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ORIGINAL ARTICLE

Superiority of Buprenorphine over Suboxone in Preventing Addiction Relapse in Opioid Addicts under Maintenance Therapy: A Double-Blind Clinical Trial

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Abstract

Background: In maintenance therapy for opioid addiction, to reduce the risk of buprenorphine (BUP) abuse, the combination of BUP and naloxone (NX) has been developed and is commercially available as suboxone (BUP/NX). This study was designed to compare addiction relapse frequency in patients receiving BUP and BUP/NX as maintenance therapy.
Methods: In this double-blind clinical trial with cross over design, 100 opioid abusers were randomly assigned to two treatment groups to receive either BUP or BUP/NX. After three months, without a time-out period, subjects undertook treatment with the other drug. The subjects were screened weekly for urinary morphine.
Results: In each of the study arms, when the patients were given BUP/NX, the number of relapses was significantly higher compared to when they received BUP (0.13±0.24 vs. 0.04±0.09, P = 0.001). If participants' age was taken into account, the number of relapses was significantly higher when BUP/NX was given in age groups of 31 to 40 years and over 50 years ($P < 0.05$). The length of addiction had also a significant impact on the number of relapses, i.e., patients with over 10-year history of addiction had higher number of relapses if they were given BUP/NX compared with BUP ($P < 0.05$).
Conclusion: BUP seems to be more effective than BUP/NX in preventing addiction relapse in opioid abusers under maintenance treatment.

Keywords: Buprenorphine; Buprenorphine; Naloxone Drug Combination; Opioid-Related Disorders; Recurrence

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INTRODUCTION

Over half of the world's opiate addicts live in Asia and opioids are still the most prevalent primary drugs of abuse among people seeking treatment in this region (1). The highest estimates of opioid use belong to the Southwestern Asian countries (1). The situation of Iran among these countries is different, because: first, opioid use ranks among the highest causes of death and burden of disease in this country; and second, neighboring Afghanistan as one the major opioid production countries, Iran has been vulnerable to drug trafficking, therefore, such illicit drugs are more likely available with lower costs in the country (2-4). To tackle this problem, several addiction treatment clinics have been established across the country using various rehabilitation treatments (5,6). The most popular method is maintenance therapy with opioid agonists such as methadone (METH), buprenorphine (BUP) and suboxone (BUP/NX) (7).

BUP, which is a partial opioid agonist, has high affinity to μ-opioid receptors. It can displace morphine, METH and other full opioid agonists from such receptors (8). Hence, full opioid agonists cannot exert an opioid effect on the receptors already occupied by BUP. In addition, BUP has a slow dissociation rate from μ receptors, which results in prolonged suppression of opioid withdrawal and blockade of exogenous opioids (8). Given these two pharmacodynamic properties, although the chance of BUP abuse persists (9,10), it is lower than that of METH (11).

To reduce the risk of BUP abuse, BUP/NX has been produced with formulation of BUP to naloxone (NX) with 4:1 ratio (9,10). It is generally known that the bioavailability of NX in BUP/NX is relatively low in sublingual delivery, while BUP has an acceptable sublingual absorption. Therefore, if the combination is taken sublingually, the patient experiences BUP effects (12); however, if administered intravenously, antagonistic effects of NX appear predominantly and the drug abuser displays accelerate withdrawal syndrome (12).

BUP/NX has recently been introduced in Iran and is gradually gaining popularity in Iranian rehab clinics. It is still a question whether or not BUP/NX is more effective than BUP to prevent addiction relapse in addict patients. Hence,

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this study was designed to compare addiction relapse frequency in patients receiving BUP and BUP/NX as maintenance therapy.

Methods

Study design and subjects

This was a double-blind randomized trial with cross over design, in which, patients involved with opioid addiction who were under maintenance treatment in 5 outpatient substance-abuse rehab clinics in Mashhad, Iran, were enrolled. Demographics of the subjects including age, marital status, educational level and occupation were collected and entered into a predesigned checklist. Moreover, the type of the abused drug and the predominant administration route were asked from each subject.

Patients with history of multi-drug abuse and those with major psychiatric co-morbidities were excluded. In total, 154 opioid addicts under maintenance treatment to quit opioid abuse were evaluated. 54 patients were excluded from the study, including 33 who were multi-drug abusers and 21 who had psychiatric co-morbidities. Finally, 100 patients were included in the analysis (Figure 1).

Patients were randomly assigned into two groups and each group underwent treatment with either BUP (Group 1) or BUP/NX (Group 2) for 3 months. When necessary, dosage of drug was adjusted for each patient in order to avoid withdrawal syndrome. After 3 months, without a time-out period, study subjects underwent the treatment with the other drug. In other words, those who received BUP in the first 3 months, were given BUP/NX in the next 3 months, and vice versa (Figure 2).

Clinical and laboratory investigations

At the beginning of the study, 3 toxicological tests were performed for each patient for detection of illicit drugs including cocaine, amphetamine and cannabis in serum or urine. During the study, study subjects were weekly screened for urinary morphine by using urine Fastep® MOR Rapid Test Strip (Polymed Therapeutics, Inc., Houston, TX, USA). This test strip has an accuracy of over 99.9% in agreement with commercially available tests, and its minimum concentration for positive result at 5 minutes was 300 ng/mL for morphine and 250 ng/ml for codeine. Regarding the reproducibility of the test strip, the negative result in samples with morphine/heroin concentration was at 50% of the cut-off and positive at 200%. Also, regarding the precision, the negative result in samples with morphine/heroin concentration was at 50% of the cut-off and positive at 150%. In addition to urine morphine test, patient's relapse into addiction was asked in each visit. Relapse was defined as any evidence of misuse of an opioid during the treatment period.

Ethics

All patients were fully informed about the study objectives, and informed consent was obtained from each. However, none of the examinees knew that they are under which of the treatment plans. Clinicians were also blinded to know which patient was allocated to either treatment groups. Examinees were notified that the information taken from them would be kept safe and would not be used other than for research purposes. After the completion of the study in a six-month period, the most effective treatment procedure was continued for each patient in the rest of their treatment process.

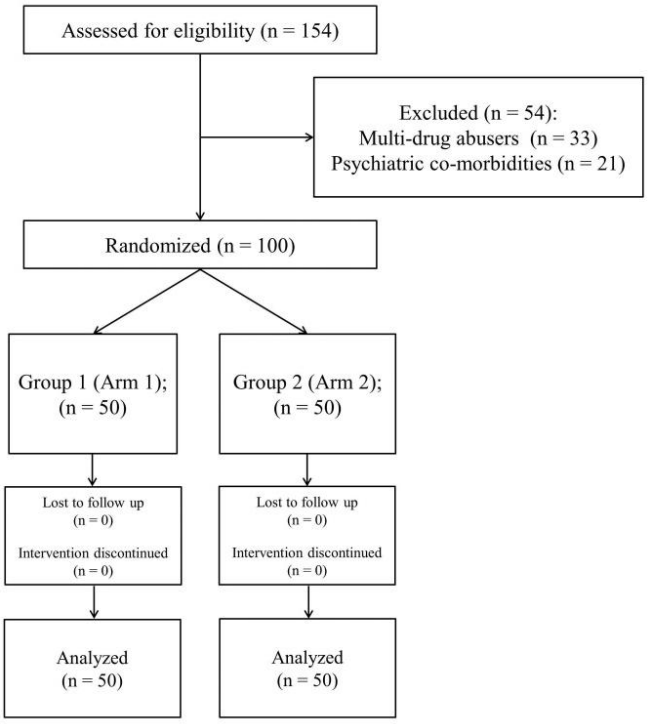

Figure 1. Consort diagram showing patient recruitments and exclusions in each arm of the study

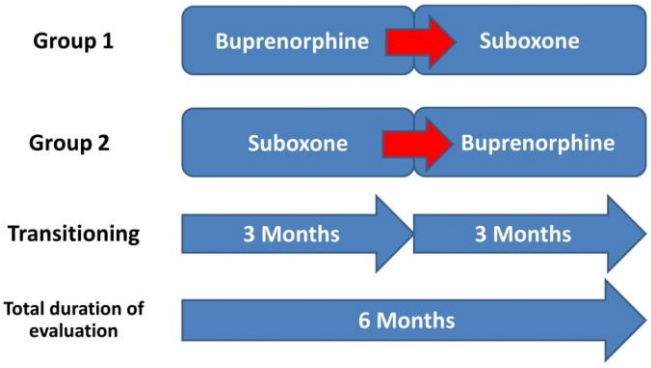

Figure 2. Study groups based on the treatment protocol

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA). As the current study is of cross-over type, prior to evaluation of the main parameters, "time effect (TE)" and "carryover effect (CE)" were taken into account and were analyzed with Pocock's Test. CE was not statistically significant (P = 0.047). This means the mutual effect of time and drug was not statistically significant. Therefore, "two sets" of data were considered in the statistical analysis.

However, TE was statistically significant, and thus, tests of both sets were used in a modified manner. Wilcoxon and Mann-Whitney tests were used to compare the effect of each treatment on the examinees.

RESULTS

Demographic features

Demographic information of the subjects is shown in Table 1. Mean (SD, min-max) age of the patients was 39.5 (10.5, 21-70) years. The majority of patients (64%) aged 31 to 50 years. Sixty-three percent of the patients were married and 83% had educational level of less than higher education. Most subjects were working in private sector (61%). The most common drug of abuse was raw opium (61%) and the most common method of abuse was smoking (54%). The majority of the subjects (62%) had abused illicit substances for less than 10 years.

Table 1. Demographic features of the subjects (n = 100)

Age (years)	N
< 31	24
31-40	39
41-50	25
> 50	12
Marital Status	
Married	63
Single	30
Divorced	7
Educational level	
No formal education	3
Primary education	40
Secondary education (High school)	40
Higher education	17
Occupational status	
Private	61
Laborer	16
Unemployed	11
Governmental	8
Retired	4
Substance of abuse	
Raw opium	61
Opium extract	21
Tramadol	10
Concentrated heroin (Iranian crack)	8
Route of administration	
Smoking	54
Combination	32
Oral	14
Duration of addiction (years)	
< 6	23
6-10	39
> 10	38

Treatments and outcomes

Mean dose of BUP or BUP/NX given to the subjects were 20±2 mg and 2±1 mg, respectively. In each of the study arms, when the patients were given BUP/NX, the number of relapses was significantly higher compared to when they received BUP (0.13±0.24 vs. 0.04±0.09, P = 0.001) (Figure 3).

If participants' age was taken into account, the number of relapses was significantly higher when BUP/NX was given in age groups of 31 to 40 years and over 50 years (P < 0.05). However, in other age groups, this difference was not statistically significant (Figure 4).

Regarding the occupation, patients working in private sector and retired subjects had significantly higher number of relapses when they used BUP/NX compared to BUP (P < 0.05) (Figure 5).

Nonetheless, no significant difference was found between the BUP and BUP/NX efficacy in terms of marital status, education level, and the type of drug abuse. The length of addiction had also a significant impact on the number of relapses, i.e., patients with over 10-year history of addiction had higher number of relapses if they were given BUP/NX compared with BUP (P < 0.05) (Figure 6).

DISCUSSION

The two pharmacodynamic advantages of BUP over METH including higher affinity to Mu receptors and slower rate of dissociating from receptor, which as a result lead to lower risk of abuse, have made BUP more suitable for maintenance therapy (13,14). Nonetheless, BUP has become a drug of abuse, particularly among those long involved with

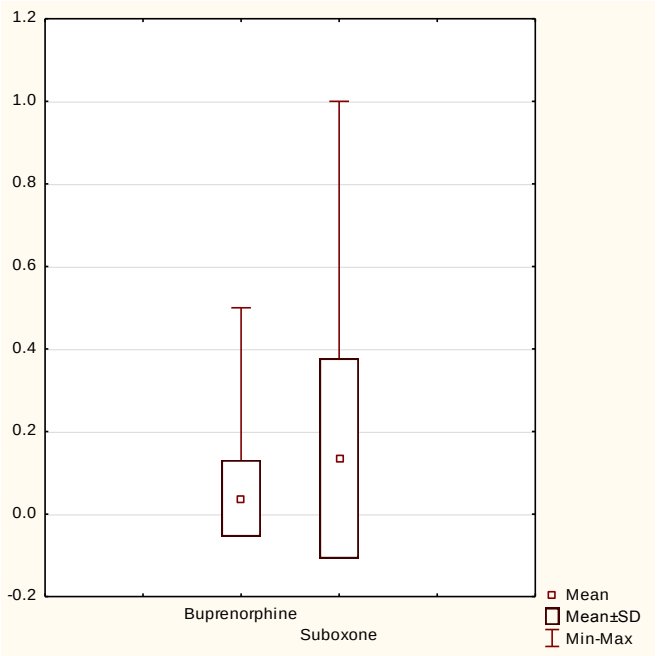

Figure 3. Mean number of relapses when patients were given buprenorphine vs. suboxone

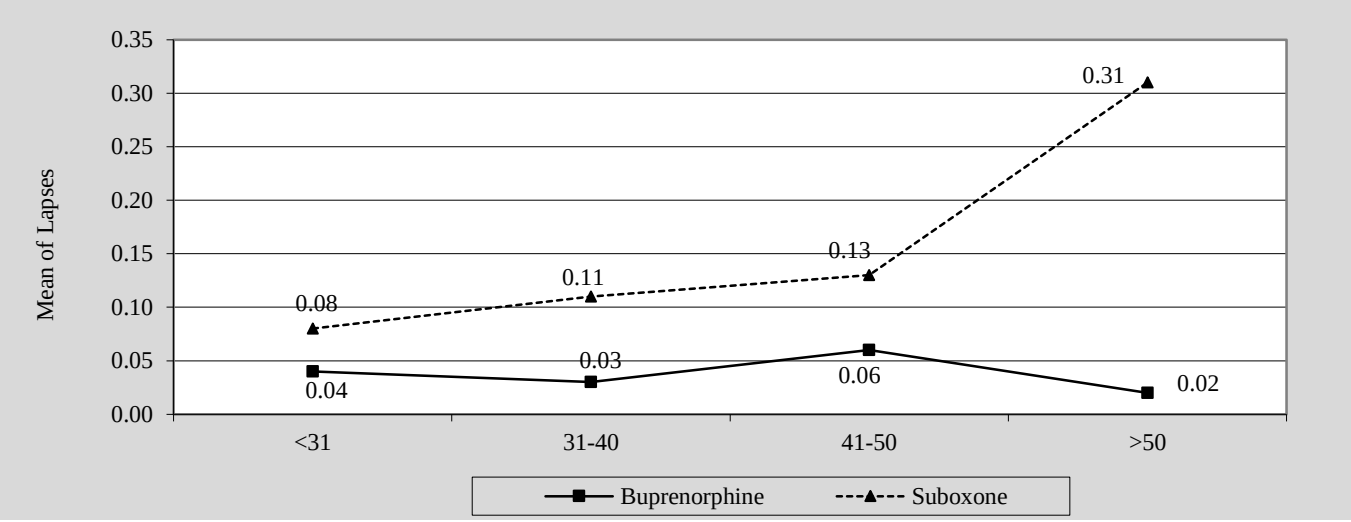

Figure 4. Mean number of relapses in different age groups divided by the treatments given

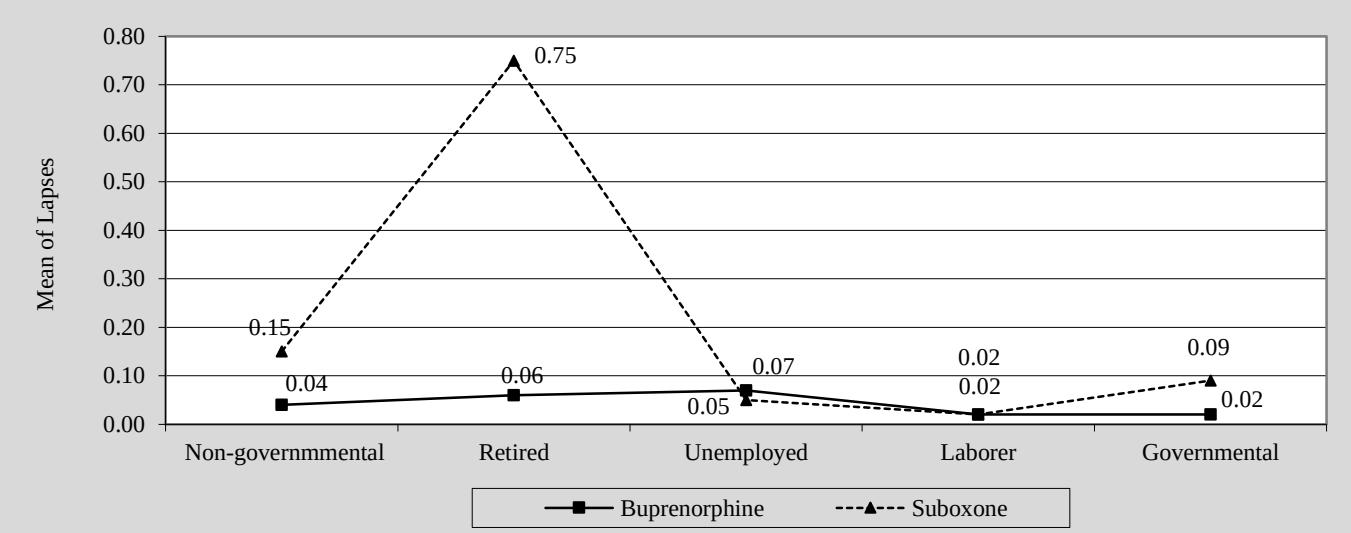

Figure 5. Mean number of relapses in different occupational statuses divided by the treatments given

heroin addiction (15,16). BUP abusers grind up the tablets, mix the powder with water, and inject the solution intravenously, which provides a rush of opioid-like sensation as the substance binds to the opioid receptors. To unravel this complication, the combination of BUP and NX, called suboxone (BUP/NX), has been produced which can decrease the risk of excessive intravenous injection by the effect of NX component (17). NX component of suboxone can reverse the effects of opioids, but it has a short half-life and so it typically does not last as long as opioids. Hence, it will temporarily prevent these drugs from binding to the opioid receptors in the brain, and consequently the abuser does not feel high, and if injected, it leads to withdrawal syndrome (17). Altogether, suboxone has less potential for abuse due to the fact that it was engineered with a ceiling effect. This means that when it is taken at increasingly higher doses, a user will not derive any additional psychological euphoria from BUP/NX, although they will from METH.

With regard to the composition of illegal opioid market in Iran (e.g. crystal-heroin, crack-heroin and sedoodi-heroin, which are popular names for condensed forms of heroin) (18-22), BUP and BUP/NX have some advantages over METH. In METH use, withdrawal from opioid therapy is prolonged and often difficult compared to BUP. In addition, the risk of METH overdose is higher than that of BUP (17). BUP has lower interactions with other drugs, and complications such as respiratory depression and cardiovascular disorders such as QT prolongation are less likely to occur compared to METH (23,24).

The results of the present study show that BUP is superior

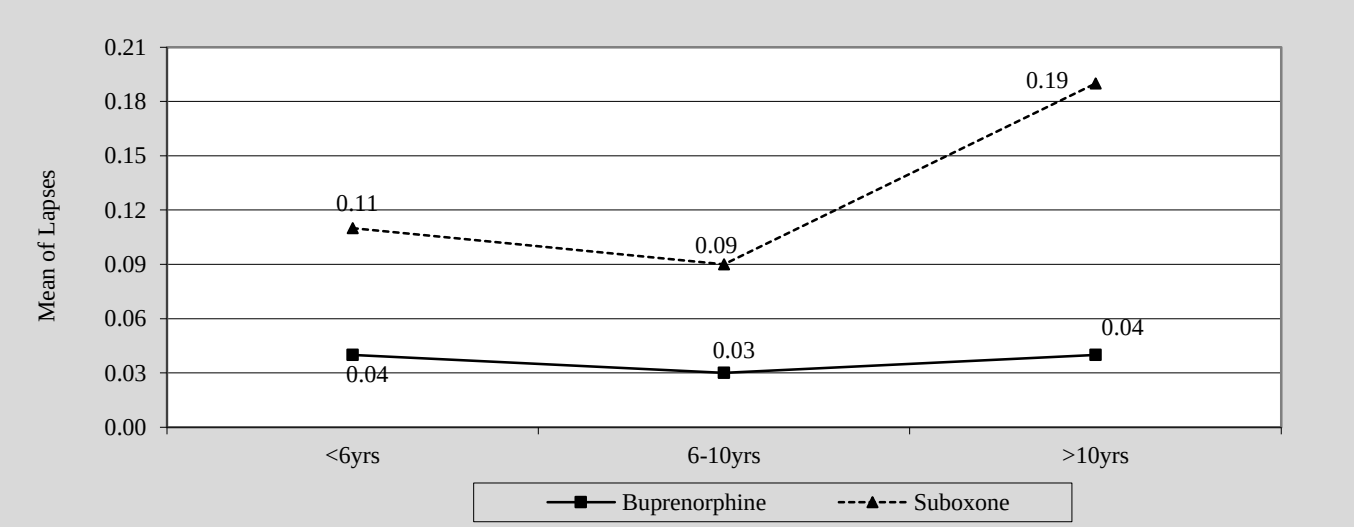

Figure 6. Mean number of relapses in different addiction histories divided by the treatments given

to BUP/NX in preventing addiction relapse among opioid abusers under maintenance treatment. There are controversial results comparing the effectiveness of BUP and BUP/NX in reduction of addiction relapse. Although Magnelli et al and Stimolo et al found that BUP/NX is better than BUP in reduction of craving and relapse (25,26), in studies conducted by Fudala et al and by Amato (27,28), BUP and BUP/NX were similar regarding the mentioned parameters. Mammen and Bell similarly showed that the addition of NX may not improve the efficacy of BUP as a maintenance drug (29). They even concluded that due to causing withdrawal syndrome, BUP/NX can act as a reinforcer for abuse of BUP or other illegal drugs (29). Bell et al, also, found no noticeable differences in relapse frequency in patients undergoing treatment with BUP/NX compared with BUP (30).

Since BUP/NX contains naloxone, which is likely to cause withdrawal symptoms in simultaneous use with opioids (17), patients may become reluctant to continue using the drug especially if given in an unsupervised manner (30). Therefore, suboxone is more associated with discontinuing of maintenance therapy. The inferiority of BUP/NX in our study could be further explained by the higher cost of this drug in black market. As we found a significantly higher relapse number in the retired subjects, it can be said that the need for financial resources would drive them to sell suboxone pills in the black market and to withdraw the treatment.

LIMITATION

A limitation of this study could be the small sample size. Hence, further studies with larger sample size are recommended. The advantage of the current study compared to similar ones is its cross-over design. Therefore, not only was each group compared to itself, but it was also compared to the other group at the same time.

CONCLUSION

BUP seems to be more effective than BUP/NX in preventing addiction relapse in opioid abusers under maintenance treatment. This is particularly correct for opioid abusers with limited financial resources and those with longer history of opioid addiction.

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