, randomized clinical trial. This investigation was performed on 86 subjects to consume either 40 mg/day atomoxetine (n=45) or placebo (n=41) for 8 weeks. Between January 2016 and June 2017, volunteers were selected from methamphetamine abusers in MMT centers in Kashan City, Iran. They completed the Cognitive Abilities Questionnaire at the first and each monthly visit to assess the cognitive functions. The collected data were analyzed using the Independent Samples t-test, Mann Whitney U test, and Chi-square in SPSS software.

Results: This study revealed that atomoxetine treatment improved some cognitive dysfunctions in methamphetamine users, including memory, inhibitory control, selective attention, decision-making, planning, sustained attention, and cognitive flexibility in methamphetamine users ($P<0.05$); however, social cognition improvement was less than others ($P=0.107$). There were only mild adverse effects in the placebo and atomoxetine groups.

Conclusion: The obtained findings indicated the efficacy of atomoxetine for improving cognitive dysfunction in methamphetamine users and suggest the potential effectiveness of atomoxetine for treating them.

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1. Introduction

Methamphetamine is a psychostimulant drug, and its dependence causes many public health problems and criminal justice cases [1]. A substantial body of evidence indicates that methamphetamine abuse can lead to persistent and severe psychiatric, cognitive, and neurological dysfunction [2, 3]. Methamphetamine dependence may lead to profound cognitive deficits [4], including deficits in executive functions, verbal memory, processing speed, response inhibition, and attention tasks [5, 6]. Executive functions are most commonly impaired in methamphetamine-addicted individuals [6]. Executive function is a broad term, including a wide range of cognitive processes and behavioral competencies. It also consists of verbal reasoning, problem-solving, planning, sequencing, focusing, multitasking, cognitive flexibility, and dealing with novelty [7-10].

Similarly, methamphetamine-dependent individuals presented deficits in memory, attention, set-shifting, response inhibition, and decision-making abilities [11-13]. The severity of impairments in verbal memory and psychomotor function for methamphetamine users were correlated with the loss of dopamine transporters in the striatum and nucleus accumbens [14, 15]. Atomoxetine, a cognitive enhancer, is marketed for Attention-Deficit/Hyperactivity Disorder (ADHD) and is a generally well-tolerated and efficacious treatment for ADHD across prolonged treatment [16, 17]. Rabiey et al. [18] demonstrated that atomoxetine has appropriate efficacy in suppressing methamphetamine craving and possible potential effects on its treatment. Furthermore, DeVito et al. [19] reported that 40 mg and 80 mg atomoxetine over three sessions had modest effects on mood and cognitive enhancement in abstinent cocaine users. Also, Weintraub et al. [20] demonstrated that atomoxetine treatment was not efficacious for treating clinically significant depressive symptoms in Parkinson's disease; however, it was associated with improved global cognitive performance and daytime sleepiness. In a Randomized Clinical Trial (RCT), atomoxetine (80 mg daily) for 8 weeks in individuals with schizophrenia has limited benefit for improving cognition [21]

Another study suggested that 3 doses of atomoxetine in smokers with schizophrenia no statistically significant improvement in performance on cognitive measures [22]. It is a selective inhibitor of the norepinephrine transporter, which regulates norepinephrine neurotransmission by facilitating the reuptake of norepinephrine into presynaptic nerve terminals. The inhibition of the norepinephrine transporter with atomoxetine increases extracellular levels of norepinephrine and dopamine in the prefrontal cortex but not the striatum [23].

Moreover, atomoxetine inhibits serotonin reuptake to a minimal extent [24]. Therefore, it is crucial to assess its effects on cognitive domains in individuals with methamphetamine-dependent patients. We hypothesized that atomoxetine would improve performance in cognitive functions including memory, inhibitory control, selective attention, decision making, planning, sustained attention, social cognition, and cognitive flexibility in methamphetamine users. A literature review revealed limited information about the effects of atomoxetine on cognitive functions in methamphetamine users. The current study aimed to evaluate the impact of 40 mg of atomoxetine on cognitive functions among methamphetamine users.

2. Materials and Methods

This was a double-blind, placebo-controlled, and randomized clinical trial. Its protocol was reviewed and approved by the Kashan University of Medical Sciences (KAUMS/94126) Research Ethics Committee per the Declaration of Helsinki and registered on the Iranian website for registration of clinical trials at http://www.irct.ir: IRCT (IRCT2016041627413N1). Besides, all study participants provided written informed consent forms (Ethical Code: IR.KAUMS.REC.1394.127).

The patients included those treated with methadone for a long time. Then, methamphetamine was used to reduce methadone complications; however, they were dependent on methamphetamine during their Methadone Maintenance Therapy (MMT) for a while. We examined in this trial the potentially beneficial effects of atomoxetine in improving cognitive dysfunctions in methamphetamine abusers who are on MMT. To study admission, the study enrolled treatment-seeking volunteers from MMT centers in Kashan City, Iran, meeting DSM-IV-TR criteria for methamphetamine dependence. They had methamphetamine and methadone positive and opioid negative urine toxicology test results at study enrolment. All study participants were screened for medical and neuropsychiatric disorders by the Structured Clinical Interview, previously designed in the Iranian National Center for Addiction Studies (INCAS). Physical examination and laboratory testing were also used for medical disorders screening by a study physician. History of drug abuse and economic and social status evaluated by the same Structured Clinical Interview of INCAS [25].

Participants included men aged 18-50 years old who met the following inclusion criteria. The treatment-seeking volunteers under MMT meeting DSM-IV-TR criteria for methamphetamine dependence who reported methamphetamine use on ≥2 days per week in the month prior and methamphetamine and methadone-positive urine toxicology test results at the beginning of the study and no other current dependence or abuse of other drugs or alcohol (except tobacco). The exclusion criteria included severe cardiovascular disorder as a history of Myocardial Infarction (MI), Cerebrovascular Accident (CVA), Congestive Heart Failure (CHF) or an unstable medical condition (e.g. untreated bacterial infection), hypertension, liver enzymes greater than 3 times the upper limit of normal, liver failure or acute hepatitis, current psychiatric disorders as bipolar disorder or schizophrenia or major depression, taking a mood stabilizer, antidepressant or antipsychotic medication (including using an Monoamine Oxidase Inhibitor (MAOI) within the preceding 2 weeks), suicide attempts or suicidal ideation, narrow-angle glaucoma, pheochromocytoma, and a history of hypersensitivity to atomoxetine.

We assessed 143 patients for eligibility and excluded 32 persons for different reasons of exclusion criteria. Then, the study subjects were randomized into two groups. During the treatment, 25 patients could not complete the trial (9 patients from the treatment group & 16 patients from the control group). Finally, the study samples included 45 patients in the atomoxetine group and 41 subjects in the placebo group, and they completed the intervention.

Randomization assignment was conducted using computer-generated random numbers. Allocation and randomization were concealed from the researchers and participants until the final analyses were completed. The randomized allocation sequence, enrolling participants and allocating them to interventions, were conducted by trained staff at the clinic. The atomoxetine and placebo were prepared precisely the same size, color, and packaging for proper blinding. Moreover, numbered drug containers were used to conceal random allocation.

The primary outcomes were memory, inhibitory control or selective attention, decision-making, planning, sustained attention, social cognition, and cognitive flexibility.

The first group received atomoxetine capsules (Tadbir Kalaye Jam Co, Iran) 40 mg/day and the other group received the placebo capsules in the same form and packages as atomoxetine. Participants were treated as outpatients for 8 weeks. Participants received a one-week supply of medication in blister packages at each visit and were instructed to self-use the medicines at home. To monitor the adherence, they were required to bring the drug packets to the clinic at the next visit for capsule counts. They completed at first and at each monthly visit the Cognitive Abilities Questionnaire [26] to assess cognitive function performance, including memory, inhibitory control, selective attention, decision making, planning, sustained attention, social cognition, and cognitive flexibility.

The Cognitive Ability Questionnaire (CAQ) was prepared on a five-point Likert-type scale, including 30 items. This questionnaire was used to evaluate 7 cognitive abilities: memory, control, selective attention,

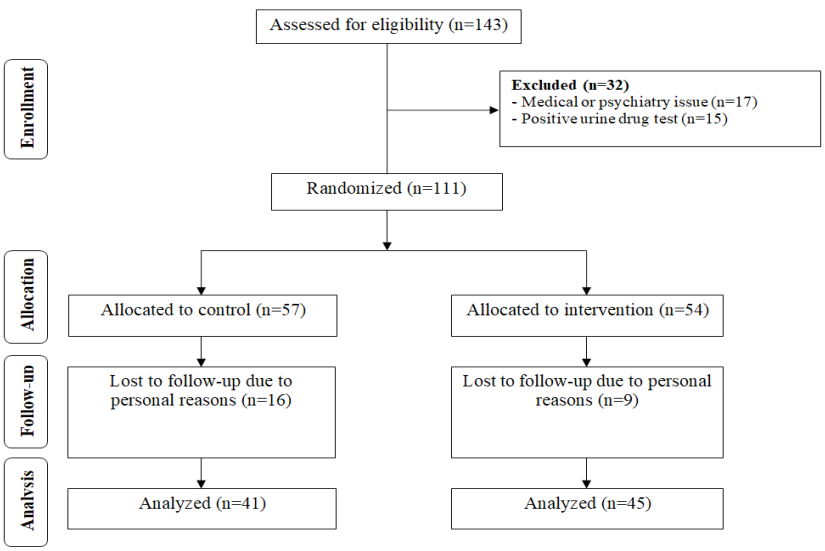

Figure 1. A summary of patient flow diagram

decision-making, planning, sustained attention, social recognition, and cognitive flexibility. This questionnaire is in the Persian language. Internal correlation (Cronbach's alpha coefficient) was 0.834, and test reliability was P<0.01 [26].

The present study's main focus was evaluating the effects of atomoxetine on cognitive function in methamphetamine dependence. To estimate the sample size, we used a randomized clinical trial sample size formula where type one (α) and type two errors (β) were 0.05 and 0.20 (power=80%), respectively. Based on a previous study [18], we used a Standard Deviation (SD) of 20.07 and 13.1 for intervention and placebo groups and a mean difference (d) of 9.5, considering craving (Desire for Drug Questionnaire) as the critical variable. The calculation shows 50 persons were required per group. Assuming a dropout of 5 persons per group, the final sample size was 55 persons per group.

Before performing the t-test, we used the Kolmogorov-Smirnov test to evaluate the normality of the data. Statistical significance was set at two-tailed P<0.05. The obtained data were analyzed in SPSS. The collected data are presented as Mean±SD. The demographic and cognitive function variables were compared between atomoxetine and placebo groups using the Chi-square test, Independent Samples t-test, and Man-Whitney U test.

3. Results

Overall, 86 patients completed the study. These study subjects presented the normal range of EKG, liver function tests (i.e., AST[1] & ALT[2]), and physical examination at the beginning. The Mean±SD Age in the atomoxetine group was 32.60±7.958 years, and in the Placebo group was 33.58±6.445 years. There were no significant differences between the two groups in demographic information (e.g. age, marital & educational status), duration of methamphetamine abuse, and history of other important substance abuse (Table 1). Figure 1 illustrates the study participants' enrollment, randomization, and follow-up.

1. Aspartate aminotransferase (AST)
2. Alanine aminotransferase (ALT)

Table 1. General characteristics of the study participants

Characteristics		No.(%) or Mean±SD		P
		Atomoxetine Group (n=45)	Placebo Group (n=41)	
Age (y)		32.60±7.958	33.58±6.445	0.540[a]
Marital status	Permanent marriage	19(42.22)	24(58)	0.301[b]
	Single/Never married	18(40)	9(22)	
	Separated/but not divorce	5(11.11)	4(10)	
	Divorced	3(6.66)	4(10)	
Educational status	Illiterate	0(0)	0(0)	0.672[b]
	Elementary	8(17.77)	9(22)	
	Primary	10(22.22)	5(12)	
	high school	13(28.88)	18(44)	
	College	12(26.66)	9(22)	
	BSc	2(4.44)	0(0)	
Age of first heroin use (y)		22.2±4.4	21.2±4.9	0.35[a]
Duration of methamphetamine use (y)		3.6±1.9	3.2±1.7	0.31[a]
Days of methamphetamine use in the last month		19.4±6.5	18.0±5.7	0.29[a]
Duration of methadone use (y)		6.7±2.1	6.8±2.1	0.81[a]

[a] Independent samples t-test; [b] Chi square test

Table 2. Cognitive functions in methamphetamine users scores before and after the study

Variables	Groups	Mean±SD			P	Effect Size	Confidence Interval (CI)
		Before Intervention	After Intervention	Differences			
Memory	Atomoxetine	17.00±3.249	13.67±3.115	3.31±3.732	0.006[c]	0.82	-1.41, -0.87
	Placebo	16.66±2.988	15.37±2.981	1.29±2.272			
Inhibitory control or selective attention	Atomoxetine	17.68±3.429	14.65±3.169	2.64±3.207	0.028[d]	0.51	-2.23, -0.19
	Placebo	17.27±3.033	16.29±3.487	1.20±2.676			
Decision making	Atomoxetine	15.30±3.085	13.21±3.226	2.05±3.200	0.046[d]	0.35	-1.77, -0.52
	Placebo	15.51±3.067	14.78±3.267	0.73±2.684			
Planning	Atomoxetine	9.23±2.177	7.65±2.181	1.60±2.073	0.036[d]	0.42	-0.75, -0.23
	Placebo	9.56±2.145	8.88±2.462	0.68±1.809			
Sustain attention	Atomoxetine	9.32±2.021	7.23±2.057	2.02±2.279	0.033[d]	0.41	-1.94, -0.21
	Placebo	9.24±1.758	±8.34±2.045	0.95±2.236			
Social cognition	Atomoxetine	9.73±1.689	11.00±1.839	-1.36±1.859	0.107[d]	0.12	1.32, 2.12
	Placebo	9.22±1.509	9.88±1.847	-0.66±2.045			
Cognitive flexibility	Atomoxetine	14.11±2.535	10.23±2.136	3.74±3.013	0.003[c]	0.69	-1.70, -0.97
	Placebo	13.22±2.253	10.98±2.372	2.24±1.090			

[c] Mann Whitney U test; [d] Independent samples t-test

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As per Table 2, atomoxetine significantly improved cognitive functions, including memory, inhibitory control, selective attention, decision making, planning, sustained attention, social cognition, and cognitive flexibility in methamphetamine use. P values indicate the differences between after and before the study in each group and result from Paired Samples t-test and Man-Whitney U test.

No significant adverse experiences were reported; however, some mild side effects were headache and Dizziness, Insomnia, Abdominal pain, nausea, constipation, dry mouth, and appetite loss.

4. Discussion

Our findings suggested that atomoxetine treatment at 40mg/day improved some cognitive functions in methamphetamine users. Atomoxetine significantly improved cognitive functions, including memory, inhibitory control, selective attention, decision making, planning, sustained attention, and cognitive flexibility in methamphetamine users but the social cognition improvement was less than others.

These findings are consistent with those of previous preclinical and clinical studies supporting the role of the noradrenergic system in mediating acute amphetamine responses. Mehmet Sofuoglu et al. reported that atomoxetine's capacity to attenuate some of the physiological and subjective responses to dextroamphetamine supports its potential use for stimulant dependence [27]. In a previous clinical trial with cocaine users, it was reported that atomoxetine might have favorable tolerability and potential abuse profile in individuals with CUDs. They are currently in early abstinence from cocaine; however, they only presented modest evidence of cognitive-enhancing effects [28]. Atomoxetine demonstrated modest effects on improving performance on a measure of discriminability (IMT d′), which taps into attention, response inhibition, and memory processes. However, this finding did not survive correction for multiple comparisons [28]. In a previous study, with only male cocaine users in the medication condition, atomoxetine improved performance on the n-back, a task of working memory and sustained attention, and speeded corrected responses on a continuous performance task, without affecting the performance on other measures of cognitive control (Stroop test), psychomotor speed and

cognitive flexibility/set-shifting (Trails) [29]. Stoops et al. reported that atomoxetine treatment did not impact the subjective effects of intranasal cocaine in stimulant users [30]. Based on the similarities between the actions of stimulants, one may expect atomoxetine to act similarly on cocaine and amphetamine responses.

However, there were significant differences between the pharmacological effects of cocaine and amphetamines. Notably, accumulating evidence indicates that norepinephrine contributes more to the effects of amphetamine than to the impacts of cocaine. In a recent study, dextroamphetamine and methamphetamine were 5-9 times more potent at the norepinephrine transporter than the dopamine transporter [31]. However, cocaine was equally potent at norepinephrine and dopamine transporter [31]. In another study, the initiation of psychomotor sensitization to dextroamphetamine, but not to cocaine, was dose-dependently inhibited by alpha1-adrenergic blocker prazosin or α2-adrenergic agonist clonidine in rats [32]. Our findings are consistent with these studies suggesting that norepinephrine contributes to acute amphetamine responses. As multiple preclinical and clinical studies indicate, norepinephrine transporter inhibitors acutely increase synaptic levels of norepinephrine. However, with prolonged treatment, norepinephrine response to pharmacological and behavioral challenges is attenuated while the tonic norepinephrine activity stays elevated. This is possibly due to neuroadaptation, including increased stimulation of inhibitory alpha2 adrenergic auto-receptors and down-regulation of the postsynaptic noradrenergic receptors [33]. We used atomoxetine 40 mg/day; however, the effects of atomoxetine are better evaluated in upper doses in the future. This may suggest that higher doses of the drug can also be more effective.

5. Conclusion

This study confirms atomoxetine's clinical and safety tolerance and its appropriate efficacy on cognitive dysfunction in methamphetamine users. Further evidence is needed to confirm our findings. This study had some limitations. The first limitation was the lack of female patients in the sample. This is because of the fewer female meth users in our country. The second limitation was evaluating patients' compliance to the atomoxetine regimen through patient reports and pill counts. This may be better evaluated and managed in future studies. Another limitation of the study is the small sample size. However, this result may warrant a replication with larger samples. Our findings suggest new avenues for future research to elucidate the brain mechanisms underlying the atomoxetine effects on cognitive enhancement to methamphetamine using functional magnetic resonance imaging. Therefore, studies assessing the effects of chronic atomoxetine therapy to evaluate long-term changes in neurocognitive and behavioral outcome measures are warranted. Further studies are warranted to examine the therapeutic utility of atomoxetine for amphetamine addiction.

Ethical Considerations

Compliance with ethical guidelines

The protocol of study was reviewed and approved by the Kashan University of Medical Sciences (KAUMS/94126) Research Ethics Committee per the Declaration of Helsinki and registered on the Iranian website for registration of clinical trials at http://www.irct.ir: IRCT (IRCT2016041627413N1). Besides, all study participants provided written informed consent forms (Code: IR.KAUMS.REC.1394.127).

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Author's contributions

Design, conceptualization, statistical analysis: Ali Rabiey, Ali Reza Moravveji, Peyman Hassani-Abharian, Peyman Mamsharifi, and Amir Ghaderi; Supervision: Hamid Reza Banafsheh; Data collection, Writing – original draft, and Writing – review & editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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