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Treatment of Intravenous Buprenorphine Dependence A Randomized Open Clinical Trial

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Abstract

Background: Buprenorphine dependence is a new issue and to our knowledge no scientific papers have been published on treatment of buprenorphine dependency. The goal of this research was to characterize intravenous buprenorphine-dependent individuals with respect to socio-demographic and other background features, and to investigate the effect of methadone in the maintenance treatment of intravenous buprenorphine dependence in comparison with sublingual buprenorphine and also oral clonidine over a 12-week treatment period. Methods: Intravenous buprenorphine-dependent patients who met the DSM-IV criteria for opioid dependence were randomized to three groups. Results: The mean age was 29.4 years (range 19-46). The majority (86.1%) had a history of opium or heroin dependency before they were introduced to intravenous buprenorphine. The mean duration of buprenorphine dependence was 1.8 years and the mean ampoule per day was 4.6 ampoules (1 ampoule contains 0.3 mg of buprenorphine in 1 ml). Completion rates by groups were 83.3% for the methadone group, 58.3% for the buprenorphine group and 11.1% for the clonidine group ($p < 0.0001$). Retention in treatment was significantly better in the methadone group than in the buprenorphine group ($p = 0.020$) and the clonidine group ($p < 0.0001$). Retention in the buprenorphine group was significantly better than in the clonidine group ($p < 0.0001$). Conclusions: The results support the efficacy and safety of oral methadone and sublingual buprenorphine tablets for intravenous buprenorphine-dependent patients (German J Psychiatry 2003; 6: 23-29).

Keywords: Intravenous buprenorphine dependence, methadone, buprenorphine, clonidine, retention in treatment

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Introduction

Substance abuse remains a crime in Iran, but the authorities are now willing for dependence to be treated as a psychiatric disorder. Drug-dependent individuals undergoing treatment are no longer prosecuted, nor are the physicians who treat them. Costs of treatment, medication and rehabilitation are paid by patients according to the approved tariffs, but the government will pay the costs for those unable to afford treatment (DCHQ, 1997). Alcohol is prohibited both by religion and law. Other illicit substances include cocaine, opioids, stimulants, LSD, cannabis, and hallucinogens.

The State Welfare Organization, which is affiliated to the Ministry of Health, Treatment, and Medical Education, is in charge of treatment and rehabilitation of substance-dependent individuals. At present, there are 12 treatment and rehabilitation centers in Iran, with one center specifically for women. Up to 1999, approximately 25,000 to

30,000 patients were admitted to these centers (90% of these referrals were ordered by courts). The treatment was residential with an average duration of stay of 2-6 months. The centers were described as having the infrastructure of an overcrowded prison. Since that time, outpatient treatment has been introduced and was initially based on detoxification with clonidine and tranquilizers, but more recently with methadone and buprenorphine. The usual duration of treatment is between 3 and 6 months, but on occasions it may be extended to 2 years. The treatment includes individual therapy, family therapy, and group therapy. Relapse rates are estimated to vary between 60% and 80% according to the duration and site of therapy. Recently, self-referral centers have developed all over the country, as have also Narcotics Anonymous groups, which now have approximately 5000 members (Razzaghi, Rahimi, Hosseini & Chatterjee, 1999).

The number of substance users in Iran is now estimated to be between 1.8 million and 3.3 million, and the number of intravenous drug users between 200,000 and 300,000 of whom 1841 are estimated to be suffering from HIV infection. 74.8% of all those suffering from HIV infection are intravenous drug users (Razzaghi, Rahimi, Hosseini & Chatterjee, 1999; DCHQ 2001; Moor 2001).

As a partial agonist of opiate receptors, buprenorphine has shown promise as a pharmacological adjunct in the treatment of opioid-dependent patients (Jasinski et al., 1978; Greanstein et al., 1992; Hawks & Chiang, 1995; Compton et al., 1995; Ling et al., 1998; O'Connor et al., 1998).

Buprenorphine has a long duration of action, blocks the euphoric effects of opioids and produces few withdrawal symptoms following abrupt cessation of use (Jasinski et al., 1978; Greenstein et al., 1992). Buprenorphine could be used as an alternative to methadone maintenance therapy (Ling et al., 1998) and as a drug to help patients in their transition from methadone maintenance to treatment with an antagonist such as naltrexone (Jaffe, 1992). It has also been used to decrease opiate withdrawal symptoms (Kosten et al., 1989; Alling et al., 1990).

The opioid euphoric effects of buprenorphine, however, may lead to psychic dependence. Patients have reported liking the opiate-like effects following its use (Bickel et al., 1988; Johnson et al., 1989).

Abuse of buprenorphine has recently assumed a threatening proportion (O'Connor et al., 1988; Basu et al., 1990; Chowdhury & Chowdhury 1990; Lal, 1991; Singh et al. 1992; Umesh Babu & Chaturvedi, 1995; Kumar, 1996; Sharama & Mattoo, 1999). Although buprenorphine was introduced as a safe analgesic, its abuse potential had been reported (Harper, 1983; Strang, 1985; O'Connor et al., 1988). For example, the first reported cases of buprenorphine abuse in India were seen from 1987 onwards (Basu et al., 1990), and then its abuse spread rapidly (Umesh Babu & Chaturvedi, 1995; Kumar, 1996).

Buprenorphine is available in Iran as injection ampoules of 1 ml (containing 0.3 mg buprenorphine, which is equianalgesic to 10 mg morphine sulphate) and rarely 2 ml, and also as sublingual tablets. The injectable ampoule is abused in Iran, mainly through the intravenous route. Buprenorphine in Iran is reportedly of Pakistani, Indian and rarely European origin, where it is manufactured under different trade names and used for detoxification and to treat symptoms of opioid withdrawal. It is also used as an analgesic. In Iran, buprenorphine has recently been produced as a medicinal product for detoxification and to treat opium or heroin-dependent individuals admitted to hospitals. In recent years, the street availability of the buprenorphine and its abuse has shown an upward trend. Although most individuals use buprenorphine injection, some combine it with injectable antihistamines, diazepam and occasionally pentazocine, in order to increase the quality and duration of action.

There have been reports of buprenorphine "abuse" in many countries, such as Australia (Quigley, Bredemeyer & Seow, 1984), Bangladesh (Ahmed & Ara, 2001), France (Obadia et al., 2001), India (Singh et al., 1992; Sharma & Mattoo, 1999; Basu et al., 2000) and New Zealand (Rainey, 1986).

A study of buprenorphine dependence is of interest for several reasons. First of all, it is imperative to know the course and outcome of a relatively new drug dependence. In the only published abstract of a paper on 22 month follow–up of 26 treated buprenorphine patients, Chavan, Tripathi & Lal (1995) reported that the vast majority of their patients were either still actively misusing buprenorphine or had shifted to heroin. Only a longer-term study with a larger sample size can put these preliminary findings into a proper perspective. Secondly, the abusers are exposed to the risks of intravenous drug abuse, such as HIV infection (Malhotra et al., 1993), other infections and even traumatic pseudoaneurysm (Basu et al. 1994). Finally, the other important question that merits an answer is: What happens to the buprenorphine dependence itself in the long term? Does it continue, exacerbate, "mature out" or get shifted to abuse of other drugs? In this regard, it is important to note that many buprenorphine patients originally start with heroin (Basu et al., 1990; Singh et al. 1992; Chavan et al., 1995; Kumar, 1996). How many of them would eventually go back to heroin or other drugs? How do these "transition" patients fare vis-à-vis those "stable" on buprenorphine? In a nutshell, what are the roots, the stem and the branches of the "tree" of buprenorphine dependence? These are some of the questions that prompted researchers to undertake studies on buprenorphine-dependent patients.

Current estimates are that a significant number of Iranian injecting drug users (IDUs) are on buprenorphine maintenance nationally. Such diffusion inevitably exacerbates previous concerns about intravenous abuse of buprenorphine, which has already been observed with lower

dosages (Temgesic) than those currently used for drug maintenance therapy (Sakol et al., 1989; Basu et al., 1994, Hammersley et al., 1995).

We present here the results of a survey, carried out on samples of IDUs in the city of Shiraz in southern Iran, which gave us the opportunity to evaluate the extent to which introduction of buprenorphine DMT has been associated with illicit intravenous abuse. Evaluation of the Iranian experience on this subject may be useful for other countries, such as the United States, where the Food and Drug Administration is currently considering market approval of buprenorphine for treatment of opioid dependence.

The goals of this research study were:

(1) To characterize intravenous buprenorphine-dependent individuals with respect to socio-demographic and other background features.

(2) To compare the efficacy of 40 mg of an oral methadone tablet with oral clonidine (0.4 mg) in the treatment of intravenous buprenorphine-dependent patients.

(3) To compare the efficacy of 4 mg of a sublingual buprenorphine tablet with 0.4 mg of clonidine in the treatment of intravenous buprenorphine-dependent patients.

(4) To compare the efficacy of 40 mg of oral methadone with 4 mg of sublingual buprenorphine in the treatment of intravenous buprenorphine-dependent patients.

Materials and Methods

Subjects

One hundred and eight unpaid male buprenorphine-dependent patients seeking treatment from an outpatient clinic in Shiraz city during 2002 were screened for participation. There were no significant differences between three groups on mean age, dose and duration of buprenorphine abuse. Shiraz is the capital city of Fars province with a population of about 1.5 million, in southern Iran. Research staff consisted of an addiction psychiatrist, a general practitioner, and a psychologist. At screening, patients were examined by a physician to establish eligibility. Prior to each interview, we explained the aims of the research study, guaranteed confidentiality, and obtained informed consent. The interviews and examinations were done on the premises of the treatment clinic because it appeared a non-threatening and suitable environment. Relatives, family members or friends accompanied most patients to the clinic; this attendance provided the opportunity to confirm some of the data obtained from the patients. Patients had to meet Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria for opioid dependence (American Psychiatric Association, 1994). Daily use of intravenous buprenorphine for at least 6 months was also a requirement. Patients were excluded from the study if they had a serious medical condition (e.g., severe heart failure, severe liver cirrhosis, or cancer) a diagnosis of alcohol dependence, or had been prescribed anticonvulsants, neuroleptics, or methadone during the previous month.

Treatment

This research was a three-group, randomized, controlled study of 108 intravenous buprenorphine-dependent patients. Subjects were allocated randomly to three groups: (1) 40 mg oral methadone per day (36 patients), (2) 4 mg sublingual buprenorphine per day (36 patients), or (3) 0.4 mg clonidine per day (36 patients). Patients were treated for 12 weeks. In addition to pharmacotherapy and daily contact with research staff, subjects were offered a weekly 0.5-hour individual counseling session for education and discussion of their problems. Efficacy was evaluated by treatment retention. The working hypothesis of the study was that methadone, 40 mg per day would be more effective than buprenorphine, 4 mg per day and clonidine 0.4 mg per day.

Induction onto methadone was done by administering 20 mg and then 40 mg over the first 2 study days and then continuing with 40 mg daily. Induction onto buprenorphine was done by administering 2 mg and then 4 mg over the first 2 study days. Induction onto clonidine was done by administering 0.2 mg and then 0.4 mg over the first 2 study days. All groups were eligible to continue at their assigned dose for up to 12 weeks.

Statistical analysis

Data analysis was done by using SPSS. Chi-squared analyses were used to test for differences in 12-week completion rates among the 3 groups, and t-test analyses were used to test for differences in means. Two-tailed tests were used throughout ($p<0.05$).

Results

The data were collected from 108 male intravenous buprenorphine abusers. Their mean age was 29.43 years (N=108, SD=6.86, range, 19 - 46 years). As shown in Table 1, there was no significant difference in the mean age of the three groups. Table 2 shows that most of the buprenorphine abusers (76.8%) were between 20 and 34 years of age and more than half (55.6%) were married. The educational

Table 1. Mean Age of Intravenous Buprenorphine Abusers (Dependents); N=108. SD, standard deviation (SD); CI, confidence intervals

Group	N	Mean (SD)	95% CI	Range
Methadone	36	29.3 (6.93)	27.0-31.65	20-46
Buprenorphine	36	29.4 (6.91)	27.1-31.7	20-45
Clonidine	36	29.6 (2.92)	27.2-31.9	19-43
Total	108	29.4 (6.86)	28.1-30.7	19-46

F=0.012; df=2, 107; p = 0.988

level of most of the subjects (82.4%) was between 6 and 12 years of study and 6.5% had only an elementary education. Twenty-five percent were laborers and 11.1% had their own business. Most of the subjects (86.1%) gave a history of opium or heroin dependency before they were introduced to buprenorphine (Table 3). The most frequently used substance prior to buprenorphine was opium (66.7%). The majority (58.3%) of the study population reported that they had been using buprenorphine for the past 6 to 12 months. Only 10.2% reported using it for more than 4 years. The main source of buprenorphine for the abusers (93.5%) was the street (Table 3).

It should be noted that buprenorphine is a relatively new addition to the list of substances abused in Iran.

The primary sources of information about buprenorphine were friends, relatives, and drug dealers. According to the subjects, the reasons for abuse of buprenorphine were: seeking pleasure, release of tension or being fresh and energetic, and suppression of the withdrawal effects of opium or heroin.

Table 2. Sample Characteristics (N=108)

	N	%
Age (years)		
<20	1	0.9
20-24	28	25.9
25-29	35	32.4
30-34	20	18.5
35-39	5	4.6
40-44	17	15.7
45-49	2	1.9
Occupation		
Unemployed	23	21.3
Private sector job	12	11.1
Laborer	25	23.1
Government employee	20	18.5
Retailer	15	13.9
Truck and taxi driver	12	11.1
Other	1	0.9
Years of education		
1-5	7	6.5
6-12	89	82.4
>12	12	11.1
Marital Status		
Single	48	44.4
Married	60	55.6

Table 3. Factors Associated With Intravenous Buprenorphine Abuse (N=108)

	Number	%
Substances previously used		
Opium	72	66.7
Heroin	21	19.4
No substance	15	13.9
Other substances currently used		
No substance	108	100
Number of ampoules per day[1]		
1-3	51	47.2
4-15	57	52.8
Duration of buprenorphine abuse[2]		
0.5 – 1 year	63	58.3
1.1 – 4 years	34	31.5
> 4 years	11	10.2
Causes of buprenorphine abuse		
Pleasurable purposes	42	38.9
Treatment for opium or heroin dependency	28	25.9
Release of tension or keeps fresh and energetic	31	28.7
Other	7	6.5
Source of supply of buprenorphine		
Street sale	101	93.5
Drug stores	4	3.7
Other	3	2.8

[1]1 ampoule = 0.3 mg buprenorphine in 1 ml; mean = 4.6 ampoules; SD=3.1 ; range, 1 - 17 ampoules
[2]Mean duration=1.8; SD=2.1; range, 0.5-10 years

Patients said that the abuse of buprenorphine was becoming increasingly popular in Iran and that its abuse was spreading very fast. They reported that the drug makes them feel fresh and energetic and able to function normally. Patients mentioned the effects of buprenorphine as: a sense of pleasure, drowsy and dreaming, relief from pain, and a sweet smell when used in combination with diazepam or antihistamines. The majority reported that cigarettes were soaked in buprenorphine, giving them a different, sweet taste. About half of the patients (47.2%) were using 1 to 3 ampoules a day (one ampoule contains 0.3 mg of buprenorphine in 1 ml).

Table 4 summarizes the frequency distribution of completers by group (methadone group, buprenorphine group and clonidine group). Figure 1 shows the Kaplan-Meier survival analysis of relapses.

Overall 55 (50.9%) of the patients completed the 12-week study. Completion rates by group were 30 (83.3%) for the 40 mg methadone group, and 4 (11.1%) for the 0.4 mg group. The clonidine group had significantly poorer retention than the methadone group (χ^2= 37.62; $p < 0.0001$). Also, the clonidine group had significantly poorer retention than the buprenorphine group (χ^2 = 17.71; $p<0.0001$). The comparison of the methadone group with the buprenorphine group was also significant (χ^2=5.45; p=0.020).

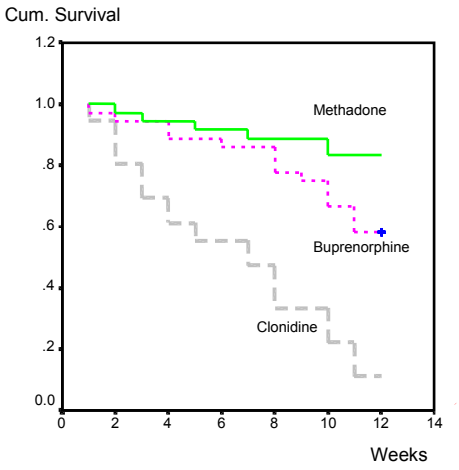

Figure 1. Kaplan-Meier Survival Analysis

Discussion

This research study raises some interesting questions regarding the abuse potentials of buprenorphine that point to the need for more research in this area.

Results from the present study indicate that some of the same effects and characteristics that make buprenorphine promising for treating opium and heroin dependents also make this medication appealing on the illegal drug market. Some of the reasons that the patients started injecting buprenorphine were to suppress withdrawal symptoms of opium or heroin and to eliminate or decrease their dependence on opioids. There is a variety of reasons why opium-dependent patients in Iran wanted to decrease their dependence on opium. At present opium is less available and more expensive than before. Methadone is not adequately available (especially for maintenance therapy) in Iran; therefore some patients used buprenorphine to self-medicate. Buprenorphine was considered a good alternative to opium because it was not expensive, easy to carry, more available than opium and produced the same effects. They reported that pleasurable effects of buprenorphine helped some patients to lead a relatively normal life and function well. Some of the patients increase the effects of buprenorphine by using it with antihistaminic agents or diazepam.

The findings of this study confirm the efficacy of oral methadone for treatment of intravenous buprenorphine-dependent patients. There was also a clear superiority of the sublingual buprenorphine over clonidine in patient retention. It is likely that even higher retention rates could have been achieved if there had been higher doses of methadone or buprenorphine, or if there had been more psychosocial treatment to address these patients' problems.

This research study was limited to intravenous buprenorphine-dependent subjects seeking treatment, and therefore may not be representative of the entire population of buprenorphine-dependent patients. However, this research study, in spite of its limitations, has generated data which could be useful in understanding, and controlling buprenorphine abuse and dependency.

Conclusions

This study shows that intravenous abuse of buprenorphine is currently inescapable up to the time that buprenorphine is used for treatment of opioid dependency. Alternative pharmacological combinations, such as buprenorphine-naloxone, which is claimed not to be injectable, may be a partial solution to prevent intravenous abuse of buprenorphine. Also it can be concluded that oral methadone or sublingual buprenorphine is a useful and safe drug for the maintenance treatment of buprenorphine-dependent patients.

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Table 4. Frequency distribution of completers by group

Group	Completers		Non-completers		Total	
	N	%	N	%	N	%
Methadone	30	83.3	6	16.7	36	100
Buprenorphine	21	58.3	15	41.7	36	100
Clonidine	4	11.1	32	88.9	36	100
Total	55	50.9	53	49.1	108	100

X^2=38.75; p<0.00011 (two-sided)
Methadone vs. buprenorphine: X^2=5.45, p = 0.020
Methadone vs. clonidine: X^2=37.62; p <0.0001
Buprenorphine vs. clonidine: X^2=17.71, p <0.0001

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