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Research Article

The Effectiveness of Bupropion in the Methamphetamines' Dependence Treatment: Randomized Double Blind Placebo Controlled Trial

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ABSTRACT

Methamphetamines are synthetic stimulants that their abuse is growing. Certain medications to treat dependence on these substances have not been confirmed yet. In this study the efficacy of bupropion in the treatment of patients with methamphetamine dependence were studied. In this double-blind controlled clinical trial 50 methamphetamine-dependent patients treated in bupropion and placebo groups were studied. Amphetamine craving with visual analogue scale, methamphetamine dependence with the Addiction Severity Index and depression with the Beck Inventory were assessed. The first group received 300 mg bupropion in two divided doses and second group received placebo twice a day. Patients were examined for 12 weeks with urine testing for drug abuse. Also at weeks 4, 8 and 12of treatment craving, severity of dependence and depression were examined.Mean Addiction Severity Index scales significantly decreased in intervention group compared to control group. Craving scores before and after treatment in Bupropion group were 77.4±8.93 and 54.24 ±10.12 and in placebo group were 76.64±9.46 and 67.56±10.73 respectively that decreased significantly bupropion group ($p<0.001$). Methamphetamine dependency treatment success rates was 52% in the bupropion group and 16% in the placebo group ($p= 0.007$).In this study it was found that bupropion significantly enhances the dependence of methamphetamine and increases the success rate of treatment.

Keywords: Bupropion, Methamphetamine, Dependence

INTRODUCTION

Methamphetamines are synthetic stimulant drugs which were first used in the 60s and 70s for treatment of obesity and depression (1). Besides limited medical applications of methamphetamines in the treatment of hyperactivity disorder, attention deficit and sleep disorders, illegal production of methamphetamine in home laboratories and their abuse is increasing day after day. According to statistics, about 24.7 million people across the world use methamphetamines each year, regularly (2 and 3).

Long-term use of high doses of methamphetamines disrupts regulation of monoamine neurotransmitters that is believed to be the physiopathological basis of addiction and withdrawal syndrome resulting from methamphetamines and incidence of cognitive disorders, memory and attention disorders, penchant for reuse, muscle aches, restlessness and tachycardia (4-6). Also, disruption in glutamate metabolism pathway that is observed in cocaine use is considered as a cause of methamphetamine addiction (7 &8).Several studies have been conducted to find effective drugs to reduce addiction to methamphetamines and many drugs have been studied; selective serotonin reuptake inhibitors such as fluoxetine and sertraline, calcium channel blockers, tricyclic antidepressants such as imipramine, baclofen and gabapentin, 5-hydroxytryptamine receptor antagonist such as

ondansetron, mirtazapine and modafinil that has some alpha-agonist effects and none of these drugs have been more effective compared to placebos (9-16).

Bupropion is a norepinephrine–dopamine reuptake inhibitor which belongs to the class of amino-ketones and has positive impact on depression treatment and on quitting smoking. Bupropion has a low potential for drug abuse and it is not fatal in high doses (17 & 18). Bupropion is connected to the dopamine transporter and increases dopamine transmission to prefrontal cortex and basal nuclei (19). By restoring depleted levels of monoamines, bupropion improves withdrawal symptoms and cognitive deficits in patients recovering from methamphetamines, thereby reduces methamphetamine use. (19).

Few studies have investigated the effects of bupropion on reducing methamphetamines addiction which have reported contradictory results. This clinical trial has investigated the effect of bupropion in the treatment of methamphetamines addiction.

MATERIAL & METHODS

Study Design and Participants

This randomized double blind placebo control trial is conducted on 50 patients with methamphetamine abuse, referred to addiction treatment centers in the city of Kashan, Iran during January to December 2013. Patients were divided into two intervention and control groups. 5 addiction treatment centers in the city of Kashan were randomly selected. Samples were selected from each of the centers based on the number of patients.Using convenience sampling method, subjects were selected among patients aged between 18-40 years who were dependent on amphetamines, on the basis of DSV-IV-TR. Patients with any chronic medical disease, neurological disorders, psychotic disorders, suicide attempt within the last 30 days, multiple simultaneous dependence, alcohol dependence during the last three years, history of eating disorders, history of head trauma and bupropion allergy were excluded from the study and replaced with another person.Demographic and clinical data such as age, gender, level of education, the degree of addiction to methamphetamine, history of drug use, the degree of drug craving and severity of depression were collected through interviews and questionnaires and inserted in checklists. Complete blood count (CBC), liver enzyme levels and urinalysis were performed for all patients to confirm methamphetamine use and results were inserted in checklists. Then, patients underwent initial evaluations for 2 weeks, in terms of clinical status and their cooperation for inclusion in the study.

Interventions

Patients were divided into two intervention and control groups using permuted-block randomization and by utilizing 4-fold and 6-fold blocks. The intervention group was treated for 12 weeks with bupropion 150 mg tablets (Abidi-Iran) twice a day and the control group received placebo with similar physical characteristics for 12 weeks.

Outcomes Measurement

Patients were followed up fortnightly by conducting urine test and by checking methamphetamine use. Patients were checked at fourth, eighth and twelfth weeks, in terms of severity of depression and drug craving. At the end of the twelfth week, patients were assessed in terms of degree of methamphetamine addiction.

Three questionnaires are used to assess the outcomes. (BDI-II) Beck Depression Inventory was used for initial and final assessment of patients in terms of severity of depression. BDI-II questionnaire consists of 21 items completed by patients. This questionnaire is adjusted on the basis of DSM-IV diagnostic criteria. Each item represents semiotic characteristics of depression such as sadness, feeling of guilt, suicidal thought and loss of interest. The first nineteen items include a 4-point scale from zero to 3 which shows the severity of depression. The remaining two items let subjects to express increases or decreases in their behaviors (behaviors such as changes in sleep patterns or appetite).

Visual analogue scale was used to measure craving for methamphetamine use. This test consists of ten images displayed on a computer for patients. They are then asked whether the image creates cravings in him or not. Participants should express their level of craving on a 7-point scale from "not at all" to "very much". Obtained number ranged between zero and seven shows their level of craving for drug use. This test has been designed and its validity has been approved by Ekhtiari et al. in 2008 (20).

The degree of methamphetamine addiction was calculated using addiction severity index (ASI). ASI is a semi-structured, face-to-face interview. This questionnaire collects patients' problems in various areas over the past 30 days, over the past year and during their lifetime. The fifth edition of this questionnaire contains 116 questions and its scoring is based on a defined algorithm manually or using software (21).

Ethical Considerations

This study is designed under the supervision and approval of the Ethics Committee of Kashan University of Medical Sciences and ethical issues are observed during all stages. Written informed consent was obtained from all participants and patients could leave the study at any time.

STATISTICAL ANALYSIS

Data were statistically analyzed using SPSS 19 software. Qualitative results are reported in the form of absolute and relative frequencies and quantitative results are reported in the form of mean±SD. Chi square, independent t-test and logistic regression are used to analyze data. P-values below 0.05 are considered as significant.

RESULTS

In this study, 50 patients with methamphetamine addiction were studied in two bupropion and placebo treatment groups in terms of addiction reduction. All the patients were male. The mean age of participants in the intervention group and the control group were 36.24±7.7 and 34.84±6.96 years, respectively and there was no statistically significant difference between the two groups in this regard (p-value=0.5). Demographic characteristics of studied patients are shown in Table 1.

The mean craving scores before beginning the study and four weeks after the treatment were not statistically significant; however, in the eighth and twelfth weeks after the intervention, the craving of patients treated with bupropion was significantly lower than the control group. Comparison of the degree of addiction at the end of the study showed that patients treated with bupropion have had significantly better conditions compared to the control group regarding subscales of: medical status, job status, legal status, family relations and psychiatric status. The success rate of treatment with bupropion has also been significantly higher than placebo treatment. Results are shown in Table 2. After controlling the confounding effects of age, level of education, length of use and depression via using logistic regression, it was found that was found that group therapy is effective on treatment of patients with methamphetamine addiction (p=0.009, OR=6.71, 95% CI=1.6- 27.78).

Table 1) Patients' demographic characteristics

Variables	Groups, n(%)		P value
	Intervention	Control	
Age group			
<35	10 (40.0)	15 (60.0)	0.16
>35	15 (60.0)	10 (40.0)	
Education			
Illiterate	4 (16.0)	3 (12.0)	0.61
Primary School	3 (12.0)	5 (20.0)	

Guidance School	7 (28.0)	8 (32.0)	
High School	10 (40.0)	6 (24.0)	
University	1 (4.0)	3 (12.0)	
Addiction duration (days)			
<18	17 (68.0)	15 (60.0)	0.56
>18	8 (32.0)	10 (40.0)	

Table 2) Treatment outcomes

Variables	Groups, n(%)		P value
	Intervention	Control	
Addiction Severity [a]			
Medical status	0.26±0.2	0.46±0.17	<0.001
Employment status	0.34±0.19	0.47±0.13	0.006
Alcohol use	0.007±0.02	0.01±0.04	0.56
Drug use	0.09±0.06	0.13±0.07	0.06
Legal status	0.05±0.06	0.11±0.1	0.02
Family/ social relationship	0.31±0.14	0.48±0.17	<0.001
Psychiatric status	0.17±0.07	0.29±0.05	<0.001
Overall status	0.18±0.05	0.28±0.04	<0.001
Craving status [a]			
Before intervention	77.4±8.93	76.64±9.46	0.77
4th week	72.08±8.91	72.76±10.62	0.8
8th week	59.96±9.92	69.2±10.94	0.003
12th week	54.24±10.12	67.56±10.73	<0.001
Treatment success [b]			
No	12 (48.0)	21 (84.0)	0.007
Yes	13 (52.0)	4 (16.0)	

[a]values presented as mean±Standard deviation

[b]values presented as No(%)

DISCUSSION

In this study, twelve weeks of administration of bupropion at a dose of 150 mg and twice a day significantly reduced craving scores in comparison to placebo administration. Also, administration of bupropion improved condition of patients in subscales of addiction severity index (ASI), including medical, occupational, legal, family and psychiatry problems. Also, in this study it was found that the success rate of treatment with bupropion has been significantly higher than placebo treatment (52% vs. 16%).

Experimental studies on different species of animals have shown that administration of bupropion is effective in the treatment of methamphetamine addiction. For example, in one study, administration of bupropion for rhesus monkey significantly reduced methamphetamine use in studied animals (22). Similar results are also reported in the study of rats (23 & and 24). Few studies have investigated the impact of this drug on human in terms of methamphetamine addiction which have led to conflicting results.

McCann et al. in a clinical trial administered bupropion for twelve weeks with a daily dose of 300 mg and considered methamphetamine withdrawal for two weeks or more as a successful treatment. In this study, the treatment success of intervention group and control group were 20% and 7%, respectively which are significantly different (25). Treatment success rate has been higher in our study; however, the effectiveness of bupropion in the treatment of methamphetamine addiction has been observed in both studies. In conflicting results, Heinzerling et al. administered the same dose of bupropion for 8 weeks for adolescent patients and found that this drug is not

effective in the treatment of addiction and the placebo receiving group has had higher treatment success rate (26). In another study, Heinzerlinget al. observed similar treatment success rates (the negativity of results of urine test at eleventh and twelfth weeks) in both bupropion and placebo treatment groups (27). In addition, Elkashef et al. administered bupropion for twelve weeks with a daily dose of 300 mg and observed no difference between the two groups in terms of treatment success rates (28). All these studies have employed similar treatment procedures; however, observed difference may be due to the differences between studied groups regarding primary characteristics such as race, age and the nature of used substances (in terms of purity and added substances).

In the present study, it was found that in the eighth and twelfth weeks after the intervention, the craving of patients treated with bupropion has been significantly lower than the control group. The effectiveness of bupropion in reducing craving for methamphetamine was first raised in 2001 in a case report where after administration of bupropion 150 mg tablets, twice a day for three weeks a significant reduction was observed in patient's cravings (29). In a clinical trial, Newton et al. studied 26 patients with methamphetamine addiction in two bupropion and placebo treatment groups and found that bupropion significantly reduces patient's cravings (30). This is consistent with the results of the present study. In contrast with these studies, Elkashef et al. in their study did not observe any positive impact for bupropion in reducing patient's cravings (28). In another study conducted by Shoptaw et al. on 73 patients, it was found that the positive impact of bupropion and placebo in reducing methamphetamine craving is similar (10). In these studies, methamphetamine doses have not been specified. Some of these differences may be attributed to the different doses of methamphetamine used by these patients. This assumption that the amount of exposure to methamphetamine can create different results in response to drugs has been confirmed in previous pre-clinical studies; so that low and high doses of methamphetamine have different effects on neuropeptide-containing neurons in striato-nigra and nucleus accumbens (31). As a result, different doses of amphetamine have different effects on monoaminergic systems in the brain and can create different and sometimes controversial reactions in response to a drug. On the other hand, differences in tools used to measure patients' cravings can also lead to different results. Besides, the sample size can affect the results, as well.

Gender may affect the results as well; since all the participants in our study were male. Other available studies have not investigated the impact of gender on treatment success rates; however, in the study of Elkashef et al. the treatment success rate has been higher in men treated with bupropion, compared to the placebo treatment group; while in women the difference between the two treatment groups was not significant (32).

Considering few studies conducted in this area, the mechanism of bupropion in reducing addiction to methamphetamine is not well known. Amphetamines affect dopamine transmission through influencing dopamine transporters and this impact is identified as the possible cause of addiction to methamphetamine (33). In in vitro studies, bupropion has inhibited amphetamine or methamphetamine-stimulated dopamine release (34--36). In an in vitro study, a direct relationship has been observed between the power of bupropion in inhibition of reuptake of dopamine and reduction of methamphetamine-stimulated dopamine release (37). On the other hand, in other studies, it has been observed that methylphenidate and bupropion by inhibiting the norepinephrine transporter have inhibited the effects of methamphetamine in norepinephrine release (38-40); however, the role of norepinephrine in creating addiction to methamphetamine is not well known.

Considering few and yet contradictory studies conducted in this area, it is difficult to conclude decisively about effectiveness of bupropion in the treatment of addiction to methamphetamine and using this drug in the treatment of

methamphetamine-addicted patients requires conducting studies with large population, with considering the dose and purity of methamphetamine used by patients and investigating its effect on different gender and age groups.

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