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Amantadine reduces persistent fatigue during post-acute withdrawal phase in methamphetamine abstained individuals: A randomized placebo-controlled trial

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ABSTRACT

Background: Persistent fatigue is a common symptom of methamphetamine withdrawal. It disrupts the individual's social and professional lives as well as increasing the risk of relapse. This study aimed to assess the effects of amantadine in the treatment of persistent fatigue in methamphetamine-abstained individuals.

Methods: A double-blind, placebo-controlled trial was conducted on 42 methamphetamine-abstained individuals who sought treatment for persistent fatigue. Participants were randomly assigned to two groups, receiving either amantadine 100 mg/day or placebo for 4 weeks. Treatment response was evaluated using Fatigue Severity Scale (FSS) and Chalder Fatigue Scale (CFS), recorded at the beginning and end of trial.

Results: A substantial reduction in both fatigue scales was found in the amantadine group, while there was no significant change in the placebo group. Fatigue reduction in the amantadine and placebo groups was, respectively, 28% versus 6% ($p < 0.001$) using the FSS and 24.3% and 4.5% ($p < 0.001$) using the CFS. In addition, both scales showed that the rate of fatigue recovery was significantly higher in the amantadine versus placebo group ($p < 0.05$).

Conclusions: Persistent fatigue in methamphetamine-abstained individuals was significantly reduced, and higher rate of fatigue recovery achieved, from daily administration of 100 mg amantadine for 4 weeks.

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Amantadine; Fatigue; Methamphetamine; Withdrawal

Introduction

Substance use is a challenging public health problem causing morbidity and mortality of individuals as well as substantial social and health-care costs (Lubman, Yucel, & Pantelis, 2004). Methamphetamine, as a potent stimulant with high abuse potential, is the second most common illicit drug worldwide (Cruickshank & Dyer, 2009; Danaee-Far, Maarefvand, & Rafiey, 2016). It can be manufactured with low cost from widely available retail products (e.g. pseudoephedrine), which makes it easily accessible for abuse (Gonzales, Mooney, & Rawson, 2010). In many cases, the initial motivation for methamphetamine use is to increase work performance and sustain longer work hours with little sleep or rest (Mahoney et al., 2014; Sharifi et al., 2017).

Long-term use of methamphetamine leads to brain injury and neurotoxicity which occur even when low doses are used (Yu, Zhu, Shen, Bai, & Di, 2015). Mechanisms that contribute to neurotoxicity include oxidative stress, loss of dopamine and serotonin systems in multiple brain areas, and excitotoxic effects mediated by excessive glutamate (Cruickshank & Dyer, 2009; Ren et al., 2016; Wang et al., 2016; Yu et al., 2015). Preclinical data show that dopamine agonists block neurotoxicity and changes in dopamine receptors caused by methamphetamine (American Psychiatric Association, 2000). In addition, antagonists of *N*-methyl-D-aspartate (NMDA) type of glutamate receptor are a therapeutic option to manage excitotoxicity (Hart, Haney, Foltin, & Fischman, 2002; Zorick et al., 2010).

Abrupt discontinuation of methamphetamine after long-term use results in withdrawal symptoms, with the acute phase usually taking 7–10 days while residual symptoms remaining for several months (Cruickshank & Dyer, 2009; McGregor et al., 2005; Pennay & Lee, 2011). One of the potentially debilitating and prevalent symptoms of methamphetamine withdrawal is severe fatigue and sleep dysfunction which may last for few months after abstinence (Lee et al., 2013; Mahoney et al., 2012, 2014; Pennay & Lee, 2011; Shoptaw, Kao, Heinzerling, & Ling, 2009; Whitehead, 2009). Given methamphetamine addicts are from a variety of professions and socioeconomic backgrounds and a majority of them are young and socially active, persistent fatigue during the withdrawal phase can potentially disrupt social reintegration and employment (Mahoney et al., 2014). In addition, post-acute withdrawal symptoms, such as persistent fatigue, can increase the risk of relapse, especially in those who use methamphetamine to increase or sustain work performance (Karila et al., 2010; McGregor et al., 2005). Hence, finding treatment modalities for post-withdrawal fatigue is important.

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Several pharmacological treatments for fatigue were assessed in a systematic review on adult palliative care and amantadine was shown to have superior effects in the treatment of fatigue in multiple sclerosis (MS) (Mucke et al., 2016). Amantadine is approved by Food and Drug Administration for use both as an antiviral and an antiparkinsonian agent (Thrash-Williams et al., 2013). It is well tolerated with mild and transient adverse effects which commonly include nausea, insomnia, drowsiness, nightmare, and constipation (Alterman et al., 1992; Shaygannejad, Janghorbani, Ashtari, & Zakeri, 2012; White, Van Doorn, Garssen, & Stockley, 2014).

The majority of research conducted to date on the efficacy of amantadine in stimulant withdrawal has been related to cocaine, however with no consistent findings (Alterman et al., 1992; Kampman, Volpicelli, Alterman, Cornish, & O'Brien, 2000). Amantadine enhances dopamine and norepinephrine release from neuronal storage sites that are depleted by chronic stimulant use (Alterman et al., 1992; Tennant & Sagherian, 1987). It also possesses NMDA antagonistic properties which are associated with neuroprotection and reducing the risk of relapse (Alterman et al., 1992; Ciccarone, 2011; Hubsher, Haider, & Okun, 2012; Romach et al., 2004; Tennant & Sagherian, 1987). Given the favorable mechanisms of amantadine for the treatment of stimulant withdrawal symptoms and its promises for the treatment of fatigue, this randomized controlled trial aimed to assess the efficacy of amantadine in fatigue treatment in methamphetamine-abstained individuals.

Materials and methods

Study design

A prospective, double-blind, randomized, placebo-controlled trial was conducted on methamphetamine-abstinent individuals who suffered from fatigue. The study took place in the outpatient addiction clinic of Imam Khomeini Hospital in Ahvaz, Iran, between August 2015 and September 2016. Symptomatic therapy is the clinic's current practice in the management of methamphetamine withdrawal and no medications are routinely administered. Symptoms such as insomnia, anxiety, and agitation are treated with sedatives or tranquilizers during the acute phase of withdrawal. In order to reduce the risk of relapse, individuals are supported through education, counseling, and medical care provided by the clinic.

Taking into account the trial's inclusion and exclusion criteria, detoxified individuals who complained from severe fatigue were enrolled in the study and randomized to amantadine or placebo groups. Amantadine in 100 mg capsules or placebo with the same appearance was administered to patients once a day for 4 weeks. Weekly urine toxicology tests were used to monitor the maintenance of methamphetamine abstinence. Outcomes were assessed at the end of week 4 and compared between the two study groups.

The study was conducted in accordance with the Declaration of Helsinki. The research was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences (identifier code: IR.AJUMS.REC.1394.315). This trial was registered in the Iranian Registry of Clinical Trials (www.irct.ir, registration number: IRCT2015111524853N2). Written informed consents were obtained from all participants prior to enrollment. The consent form described the study, outlined the possible risks, and indicated that an experimental medication or placebo would be consumed daily.

Medication compliance

Medication adherence was measured using weekly pill counts justified against reports of medication-taking to calculate the proportion of dispensed pills that were taken. Participants attended the clinic weekly to undertake urine toxicology tests and receive a 1-week supply of medication in exchange of the previous week's package with any unused medication. Medication adherence was defined as participants' administering medication for >80% of prescribed days (Fairbairn et al., 2008). At the end of week 4, participants with pill count less than 23 (82%) were excluded from the analysis.

Variables

Since fatigue is a subjective experience, two self-report scales rated by a physician were chosen to quantify the severity of the symptom.

Fatigue severity scale

Fatigue Severity Scale (FSS) is often used as an outcome measure in intervention studies to evaluate the change in fatigue over time (Whitehead, 2009). FSS is a nine-item instrument that assesses the effects of fatigue on daily activities with proven psychometric properties and structural validity (Valko, Bassetti, Bloch, Held, & Baumann, 2008; Whitehead, 2009). It is essentially a questionnaire comprising nine questions, each scored between 1 and 7. The FSS score is calculated as the mean score of the nine items, where a higher score represents a more severe fatigue (Fereshtehnejad et al., 2013). Fatigue severity is categorized into three levels based on FSS: severe fatigue (score ≥5), borderline fatigue (score between 4 and 5), and non-fatigue (score ≤4) (Lerdal, Wahl, Rustoen, Hanestad, & Moum, 2005). FSS is translated into several languages including Farsi with consistent reliability and validity (Fereshtehnejad et al., 2013).

Chalder fatigue scale

A brief and easy-to-administer fatigue scale was developed by Chalder et al. (1993). It is widely used as a reliable scale to measure physical and mental fatigue in chronic fatigue syndrome. It has 11 items with responses related to symptom frequency (0 = less than usual, 1 = no more than usual, 2 = more than usual, 3 = much more than usual). The total score, ranged between 0 and 33, is obtained by summing individual scores and a higher total score indicates a more severe fatigue (Jason et al., 2011). Recovery from fatigue and return to normal function is defined as Chalder Fatigue Scale (CFS) score <18 (Flo & Chalder, 2014).

Inclusion and exclusion criteria

Adult individuals (aged >18) who were abstained from methamphetamine, supported by urine toxicology test, and sought treatment for fatigue were assessed for fatigue level. Those with FSS >4 and CFS >18 underwent medical history and physical examinations. Participants with any of the following criteria were excluded: 1—sleep disorder; 2—concurrent medical illness including acute viral infection (such as influenza), cardiovascular diseases, diabetes, hyper/hypothyroidism, or anemia; 3—axis I psychiatric disorder based on DSM-IV criteria; 4—current dependence on alcohol, opiates, cocaine, or other illicit drugs.

The maintenance of abstinence, checked by weekly urine toxicology tests, was a necessity for study completion and participants with a positive test result at any stage were excluded from analysis. Individuals who did not adhere to medication compliance were also excluded.

Sample size and statistical analysis

Based on data from a previous trial of amantadine in the treatment of MS-induced fatigue (Ashtari, Fatehi, Shaygannejad, & Chitsaz, 2009), considering 80% power and alpha = 0.05, and assuming an attrition rate of 20%, a sample size of 42 (21 in each group) was calculated. All interval variables were tested for normality of distribution. IBM SPSS Statistic 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. A p-value of 0.05 was considered as significant. Categorical variables were reported as number (%) and continuous variables as mean ± standard deviation (Mikhalski et al.). Demographic characteristics and baseline FSS and CFS scores were compared between the two groups using T-test or Chi-square, whichever was appropriate.

Allocation, randomization, and blinding

The participants were randomized to receive either amantadine (Amin Pharmaceutical Company, Isfahan, Iran) or placebo using a simple computerized randomization program. The placebo capsules were made in the School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences with the same appearance and packaging to those of amantadine. Staff responsible for packaging of capsule containers and randomization process were not further involved in the study. All participants were visited by the same physician throughout the study who rated the FSS and CFS scores and prescribed the trial medications. The participants, physician, and statistician were blind to allocation.

Data collection

At the time of enrollment, an informed consent was obtained and a structured interview assessing demographic data, drug use, and treatment history was conducted. The following data were recorded for each participant: age, marital status, education, employment status, duration and the last time of methamphetamine use, and history of previous withdrawal attempts. Both fatigue measuring scales were explained to the participants and questionnaires of FSS and CFS were recorded by the physician at the baseline visit and then at the end of trial. Adverse effects, maintenance of abstinence, and compliance to medication were assessed during weekly visits to the clinic.

Outcomes

The efficacy of amantadine was evaluated using both measures of FSS and CFS. The primary and secondary outcomes were assessed at the end of trial and defined as the comparison between the two groups in 1—the reduction of both fatigue scales, and 2—the percentage of individuals reaching fatigue recovery, respectively. Fatigue recovery was assessed based on the two scales separately: once as FSS ≤4 and the other as CFS <18.

Results

A total of 86 treatment-seeking volunteers were screened for eligibility, of whom 42 individuals met the inclusion criteria and were randomized into two groups of 21 (Figure 1). During the course of the trial, the following exclusions were made: two participants were lost to follow-up, three did not adhere to medication compliance, and two had positive urine toxicology test. Consequently, 35 individuals including 17 in the amantadine group and 18 in the placebo group completed the trial and were considered in the analysis.

The results from per-protocol analysis showed that participants were all male and from the same race (Persian), aged between 22 and 40 years (mean 30.9 ± 4.7) and 45.7% married. All had a history of methamphetamine use for at least three times a week and stated smoking as the route of methamphetamine use prior to abstinence. The mean duration of methamphetamine dependence was 17.5 ± 6.3 months and the mean duration of abstinence was 1.6 ± 0.7 months. Eighty percent of participants were either employed or student to whom fatigue treatment was particularly important. The mean baseline FSS and CFS scores were 5.7 ± 0.5 and 22.8 ± 3.1, respectively. Considering the groups separately, 14 (82%) versus 16 (89%) individuals suffered from severe fatigue and 3 (18%) versus 2 (11%) individuals had borderline fatigue in the amantadine and placebo groups, respectively. The baseline characteristics, medication history, and the mean FSS and CFS scores of participants were not statistically different between the amantadine and placebo groups (Table 1).

At the end of trial, both fatigue scales were significantly lower in the amantadine group than those of the placebo group. Table 2 shows the final FSS and CFS scores for both study groups. A mean reduction of 28.0% versus 6.0% ($p < 0.001$) in the FSS and 24.3% versus 4.5% ($p < 0.001$) in the CFS were observed in the amantadine and placebo groups, respectively.

Recovery from fatigue was also assessed at the end of trial. Using FSS scores, eight participants (47%) in the amantadine group got recovered, seven (41%) were borderline, and two (12%) remained with severe fatigue. The results in the placebo group were, respectively, 1 (6%), 2 (11%), and 15 (83%) individuals

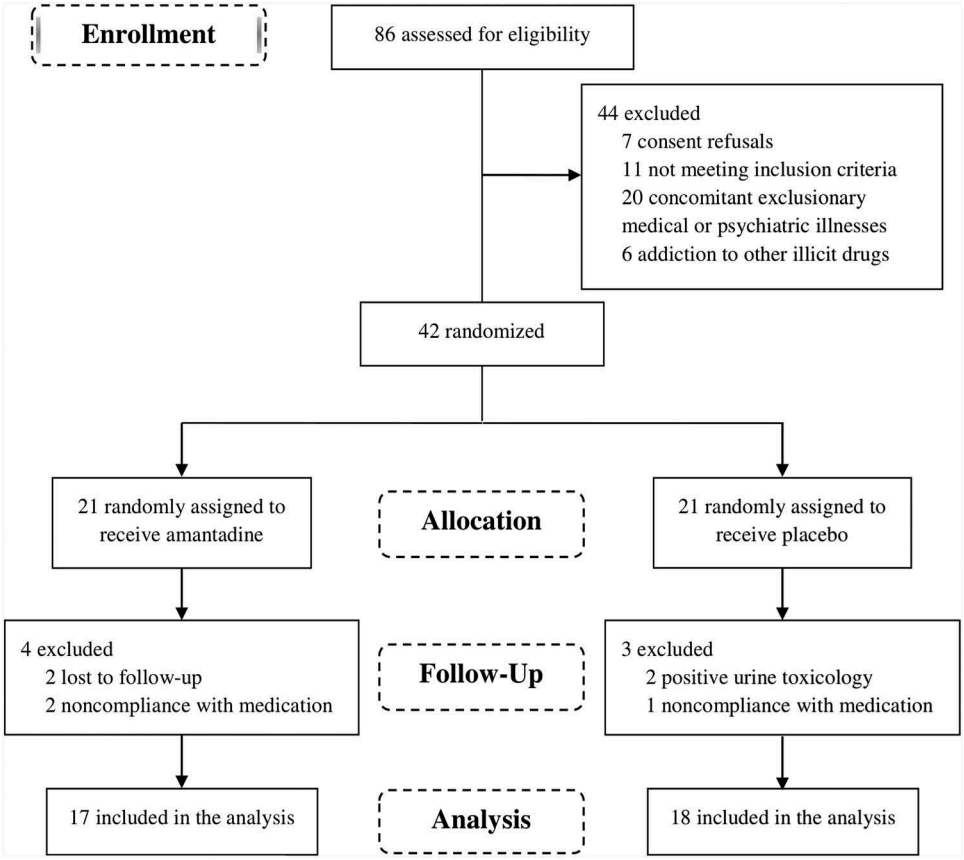

Figure 1. Randomization, treatment, and follow-up procedures.

Table 1. Baseline characteristics of the participants.

	Groups		Statistics		
	Amantadine (N = 17)	Placebo (N = 18)	$t(33)$	χ^2	p-Value
Age (years), mean ± SD	29.3 ± 4.4	31.6 ± 5.6	−1.3		0.18
Marital status, n (%)				0.69	0.40
Single	8 (47%)	11 (61%)			
Married	9 (53%)	7 (39%)			
Education, n (%)				0.25	0.89
Bachelor	7 (41%)	6 (33%)			
Diploma	9 (53%)	11 (61%)			
Illiterate	1 (6%)	1 (6%)			
Employment, n (%)				0.29	0.86
Employed	10 (59%)	12 (67%)			
Unemployed	4 (23%)	3 (16.5%)			
Student	3 (18%)	3 (16.5%)			
Length of regular methamphetamine use (months), mean ± SD	16.9 ± 6.5	18.1 ± 5.6	−0.49		0.62
Length of methamphetamine abstinence (months), mean ± SD	1.7 ± 0.7	1.6 ± 0.6	0.22		0.82
Individuals with previous methamphetamine withdrawal attempt, n (%)	8 (47%)	10 (55.5%)		0.25	0.61
Medication history				4.8	0.31
Benzodiazepines (alprazolam, chlordiazepoxide, clonazepam)	6 (35%)	4 (22%)			
Atypical antipsychotics (risperidone/quetiapine)	2 (12%)	5 (28%)			
β-Blockers (propranolol)	1 (6%)	4 (22%)			
H_2-blocker/Proton pump inhibitors (famotidine, omeprazole)	3 (17%)	1 (6%)			
GI antispasmodic/anticholinergics (mebeverine, clidinium)	2 (12%)	1 (6%)			
Baseline scores, mean ± SD			0.30		0.76 0.64
FSS score (range: 1–7)	5.7 ± 0.6	5.6 ± 0.4			
CFS score (range: 0–33)	23.1 ± 3.2	22.5 ± 3.1	0.46		
Fatigue severity				0.30	0.58
Severe fatigue (FSS ≥5)	14 (82%)	16 (89%)			
Borderline fatigue (4 < FSS < 5)	3 (18%)	2 (11%)			

SD: Standard deviation; FSS: Fatigue Severity Scale; CFS: Chalder Fatigue Scale; GI: gastrointestinal.

(Figure 2). Thus, the percentage of fatigue recovery was significantly greater in the amantadine group (47%) than the placebo group (6%), with $p < 0.01$. Assessing fatigue recovery using CFS scores showed eight (47%) individuals in the amantadine group versus two (11%) in the placebo group reaching recovery, with $p < 0.05$.

There was no statistically significant difference between the amantadine and placebo groups with respect to the adverse effects

Table 2. Results of fatigue measurements at the end of trial.

	Groups		Statistics	
	Amantadine (N = 17)	Placebo (N = 18)	t (33)	p-Value
FSS score (range: 1–7)	4.1 ± 0.6	5.3 ± 0.5	−5.8	<0.001
CFS score (range: 0–33)	17.3 ± 3.5	21.4 ± 2.9	−3.8	0.001

FSS: Fatigue Severity Scale; CFS: Chalder Fatigue Scale.

Table 3. Reported adverse effects during the trial.

	Groups		Statistics	
	Amantadine (N = 17)	Placebo (N = 18)	χ^2	p-Value
Adverse effects			6.8	0.08
Insomnia, n (%)	3 (18%)	0		
Anorexia, n (%)	2 (12%)	1 (6%)		
Nausea, n (%)	0	2 (11%)		
Dizziness, n (%)	2 (12%)	0		

($p > 0.05$), as shown in Table 3. Reported adverse effects were mild and transient and did not result in major discomfort. The three cases of medication noncompliance were due to negligence and not because of adverse drug reaction.

Discussion

To the best of the authors' knowledge, this is the first randomized, controlled trial of amantadine use in fatigue treatment of methamphetamine-abstained individuals. The results based on two fatigue measurement scales showed that amantadine 100 mg/day administered over 4 weeks significantly reduced fatigue severity and increased the rate of fatigue recovery. About half of the participants treated with amantadine achieved fatigue recovery at the end of trial, while this was around one in 10 in the placebo group.

Most of the treatment-seeking individuals were young and socially active and half of the participants (51.4%) had previous withdrawal attempts. Post-withdrawal fatigue may disrupt the individual's social and professional activities as well as increasing the risk of relapse. The outcome from this study, demonstrating the efficacy of amantadine in reducing fatigue severity, is valuable and can encourage further research on assessing its impacts on the quality of life and rate of relapse.

Amantadine in a dose range of 100–400 mg/day has been used in the pharmacologic treatment of cocaine dependence (de Lima, de Oliveira Soares, Reisser, & Farrell, 2002). Tennant and Sagherian (1987) showed that the administration of amantadine 100 mg/day for 10 days is effective in alleviating the symptoms of cocaine withdrawal. Since the current study was designed to specifically manage persistent fatigue, as one of several symptoms of methamphetamine withdrawal, the minimum effective dose of 100 mg/day over an extended period of 4 weeks was chosen. This also reduced the risk of potential adverse effects, especially central-nervous-system side effects (Sears & Clements, 1987). No statistically significant difference in adverse effects was found between the amantadine and placebo groups in the trial, which is in agreement with previous studies (de Lima et al., 2002; Foroughipour et al., 2013; Sears & Clements, 1987; White et al., 2014). The outcomes from this study thus support the efficacy and safety of low-dose amantadine in the treatment of persistent fatigue in methamphetamine-abstained individuals.

The study utilized two scales to measure fatigue severity, including FSS and CFS. The scales were independently used and outcomes were presented based on both scales. The comparison of results obtained from the two scales showed similar findings for fatigue severity reduction and fatigue recovery. Thus, future studies on methamphetamine-abstained individuals may consider either of the FSS or CFS scores for fatigue assessment.

A notable finding from the trial was that the time between the last use of methamphetamine and admission to the study for fatigue treatment ranged from 3 to 12 weeks (mean of 6.9 ± 3.0 weeks). Generally, there is little consensus regarding the persistence of methamphetamine-withdrawal symptoms, often ranging from several weeks to several months after abstinence (Pennay & Lee, 2011). This trial shows that the fatigue symptom could persist for a considerable period after abstinence and suggests that a minimum of 3 months follow-up would be essential for timely administration of appropriate interventions and managing ongoing symptoms, such as fatigue, to reduce the risk of relapse.

Limitations

One limitation of this study was the lack of female participants, because in general the population of male addicts to stimulants is substantially higher than females. In addition, in Iran, males are generally responsible for family income and fatigue could greatly

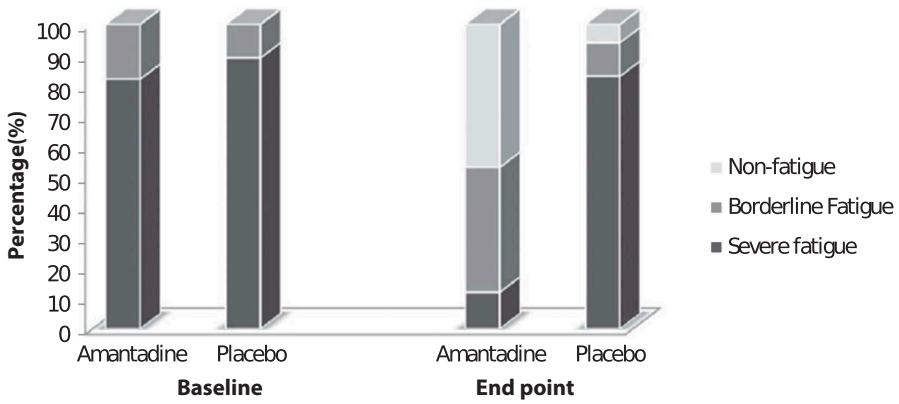

Figure 2. FSS-based treatment response in the amantadine and placebo groups.

jeopardize family welfare and finance. Thus, individuals seeking fatigue treatment in Iran are often male. Nevertheless, the population of female addicts is rising and the inclusion of female participants in future studies is encouraged. The second limitation was that fatigue severity was assessed at baseline and the end of study, i.e., the end of week 4. Weekly assessments can help to determine time to effect more precisely. Third, the sample size was relatively small; however, statistically significant results were obtained for both primary and secondary outcomes, which shows that the results would be applicable to larger population. Forth, despite that the acute withdrawal phase was not excluded from study entrance, all study participants were in the post-acute phase of withdrawal. This is most likely due to the existence of several other severe symptoms during the acute phase which make fatigue relatively less critical. Fifth, the trial was designed to measure fatigue reduction over 4 weeks of amantadine administration and therefore studying longer term outcomes was not within the scope of the trial. The assessment of long-term impacts, especially on reducing the risk of relapse and returning to social and professional activities, would also be valuable. Sixth, despite weekly pill counts were used to measure medication compliance, this may not provide certainty for medication adherence.

Disclosure of potential conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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