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Original Article

Anxiety treatment of methamphetamine-dependent patients with buprenorphine: A randomized, double-blind, clinical trial

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Abstract

Objectives: In this double-blind, randomized clinical trial, the effectiveness of buprenorphine (BUPRE) in the reduction of anxiety symptoms among the methamphetamine (MA) dependents was evaluated. **Materials and Methods:** The 60 MA-dependent patients were randomly assigned to three groups (0.1 mg, 1 mg, and 8 mg of BUPRE), The Hamilton Anxiety Rating Scale was administrated to assess the anxiety symptoms daily at baseline and second to the 5th day after intervention. The inclusion criteria were the MA dependence, age of over 18 years, and absence of any chronic physical illnesses; exclusion criteria were the presence of other drug dependence in combination with MA. The mixed-design analysis of variance was performed for data analysis. **Results:** A significant main effect of time (F = 51.456, P < 0.001) and group (F = 4.572, P = 0.014) and group-by-time interaction (F = 8.475, P < 0.001) were detected. **Conclusions:** This finding supports the efficacy of BUPRE to decrease anxiety. High doses of the drug (1 and 8 mg) were more effective than 0.1 mg. Here was not a significant difference between anxiety score when patients received 1 mg of BUPRE instead of 8 mg.

Keywords: *Anxiety, Buprenorphine, Methamphetamine, Substance use disorders*

Introduction

Methamphetamine (MA) dependence is a significant public health problem that has serious medical, psychological, and social consequences [1]. Prevalence of MA dependence reported <1% in the general population globally and also in Iran [2]. However, it is the difference among clinical patients, it reported 60.3% among men and 89.5% among women in methadone treatment services [3]. Clinical studies show that MA abuse can progress mental symptoms from a nonpsychotic to prepsychotic and then severe psychotic symptoms and may make persons vulnerable to a relapse of psychotic symptoms in long term [4]. MA dependence increases suicidal ideations and depressive symptoms [5].

MA dependence increases the risk of brain impairment [6]. Neuroimaging studies showed that long-term MA use may lead to widespread damage to the neuron system and as a result cognitive impairment, such as attention deficits, decreased memory performance, and weakening of executive function [7]. These impairments make a contribution to induce other psychiatric disorders such as mood disorders (32.3% comorbidity, 10.6% induced by MA), anxiety (26.5% comorbidity, 3.7% induced by MA), and psychotic symptoms (28.6 comorbidity, 13.2% induces by MA) [8].

Comorbid of psychiatric disorder with MA abuse or dependence [5,8-10] is one of the most barriers to treatment of MA dependence[11] and other substance use disorders [12], they led to more likely relapse in these patients [5,13,14]. Anxiety is reported as one of the comorbid psychiatric disorders of MA dependence, in the range of 25%[8] to 76% [15]; they experience a high level of anxiety that drives them to seek illegal drugs [16]. Moreover, a follow-up study on MA users revealed that those with anxiety comorbidity were more likely to meet the criteria for alcohol and other SUDs after 3 years than the nonanxious group [12]. Therefore, effective intervention for MA dependence should consider comorbid disorders too.

The efficacy of BUPRE to reduce substance use cravings has been demonstrated [17-23]. Several lines of clinical data also discover the key role of BUPRE for the treatment

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of comorbid psychiatric disorders[24] or significant impact to psychopathological symptoms reduction, including "worthlessness-being trapped, somatization, and panic-anxiety and violence-suicide" [25,26]. Anxiety reduction was detected in the opioid-dependent patients with BUPRE [27,28]. There are few studies with full protocol of BUPRE intervention including dosage or treatment duration to reduce anxiety symptoms. We can refer to one randomized clinical trial and follow-up study that starts with 4 mg/day of BUPRE-naloxone and increases it to 8–24 mg/day (oral) for 12 weeks [29]. Such research studies are in major advance, and more evidence is a need. This randomized control trial (RCT) study was designed to investigate the role of BUPRE in anxiety reduction in MA-dependent patients in 4 days repeatedly after baseline.

Materials and Methods

Study design

This randomized double-blind clinical trial used a "within-between subject design" with the main and interactional effect of BUPRE and time. After evaluating the baseline of anxiety symptoms, the participants were assigned randomly into three groups, as a follow, control group (received 0.1 mg BUPRE) and two treatment groups (either 1 mg of BUPRE and another 8 mg daily), participants measured 4 times after baseline in consecutive days by Hamilton anxiety scale [Figure 1].

Participants

Participants of the study were selected among MA-dependent outpatients referring to Ebnesina Hospital, affiliated to Shiraz University of Medical Sciences. Inclusion criteria were, met the DSM-5 criteria for MA use disorder, smoking MA every day for at least 1 year, 18 years of age or older, consent to participate in the research study, and exclusion criteria were any chronic physical illness, current dependence or abuse of any other drugs, the total sample size was estimated equal 60 for three groups in 5 repeated measure with considering effect size of $F \geq 0.2$, alpha error <0.05, and power of test ≥ 0.8.

Measures

The Hamilton Anxiety rating scale measures the severity of anxiety symptoms [30], the scale consists of 14 items, each item recognizes a series of symptoms, this scale evaluates both psychic and somatic anxiety. Scoring of items establish at 0 (no symptoms) to 4 (severe symptoms), total score could obtain in the range of 0–56, this scale identifies three levels of anxiety according to the total score: mild severity (0–17), mild-to-moderate severity (18–24), and moderate to severe (25–30). The Persian version of the scale was used in the current study.

The Structured Clinical Interview for DSM-5

The criteria of the diagnostic and statistical manual of mental disorders fifth edition (DSM-5)[31] were used to diagnose MA use disorder.

Procedures

The study was conducted in 2017 in Ebnesina Hospital, affiliated with Shiraz University of Medical Sciences; all individuals gave written informed consent to participate in the study. They were interviewed by a psychiatrist according to Structured Clinical Interview for DSM-5 to ensure of meeting criteria for MA dependence, the baseline score for anxiety symptoms was assessed by Hamilton anxiety rating scale, then they assigned to three experimental groups randomly, doses of BUPRE for each group were as follow: 0.1 mg for the control group, 1 mg for treatment group$_1$ and 8 mg for treatment group$_2$. Randomization was done by the computer.

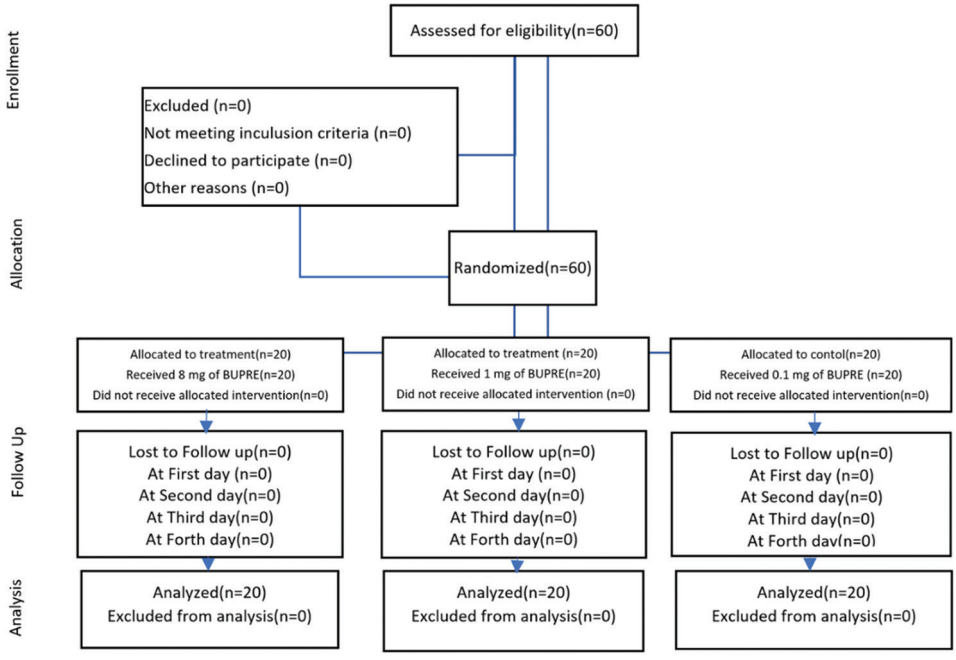

Figure 1: Participant flow chart for the clinical trial of bupropion for the treatment of anxiety among methamphetamine dependents

All participants fulfill the HAM-A for 4 days after the baseline assessment. Finally, the process of anxiety symptoms was compared by days (time), group, and interactional effects of group*time. All procedures of study were reported according to revised CONSORT statement [32]. The Ethics committee of Shiraz University of Medical Sciences reviewed and approved the final protocol of the study approval number: IR.SUMS.14237-01-01-1396, and IRCT registration number is IRCT2017081525160N8.

Potential source of bias

The sources of bias in RCT studies are varied. The most important of which can be mentioned Selection bias, Ascertainment bias, Choice-of-question bias, Regulation bias, Measurement bias, and Withdrawal bias. We try to control selection bias with true randomization, all participants had the same opportunity to be allocated to each of the study groups. The three groups were homological in terms of characteristics that could influence the outcome as confounders. Ascertainment and Choice-of-question bias was controlled by keeping unware both subjects and administrators of the amount of BUPRE received, this study was double blinded. To control measurement bias, a valid tool was used and all participants fulfilled that in the same situation. The length of this study was not long, therefore there were not any withdrawal bias included participants' dropout.

Statistical analysis

Demographic variables were described by mean with standard deviation or frequencies and percent (%). The mixed-method included repeated measure analysis with between factor subset of General Linear Model was performed to extract the mains and interactional effects. Wilks' lambda, Greenhouse-Geisser, and F values were used to measure how time, grouping, and time*grouping affected the severity of anxiety symptoms. Other analyses included the Bonferroni test for pairwise comparison at the time and also group factors, partial Eta square to estimated effect size, and plot to present the interactional effect of time*grouping. Data were analyzed by IBM SPSS Software, version 25.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ were considered statistically significant.

Results

The sample of the study was 60 MA-dependent men who were seeking treatment in Ebnesina Hospital, affiliated to Shiraz University of Medical Sciences, the demographic characteristics of participants are presented in Table 1, all three groups are similar according to demographic characteristics. The average participants' age was 35.33 years, 45% of participants were single, 33.3% got married, and 21.7% were divorced. Only 5% of participants were employed, while 28.3% and 66.7% were unemployed and self-employed, respectively.

Descriptive data are presented in Table 2 for outcome repeated measure and also baseline measure. Three treatment groups were not different at baseline of the severity of anxiety symptoms ($F_{2,57} = 0.459$, $P = 0.634$).

Result of Table 3 shows the significant effects of groups (doses of BUPRE), time, and groups*time on anxiety symptoms. Anxiety score intended to reduce according to pairwise comparison within the intervention; there is a significant difference between the severity of anxiety on the 2nd day compared to the baseline and also in comparing the following days with the baseline.

There is also a significant difference between the three groups, and pairwise comparisons based on the Bonferroni test show that there are significant differences between the group who received 0.1 mg BUPRE with 2 other treatment groups who received 1 and 8 mg BUPRE in the score of anxiety. There is no significant difference between those who received 1 mg or 8 mg in terms of reducing anxiety.

Table 1: Comparison of demographic characteristics for the control and intervention groups of study

	Control	Intervention		Total	*P*
	0.1 mg (*n*=20)	1 mg (*n*=20)	8 mg (*n*=20)		
Age (mean±SD)	38.20±9.63	33.25±9.07	34.55±9.46	35.33±9.47	0.233
Years of drug abuse (mean±SD)	7.45±7.97	4.80±4.71	7.45±7.56	6.57±6.90	0.380
Marriage status, *n* (%)					
Single	6 (30.0)	12 (60.0)	9 (45.0)	27 (45.0)	0.233
Married	10 (50.0)	5 (25.0)	5 (25.0)	20 (33.3)	
Divorced	4 (20.0)	3 (15.0)	6 (30.0)	13 (21.7)	
Education, *n* (%)					
Illiterate	0	1 (5.0)	0 (0.0)	1 (1.7)	0.621
Middle school	13 (65.0)	8 (40.0)	12 (60.0)	33 (55.0)	
High school	6 (30.0)	9 (45.0)	7 (35.0)	22 (36.7)	
High education	1 (5.0)	2 (10.0)	1 (5.0)	4 (6.7)	
Job, *n* (%)					
Unemployed	4 (20.0)	7 (35.0)	6 (30.0)	17 (28.3)	0.882
Self-employed	15 (75.0)	12 (60.0)	13 (65.0)	40 (66.7)	
Employed	1 (5.0)	1 (5.0)	1 (5.0)	3 (5.0)	

Table 2: Descriptive data of severity of anxiety symptom based on time and group

	Group			Total (n=60), n (%)
	Control	Intervention		
	0.1 mg (*n*=20), *n* (%)	1 mg (*n*=20), *n* (%)	8 mg (n=20), n (%)	
Time				
Baseline	18.15 (10.02)	17.25 (8.25)	20.05 (9.93)	18.48 (9.35)
Day 1	11.45 (9.41)	8.05 (5.24)	8.30 (5.50)	9.26 (7.03)
Day 2	12.40 (10.60)	7.10 (4.97)	6.75 (5.10)	8.75 (7.70)
Day 3	14.70 (9.00)	8.40 (5.06)	5.05 (4.94)	9.38 (7.65)
Day 4	17.55 (9.92)	9.25 (6.77)	4.70 (5.21)	10.50 (9.16)
Marginal mean	14.85	10.01	8.97	

Table 3: Test of within-between subjects' effects for severity of anxiety symptoms

	SS	df	MS	*F*	*P*	Partial Eta squared[a]	Power of test
Time	3992.88	4	998.22	51.46	<0.001	0.47	0.99
Group	1969.38	2	984.693	4.57	0.014	0.14	0.76
Time*Group	1315.21	8	164.40	8.48	<0.001	0.23	0.96

[a]Effect size estimated. SS: Sum of square, MS: Mean of square, *: Interaction

It can be seen in Figure 2 and also Table 4 that the effectiveness of the BUPRE over time (time-variable) is related to the doses of BUPRE (group variable). Looking at the 3 lines, although anxiety symptoms have increased in both treatment groups (1 and 8 mg of BUPRE) compared to the control group (0.1 mg of BUPRE), the time produces much of a change in the anxiety scores for 8 mg doses of BUPRE.

Discussion

This randomized clinical trial investigated the effectiveness of BUPRE to decrease the severity of anxiety symptoms among MA-dependent patients. As the results revealed, the impact of the main effects and the interactional effect was significant to decrease the severity of anxiety symptoms. Both treatment groups significantly reduced anxiety symptoms. Although there were not significant differences between 2 treatment groups (1 and 8 mg of BUPRE) to decrease the anxiety symptoms, the interactional effect showed doses of BUPRE are related to the passing of time, in the case of 1 mg of BUPRE, the severity of anxiety reduced significantly but this reduction remains invariant. While for the treatment group who received an 8 mg dose of BUPRE, not only the severity of anxiety symptom decreased significantly, the reduction trend survived for 4 days after baseline.

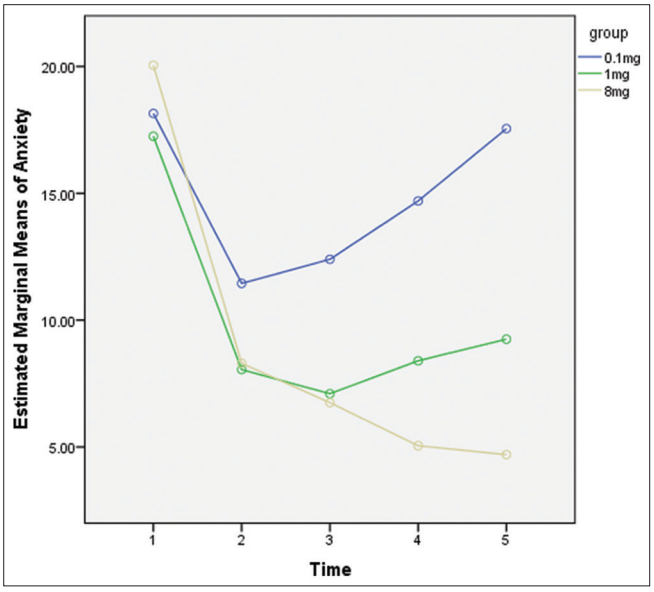

Figure 2: Main and interactional effects of study factors

Table 4: Pairwise comparisons within-between Groups by Bonferroni test

Pairwise comparison	Overall		BUPRE 0.1 mg		BUPRE 1 mg		BUPRE 8 mg	
	MD	*P*	MD	*P*	MD	*P*	MD	*P*
Time								
d_0-d_1	9.22	<0.001	6.70	<0.001	9.20	<0.001	11.75	<0.001
d_0-d_2	9.73	<0.001	5.75	0.001	10.15	<0.001	13.30	<0.001
d_0-d_3	9.10	<0.001	3.45	0.049	8.85	<0.001	15.00	<0.001
d_0-d_4	7.98	<0.001	0.60	0.749	8.00	<0.001	15.35	<0.001
d_1-d_2	0.51	0.269	−0.95	0.448	0.95	0.122	1.55	<0.001
d_1-d_3	−0.12	0.855	−3.25	0.043	−0.35	0.735	3.25	<0.001
d_1-d_4	−1.23	0.110	−6.10	0.001	−1.20	0.393	3.60	<0.001
d_2-d_3	−0.63	0.386	−2.30	0.263	−1.30	0.100	1.70	0.001
d_2-d_4	−1.75	0.045	−5.15	0.028	−2.15	0.085	2.05	0.006
d_3-d_4	−1.12	0.001	−2.85	<0.001	−0.85	0.178	0.35	0.420
Group								
G_1-G_1	4.80	0.023						
G_1-G_8	5.88	0.006						
G_1-G_8	1.04	0.618						

BUPRE: Buprenorphine, MD: Mean difference

Although there are new findings that reveal BUPRE's Impact on Reducing Psychiatric Symptoms, there is an old tip by Emil Kraepelin that had recommend BUPRE to treat psychiatric disorders [24]. The finding of the current study is notable and provides valuable pieces of evidence to the role of BUPRE to decrease anxiety symptoms. High comorbidity of anxiety in MA users [12,33] is associated with nonsatisfaction treatment outcomes and a higher rate of relapse [34]. Mental illness comorbidities can significantly affect adherence to treatment (13). BUPRE has shown antidepressant [35-37] and anxiolytic [27,28,35], it reduced suicide ideation and also self-injury [36,38].

Studies have shown that BUPRE's effect is beyond opioid users[39] and reduces attention to negative emotion and also fearful stimuli [28], although the emotional processes that have improved on the impact of BUPRE are not known yet, an opioid system of the brain is involved in negative emotional responses mostly [37]. BUPRE gets involved kappa-opioid in stress systems implicated [40]. Kappa opioid receptors (KORs) in the central nervous system are referred to as regulators in mental illnesses such as anxiety and addiction [41]. Three opioid receptors (μ, δ, κ) have distributed in regions of the brain that involves in the stress response including the red nucleus of the stria terminals, central amygdala, and paraventricular nucleus of the hypothalamus [42]. There has been recognized another neuronal circuitry that is impacted by KOR signaling and has key peptides in anxiety-related disorders [41]. Several scholars have demonstrated the efficacy of BUPRE to reduce negative emotions. Such findings rationalize the importance of effective intervention to reduce comorbid psychiatric disorders (anxiety and others) to facilitate the substance use treatment and may decrease the burden of mental health services.

Attention to comorbid disorders with substance use disorders and the role of drugs and some nondrug therapies has already been studied for many years. Some scholars have compared the effects of buprenorphine and methadone to reduce symptoms of other psychiatric disorders, buprenorphine has revealed better outcomes than methadone [20,23,25], and it was associated with less side effects than MMT, there is also growing evidence that higher doses of buprenorphine (16–32 mg) are more efficacious than lower doses [22].

Limitation

Substance use disorders are complex in nature, and there are many difficulties in evaluating the effectiveness of any treatment. We do not know whether the anxiety treated is primary or secondary that drive due to substance abuse, and therefore, we do not know which anxiety has been treated.

It can be suggested that future studies be carried out by forming a Four-Group Solomon design that includes both anxious individuals. However, in the current study, we tried to minimize this problem by estimating the effect size in the statistical method as well as precise control in the design methodology.

Conclusions

BUPRE showed an effective role in improving anxiety severity symptoms among MA dependence. In a situation where we are dealing with psychiatric comorbid disorders with substance use disorders and also in a situation where the polydrug addiction is increasing.

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Conflicts of interest

There are no conflicts of interest.

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