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The Efficacy of N-acetilcysteine for the Treatment of the Metamfetamin-addicted Patients Under Methadon Therapy: A Double-blind Clinical Trial

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Abstract

Background: Methamphetamine dependence is a growing global problem. Currently, there are no approved pharmacotherapy options for the management of methamphetamine dependence. One of the alternatives to manage this addiction is the use of N acetylcysteine (NAC) due to its capacity to restore homeostasis in the brain glutamate systems disrupted in addiction and its ability to reduce craving and the risk of relapse.

Methods: Methamphetamine-dependent volunteers under methadone treatment (n = 38) were randomized to receive daily doses of 1200 mg of NAC, or placebo. The participants were followed for 12 weeks (two visits weekly). Craving and Beck Inventory Depression (BDI) was determined at the beginning of the study and also after one month, two months, and three months. Addiction severity index (ASI) was recorded at the beginning of the study and after three months. The data were analyzed via SPSS version 16.0 (SPSS Inc. Chicago, Illinios, USA)

Results: The mean score of craving and BDI reduced after two months with NAC treatment. ASI (e.g., substance, familial, and psychiatric categories) was significantly reduced at the end of the study in the NAC group compared to placebo ($P < 0.001$). The success of the treatment in groups of NAC and placebo were 84% and 73%, respectively ($P = 0.001$). 63.2% of the NAC group patients avoided substance use for more than a month, but this was 10.5% in the placebo group ($P = 0.001$).

Conclusions: The NAC showed good efficacy in suppressing methamphetamine craving, addiction severity index, and depression. It may be a useful pharmacological treatment for methamphetamine dependency.

Keywords: Methamphetamine, N-acetylcysteine, Methadone, Dependency, Craving

1. Background

Methamphetamine dependency is one of the greatest public health problems around the world, associated with a wide range of psychiatric, medical, and social problems (1). According to recent studies, approximately one percent prevalence of methamphetamine use among the world's population (aged 15 - 64) increases the concern about the global hazards of this substance (2).

Methamphetamine dependency affects the individual's healthy social life. it leads to continuous consumption and false illusion from which a person will not be able to achieve lasting remission (3).

Although the information about the neurobiological sequences of methamphetamine dependency is increasing, no drug has been found as effective as a placebo to reduce methamphetamine use (4). The drugs used in the previous clinical trials include serotonin reuptake inhibitors (fluoxetine (5) and sertraline (6), calcium channel blockers (Amlodipine), three-cyclic antidepressants (imipramine, baclofen, gabapentin) 5-hydroxy tryptamine receptor antagonist (endonestrone, midarazapine), and antidepressant drugs, none of which have not been effective in the treatment of methamphetamine abuse (7-11). Studies that examine the efficacy of bupropion and modafinil, alpha-agonist drugs have shown inconsistent results on the dependency of methamphetamine (6, 12).

Despite such drugs, there are some observations that show glutamate abnormalities involves in the craving for substances. N-acetyl-cysteine plays a role in either the inhibition of glutamate receptors or reduction in released glutamate from the synapse. It also regulates the cysteine syn-

thesis and glutamate releasing at the synaptic surface and stimulates the NMDA autoreceptor (13, 14).

Another potential effect of N-acetyl-cysteine is the anti-inflammatory effect that prevents the production of cytokines and regulates glutamate and oxidative stress by stimulating glutathione production and regulating cysteine-glutamate anti-porter (15).

Nevertheless, no effective drug has been identified to treat methamphetamine addiction. Few studies evaluated the efficacy of n-acetylcysteine in the treatment of methamphetamine-dependent patients, which have been methodologically limited and revealed contradictory results (13, 16, 17).

2. Objectives

Therefore, the present double-blind clinical trial aims to exactly determine the efficacy of N-acetylcysteine in the treatment of methamphetamine-dependent patients treating with methadone.

3. Methods

3.1. Trial Design and Participants

This is a double-blind clinical trial. The study population includes methamphetamine-dependent patients treating with methadone, referring to addiction treatment centers in 2015. These centers were randomly selected from the list of all addiction treatment centers located in Kashan city.

The methamphetamine addicted people were accidentally assigned to intervention and placebo groups according to DSM-IV TR criteria, each patient went to the center twice a week for urine samples.

Vital signs, incidence of any side effects, and the results of urine analysis were recorded in each session. The repetition of the Beck Scoring System to determine the degree of depression and also drug craving test were done at the 4th, 8th, and 12th weeks. A complete physical and laboratory examination and ASI were performed for the patient at the end of 12 weeks.

The level of avoidance from methamphetamine consumption during the treatment period was revealed by determining the proportion of people with negative urine tests in each group. The primary outcome of the study was considered as the number of weeks that all of the qualitative tests evaluating the methamphetamine were negative, and the secondary outcome was the number of consecutive days that the person had not taken methamphetamine. The success of the treatment was defined as not taking methamphetamine for 21 days or the report of not taking methamphetamine more than 50% of initial consumption by the individual himself. To prevent measurement error, both of the measuring operator of outcomes and the patients were blinded to the type of treatment.

Before the implementation of the research, the detailed explanations were given by the second author to the patients in a meeting held individually for each one. Also, all questionnaires and information were completed anonymously and only by the allonym. After completion of the checking and importing it into the data analysis software, all personal information was eliminated. This study was approved by IR.KAUMS.MEDNP.REC.1396.115 code of ethics by the Deputy of Research and Technology of Kashan University of Medical Sciences. The research was also registered at the Iranian Center for Clinical Trials with code: IRCT20170524034111N1.

3.2. Inclusion and Exclusion Criteria

The inclusion criteria were age over 18, dependence on methamphetamine based on the Structured Clinical Interview for the DSM-IV-TR (SCID), informed consent, lack of medical conditions requiring hospitalization, the absence of a current neurological disorder including organic brain diseases, dementia or psychiatric disorders that are unrelated to methamphetamine abuse such as schizophrenia, bipolar disorder, or suicide attempt within 30 days prior to the onset of the study, no current use of drugs that have interactions with N-acetylcysteine, lack of current dependence on cocaine, alcohol, and benzodiazepines, and lack of alcohol dependence during 3 years before the study began. Exclusion criteria also contained seizure, discontinuation of drug therapy, detection of any substance abuse in DSM-V (except caffeine and nicotine) and reluctance from being maintained in the study.

3.3. Sample Size

The sample size was calculated as 19 for each group considering both the results of the previous studies and the craving in two groups of N-acetylcysteine (3.38 ± 1.16) as well as placebo (5.96 ± 1.03) with the confidence level of 95%, type I error of 20%, and a precision of 1. P-value less that 0.05 was considered significant (18).

$$n = \frac{\left(s_1^2 + s_2^2\right)^2 \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2}{\left(\overline{x}_1 - \overline{x}_2\right)^2} \quad (1)$$

3.4. Intervention

The intervention group received 1200 mg N-acetylcysteine daily in two divided doses for 12 weeks, and the placebo group received a similar placebo in size

and shape in the same manner. The subjects were initially evaluated for 2 weeks in which a complete medical history and physical examination were performed. The complete blood count and liver function tests were done. The urine sample was taken to determine the baseline methamphetamine content in patients. The presence of, at least, one positive urine sample for methamphetamine was necessary in the 2-week initial assessment. The participants were either entirely known about the directions and side effects of n-acetylcysteine or justified for taking medication and placebo.

To assess the patient's commitment to this, both groups went under supervision a week before starting the treatment to be evaluated for taking the placebo and their reference to the hospital to answer the questions. These patients were also supervised during their treatment in our study.

3.5. Instruments

3.5.1. Beck Depression Inventory - Second Edition (BDI-II)

The BDI-II questionnaire is a modified version of BDI, which takes 5 - 10 minutes to be filled. The maximum score of the subject is 63, indicating more symptoms of depression. The scale validity shows its correlation with previous versions (e.g., 0.93). Its correlation coefficient with the Hamilton scale for depression, the Beck Despair Scale, and the Beck Suicide Idea Scale is 0.71, 0.68, and 0.73, respectively. In Iran, the alpha coefficient, the correlation coefficient between the two sides, and the coefficient of re-test for one week for BID-II were reported 0.91, 0.89, and 0.94, respectively (18, 19).

3.5.2. The Structure of the Craving for Methamphetamine Abuse

This structure was scored by visual analogue scale test. The test consisted of ten images a person sees on a computer, in each image, from the subject is asked how much this image craves him. The examinant should display the level of his craving on a 7-degree scale ranged from none to extreme. A number between zero and seven was obtained.

This test was designed based on the studies conducted by Ekhtiari et al. (2006, 2008, and 2010). Cronbach's alpha coefficient of the test for methamphetamine users was 0.90 for all images indicating a great internal consistency (20).

3.5.3. Addiction Severity Index

The severity of the methamphetamines addiction was calculated by the Addiction Severity Index (ASI) scoring system. ASI is a semi-structured interview conducted face-to-face with patients. This questionnaire listed the patient's problems in every issue during the past 30 days, in the past year, and during their lives. In each section, it obtains a combined score (0 - 1) and grades the individual's status in that section. The validity and reliability evaluation of the Persian version of this questionnaire was cnducted by Atef Vahid et al., the Research Deputy of the University of Tehran, and with the collaboration of the National Center for Addiction Studies (21).

3.5.4. Data Analysis and Statistical Survey

The comparability of study groups was checked applying independent *t*-test and chi-square tests. The repeated measure analysis was used to assess the effect of treatment ($P = 0.05$).

The findings of the study were described with the central and peripheral indices and displayed with a table and a chart. Based on the distribution of the outcomes, a pre and post paired *t*-test and Wilcoxon was performed. Two groups were compared with the *t*-test or Mann-Whitney. The effect of confounding variables was assessed by subgroup analysis or regression analysis. ANCOVA test was used in the case of clear differences in the initial values.

4. Results

The present study investigated the effect of N-acetylcysteine in the treatment of 38 methamphetamine-dependent out-patients hospitalized in Kashan's methadone maintenance treatment centers in 2017.

As Table 1 shows, the mean age was 27.58 $\pm$ 4.85 years in the N-acetylcysteine (NAC) group and 28.2 $\pm$ 4.3 years in placebo group showing no significant difference between the two groups ($P = 0.781$). The number of participants in N-acetylcysteine and placebo groups were 84.2%, 73.7% male, respectively ($P = 0.426$).

Table 1. Sexual Frequency Distribution and Mean Age of Patients in the Two Groups

Variable	N-acetylcysteine (N = 19)	Placebo (N = 19)	P Value
Age (year)	27.58 $\pm$ 4.85	28.00 $\pm$ 4.42	0.781[a]
Sex, No. (%)			0.693[b]
Male	16 (84.2)	14 (73.7)	
Female	3 (15.8)	5 (26.3)	
Education, No. (%)			0.693[b]
Secondary school	16 (84.2)	14 (73.7)	
Diploma and higher	3 (15.8)	5 (26.3)	

[a] T-test
[b] Fisher's exact test

Table 2 shows the frequency distribution of drug abuse per month and the average daily intake of the drug in

the two groups. The daily intake of the drug in NAC and placebo groups was 6.47 ± 1.61 and 5.05 ± 1.68 g/day, respectively, which revealed a significant difference between the two groups (P = 0.012).

Table 2. The Frequency Distribution of Substance Use per Month and the Average Daily Intake of Drugs in the Two Groups

Variable	N-acetylcysteine (N = 19)	Placebo (N = 19)	P Value
Substance use per day	6.47 ± 1.61	5.05 ± 1.68	0.012[a]
Substance use per month, No. (%)			0.501[b]
Fewer than 18 days a month	8 (42.1)	6 (31.6)	
More than or equal to 18 days a month	11 (57.9)	13 (68.4)	

[a] T-test
[b] Fisher's exact test

Table 3 shows the frequency distribution in the avoided duration of drug abuse and the success in treatment for two groups. The success of treatment in both NAC and placebo groups was 84% and 73%, respectively (P = 0.001). 63.2% of patients in the NAC group and 10.5% in the placebo group avoided drug abuse more than one month (P = 0.001).

Table 3. The Frequency Distribution of Avoiding Drug Use and the Success of Treatment in Two Groups

Variable	N-acetylcysteine (N = 19)	Placebo (N = 19)	P Value
Avoiding substance consumption, No. (%)			0.001[a]
Fewer than 1 month	7 (36.8)	17 (89.5)	
More than 1 month	12 (63.2)	2 (10.5)	
Success in treatment, No. (%)			0.001[a]
Yes	12 (84.2)	2 (73.7)	
No	7 (15.8)	17 (26.3)	

[a] Fisher's exact test

Before analysis, the pre-requisite assumption of the test was checked with the Mauchly test. In cases where the assumption was not met, the Greenhouse-Geisser correction applied. The result of the analysis showed a significant reduction at craving rate over time (F = 400.67), P < 0.001).The between-group comparison revealed a significant reduction rate in the NAC group (F = 18.35), P < 0.001).There was an interaction between group and time (F = 23.13, P < 0.001). In other words, the treatment effect of NAC increased over time (Figure 1).

The repeated measure analysis showed a within-group significant reduction of BDI-II score over time (F = 1.19, P < 0.001). The between-group comparison showed no significant difference; however, there was an interaction between the effect of NAC's effect and time (F = 362.25, P < 0.001). In other words, the score of BDI reduced over time greatly compared to the placebo group (Figure 2).

Table 4 shows the mean of ASI for methamphetamine before and after treatment in both groups. The score was significantly lower in subgroups of drug, family, and psychiatry at the end of treatment in NAC than in the placebo group.

Table 4. The Mean of the Degree of Dependence of Methamphetamine (ASI) Before and After Treatment in Both Groups

Degree of Methamphetamine Dependency (ASI)	N-acetylcysteine (N = 19)	Placebo (N = 19)	P Value[a]
Medical			
Before	0.39 ± 0.27	0.38 ± 0.31	0.817
After	0.29 ± 0.27	0.33 ± 0.31	0.544
Job			
Before	0.58 ± 0.26	0.57 ± 0.29	0.815
After	0.27 ± 0.25	0.32 ± 0.30	0.537
Alcohol			
Before	0.43 ± 0.26	0.48 ± 0.29	0.540
After	0.26 ± 0.23	0.39 ± 0.28	0.107
Substance			
Before	0.63 ± 0.26	0.81 ± 0.20	0.024
After	0.26 ± 0.23	0.71 ± 0.20	< 0.001
Logical			
Before	0.58 ± 0.26	0.57 ± 0.29	0.817
After	0.29 ± 0.27	0.33 ± 0.31	0.538
Family			
Before	0.39 ± 0.27	0.38 ± 0.31	0.817
After	0.26 ± 0.23	0.71 ± 0.20	0.001
Psychiatry			
Before	0.58 ± 0.26	0.57 ± 0.29	0.815
After	0.17 ± 0.22	0.71 ± 0.20	< 0.001

[a] Mann-Whitney test

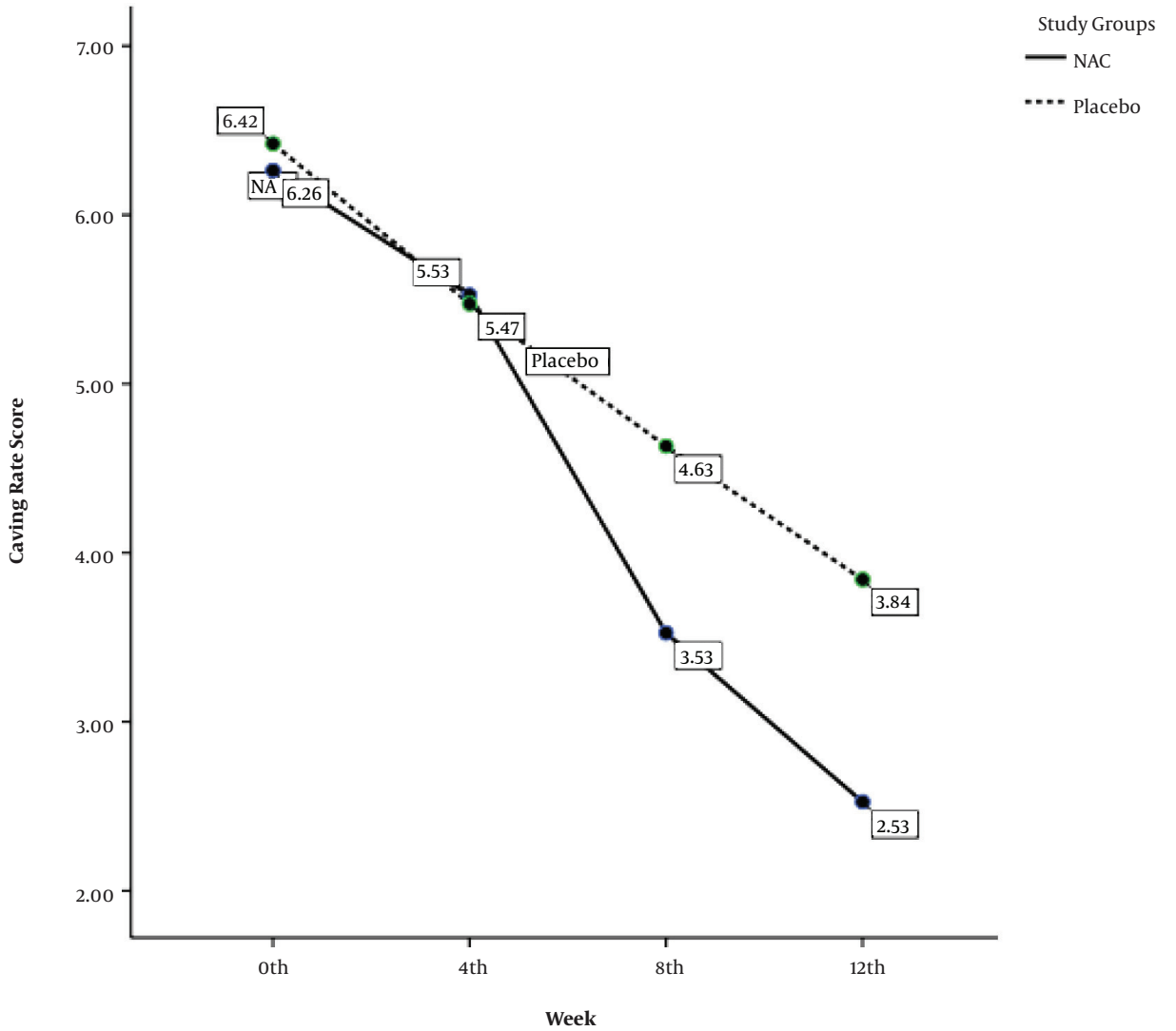

Figure 1. The effect of NAC on medical caving score

5. Discussion

The present study aimed to determine the effect of N-acetylcysteine in methamphetamine-dependent patients treating with methadone. 38 patients were randomly divided into two groups of 19 to receive NAC or placebo. The mean scores of both craving rate and BDI decreased by NAC after two months in all 38 patients who completed the study.

At the end of the study, ASI (including subgroups of drug, family, and psychiatry) significantly decreased in the NAC group compared to that in the placebo group ($P < 0.001$). The success of the treatment in the NAC and placebo groups was 84% and 73%, respectively ($P = 0.001$). 63.2% of the patients in the NAC group and 10.5% in the placebo group avoided taking drugs more than a month ($P = 0.001$).

Few studies have assessed the effect of N-acetylcysteine on the treatment of methamphetamine-dependent patients. Mousavi et al. in 2015 investigated the effect of N-acetylcysteine in the treatment of 23 patients addicted to methamphetamine. They found that N-acetylcysteine and matrix reduced the craving for methamphetamine use (22) which is similar to our results. In addition to increasing the sample size, we determined the amount of daily intake and increased the duration of treatment with N-acetylcysteine at the same dose of 1200 mg/day. We also

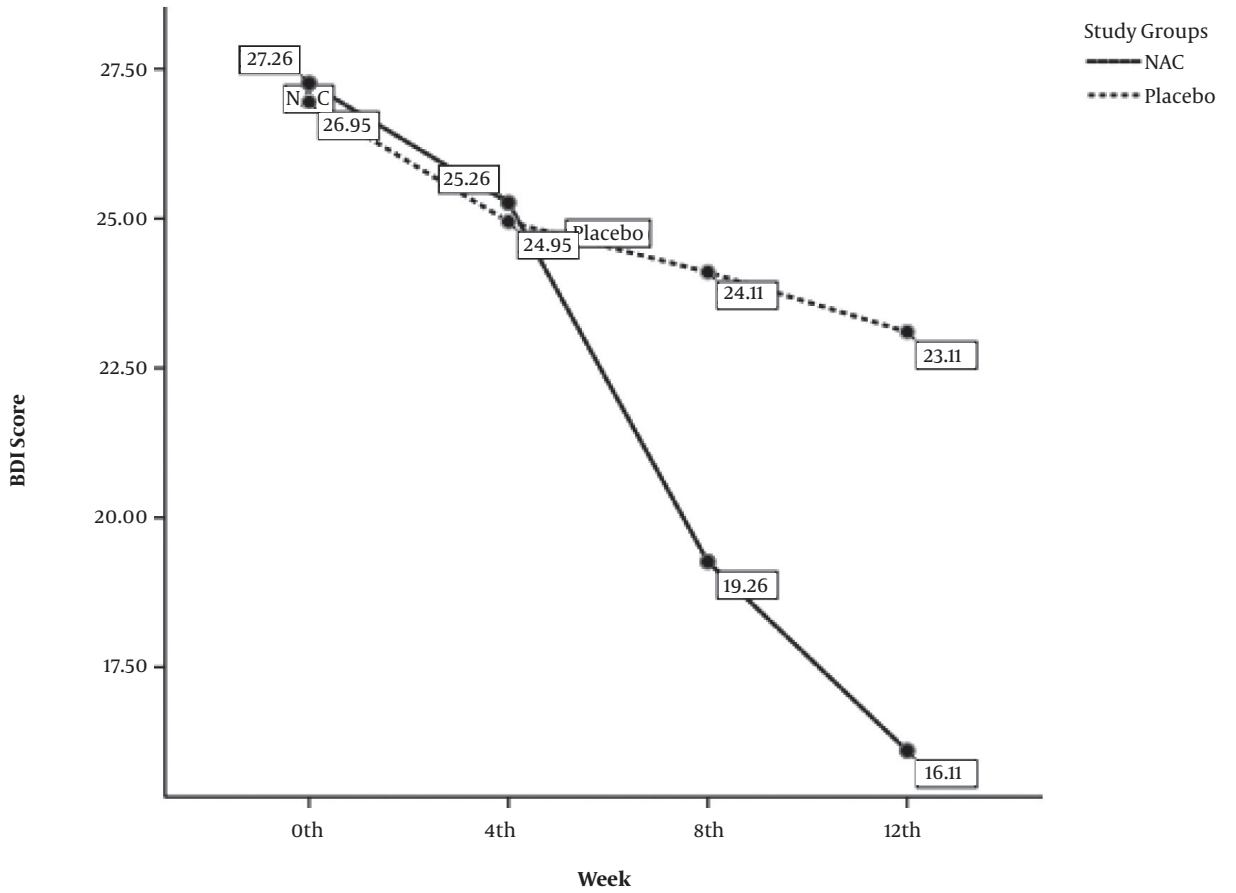

Figure 2. The effect of NAC on the BDI score

measured other criteria, such as ASI, depression, and duration of avoidance. In this study, there were different tests for methamphetamine abuse craving and drug administration. Moreover, Th patients were also being treated by methadone. It is believed that the synergism effect between methadone and N-acetylcysteine on glutamate regulation can be effective on study results as well.

LaRowe et al. conducted a study on 13 cocaine-dependent patients who received both N-acetylcysteine and placebo for 3 days. After one week, the results showed that N-acetylcysteine reduced the drug withdrawal symptoms as well as the craving for cocaine 13. Such results are consistent with our study.

Laro et al. (2013) found that acetylcysteine did not decrease cocaine abuse rates (23). This study was not contradictory to the results of our study due to some problems, including low sample size, lack of random allocation, and random selection.

Glutamate abnormality has an important role in drug abuse craving, and N-acetylcysteine inhibits glutamate receptors. It decreases glutamate releasing from synapse.

studies with greater sample size regarding the amount and the purity of the substance consumed by the patient in different sex and age groups.

The intake of 1200 mg N-acetylcysteine per day for 12 weeks can reduce the craving for methamphetamine consumption, the severity of the addiction, and depression.

It is suggested that the results of this study be interpreted according to the limitations, such as the uncertainty about the use of methamphetamine by the patient. To complete the present study, different doses of N-acetylcysteine should be examined, larger studies should be conducted with larger sample sizes, and other confounding factors should be considered, such as personality disorders, anxiety. Despite the mentioned limitations, this study provides guidance on how to prescribe one of the few existing drugs with efficacy in the treatment of methamphetamine dependency.

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Footnotes

Authors' Contribution: Study concept and design: Karami and Assarian. Acquisition of data: Karami and Ghoreishi. Analysis and interpretation of data: Karami, Sehat, and Ghoreishi. Drafting of the manuscript: Ghoreishi and Karami. Critical revision of the manuscript for important intellectual content: Ghoreishi and Karami. Statistical analysis: Sehat. Administrative, technical, and material support: Assarian, Ghoreishi, and Karami. Study supervision: Ghoreishi.

Clinical Trial Registration Code: The research was also registered at the Iranian Center for Clinical Trials with code: IRCT20170524034111N1.

Conflict of Interests: None declared.

Ethical Approval: Prior to the implementation of the research, the detailed explanations were given by the second author to the patients in a meeting held individually for each one. Also, all questionnaires and information were completed without the actual name of the participants and only by the anonymous. After completing the checking and importing it into the data analysis software, all personal information was eliminated. This study was approved by IR.KAUMS.MEDNP.REC.1396.115 code of ethics by the deputy of research and technology of Kashan University of Medical Sciences.

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Informed Consent: Participants provided inform consent.

References

1. Mausbach BT, Semple SJ, Strathdee SA, Zians J, Patterson TL. Efficacy of a behavioral intervention for increasing safer sex behaviors in HIV-positive MSM methamphetamine users: results from the EDGE study. *Drug Alcohol Depend*. 2007;**87**(2-3):249–57. doi: 10.1016/j.drugalcdep.2006.08.026. [PubMed: 17182196]. [PubMed Central: PMC1904343].
2. Degenhardt L, Ferrari AJ, Calabria B, Hall WD, Norman RE, McGrath J, et al. The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 study. *PLoS One*. 2013;**8**(10). e76635. doi: 10.1371/journal.pone.0076635. [PubMed: 24204649]. [PubMed Central: PMC3811989].
3. Everitt BJ, Wolf ME. Psychomotor stimulant addiction: a neural systems perspective. *J Neurosci*. 2002;**22**(9):3312–20. [PubMed: 11978805]. [PubMed Central: PMC6758398].
4. Volkow ND, Chang L, Wang GJ, Fowler JS, Leonido-Yee M, Franceschi D, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry*. 2001;**158**(3):377–82. doi: 10.1176/appi.ajp.158.3.377. [PubMed: 11229977].
5. Shearer J, Gowing LR. Pharmacotherapies for problematic psychostimulant use: a review of current research. *Drug Alcohol Rev*. 2004;**23**(2):203–11. doi: 10.1080/09595230410001704190. [PubMed: 15370027].
6. Batki SL, Moon J, Bradley M, Hersh D, Smolar S, Mengis M, et al. Fluoxetine in methamphetamine dependence—a controlled trial: preliminary analysis. *Problems of Drug Dependence*. 1999.
7. Shoptaw S, Huber A, Peck J, Yang X, Liu J, Jeff D, et al. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2006;**85**(1):12–8. doi: 10.1016/j.drugalcdep.2006.03.005. [PubMed: 16621339].
8. Galloway GP, Newmeyer J, Knapp T, Stalcup S, Smith D. A controlled trial of imipramine for the treatment of methamphetamine dependence. *Journal of Substance Abuse Treatment*. 1996;**13**(6):493–7. doi: 10.1016/s0740-5472(96)00154-7.
9. Heinzerling KG, Shoptaw S, Peck JA, Yang X, Liu J, Roll J, et al. Randomized, placebo-controlled trial of baclofen and gabapentin for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2006;**85**(3):177–84. doi: 10.1016/j.drugalcdep.2006.03.019. [PubMed: 16740370].
10. Johnson BA, Ait-Daoud N, Elkashef AM, Smith EV, Kahn R, Vocci F, et al. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. *Int J Neuropsychopharmacol*. 2008;**11**(1):1–14. doi: 10.1017/S1461145707007778. [PubMed: 17470315].
11. Cruickshank CC, Montebello ME, Dyer KR, Quigley A, Blaszczyk J, Tomkins S, et al. A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. *Drug Alcohol Rev*. 2008;**27**(3):326–33. doi: 10.1080/09595230801935672. [PubMed: 18368615].
12. McGregor C, Srisurapanont M, Mitchell A, Wickes W, White JM. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: a comparison of mirtazapine and modafinil with treatment as usual. *J Subst Abuse Treat*. 2008;**35**(3):334–42. doi: 10.1016/j.jsat.2007.12.003. [PubMed: 18329221].
13. Brackins T, Brahm NC, Kissack JC. Treatments for methamphetamine abuse: a literature review for the clinician. *J Pharm Pract*. 2011;**24**(6):541–50. doi: 10.1177/0897190011426557. [PubMed: 22095579].
14. LaRowe SD, Mardikian P, Malcolm R, Myrick H, Kalivas P, McFarland K, et al. Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. *Am J Addict*. 2006;**15**(1):105–10. doi: 10.1080/10550490500419169. [PubMed: 16449100]. [PubMed Central: PMC1513138].
15. Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2009;**66**(7):756–63. doi: 10.1001/archgenpsychiatry.2009.60. [PubMed: 19581567].
16. Sansone RA, Sansone LA. Getting a Knack for NAC: N-Acetyl-Cysteine. *Innov Clin Neurosci*. 2011;**8**(1):10–4. [PubMed: 21311702]. [PubMed Central: PMC3036554].
17. Asevedo E, Mendes AC, Berk M, Brietzke E. Systematic review of N-acetylcysteine in the treatment of addictions. *Braz J Psychiatry*. 2014;**36**(2):168–75. doi: 10.1590/1516-4446-2013-1244. [PubMed: 24676047].

18. Mousavi SG, Sharbafchi MR, Salehi M, Peykanpour M, Karimian Sichani N, Maracy M. The efficacy of N-acetylcysteine in the treatment of methamphetamine dependence: a double-blind controlled, crossover study. *Arch Iran Med*. 2015;**18**(1):28–33. [PubMed: 25556383].
19. Ghassemzadeh H, Mojtabai R, Karamghadiri N, Ebrahimkhani N. Psychometric properties of a Persian-language version of the Beck Depression Inventory–Second edition: BDI-II-PERSIAN. *Depress Anxiety*. 2005;**21**(4):185–92. doi: 10.1002/da.20070. [PubMed: 16075452].
20. Davoudi MR, Omidi A, Sehat M. Comparison of anxiety and depression symptoms between male daily smokers and nondaily smokers resident in Kashan city during 2016-2017. *Feyz Journal of Kashan University of Medical Sciences*. 2017;**21**(5):490–7.
21. Ekhtiari H, Alam-Mehrjerdi Z, Nouri M, George S, Mokri A. Designing and evaluation of reliability and validity of visual cue-induced craving assessment task for methamphetamine smokers. *Basic and Clinical Neuroscience*. 2010;**1**(4):34–7.
22. Wu TY, Lin CY, Arestedt K, Griffiths MD, Brostrom A, Pakpour AH. Psychometric validation of the Persian nine-item Internet Gaming Disorder Scale - Short Form: Does gender and hours spent online gaming affect the interpretations of item descriptions? *J Behav Addict*. 2017;**6**(2):256–63. doi: 10.1556/2006.6.2017.025. [PubMed: 28571474]. [PubMed Central: PMC5520122].
23. McKetin R, Dean OM, Baker AL, Carter G, Turner A, Kelly PJ, et al. A potential role for N-acetylcysteine in the management of methamphetamine dependence. *Drug Alcohol Rev*. 2017;**36**(2):153–9. doi: 10.1111/dar.12414. [PubMed: 27241765].