

Treatment of Heroin Dependence

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Abstract

Objective: To test the efficacy of naltrexone, methadone and buprenorphine over a treatment period of 12 weeks. **Methods:** Subjects were randomized to receive naltrexone, methadone, or buprenorphine in a comparative study. **Participants:** Ninety-three (93) heroin-dependent males who met the DSM-IV criteria for heroin dependence and were seeking treatment. Subjects received methadone (31 patients), or buprenorphine (31 patients), or naltrexone (31 patients) in 2001 and 2002. **Results:** The mean dose of heroin use per day was 1.9 gm, and the mean duration of current heroin use was 2.8 years. Days retained in treatment were measured. Completion rates by group were 93.5% for the methadone group, 67.7% for the buprenorphine group, and 41.9% for the naltrexone group ($p < 0.0001$). Retention in the 60 mg methadone group was significantly better than in the 6 mg buprenorphine group ($p = .01$) and in the 50 mg naltrexone group ($p < 0.0001$). Buprenorphine group was significantly better than 50 mg naltrexone group ($p=0.04$). **Conclusion:** The results support the efficacy of methadone, buprenorphine, and naltrexone for treatment of heroin dependence (German J Psychiatry 2004;7(2): 1-5).

Keywords: heroin dependence; substance abuse, naltrexone, methadone, buprenorphine

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Introduction

Little is published about substance dependence, especially heroin and opium, in Iran. Opium (a kind of opiate, derived from opium poppy) is used (usually by opium pipe) as seeking pleasure, painkiller, and hypnotic and also for treatment of premature ejaculation.

Substance dependence is considered a crime but the authorities are ready to consider substance dependence and abuse as a psychiatric disorder. Neither substance dependants, who are undergoing treatment, nor specialist doing treatment would not be persecuted. The costs of treatment, medication and rehabilitation are to be paid by the substance-dependent patients according to the approved tariffs but the government will pay the costs for those unable to pay (DCHQ, 1997). Alcohol is both religiously and legally prohibited. Illicit substances are heroin, opium, alcohol, cannabis, stimulants, LSD, and other 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 patients. At the present time, there are 12 treatment and rehabilitation centers with one center for women, in the country. Up to the 1998/1999 approximately 25,000 to 30,000 individuals were admitted to these centers (90% of these referrals were ordered by courts). The average duration of stay is 2 to 6 months. The centers were described as having the infrastructure of an overcrowded prison. Now these centers are closed and the new approach is the introduction of outpatient treatment centers. Treatment is generally modeled on detoxification with clonidine and tranquilizers, and recently with buprenorphine or methadone. The duration range of treatment is between 3 to 6 months, including individual therapy, family therapy, and group therapy. Some times, duration of therapy may be extended to 2 years. There has also been the development of self-referring centers and Narcotic Anonymous centers with an approximately 5,000 members throughout the country. Relapse rates are estimated to vary between 60% to 80% according to the duration and site of therapy (Razzaghi, Rahimi, Hosseini & Chatterjee, 1999).

At present, number of substance users is estimated to be between 1.8 million to 3.3 million, number of I.V.drug users between 200,000 to 300,000 and number of HIV infections in I.V.drug users is estimated to be 1,841, or 74.8% of all HIV infections are I.V. drug users (Razzaghi, Rahimi, Hosseini & Chatterjee, 1999; DCHQ 2001; Moore 2001).

As was told, treatment is generally modeled on detoxification with clonidine and tranquilizers, however, recently drug policy makers accepted treatment with naltrexone, buprenorphine or methadone for opium and heroin dependants.

Methadone or buprenorphine could be used for treatment of opioid-dependent patients. And as a new therapy, buprenorphine has several potential advantages. Buprenorphine is a partial agonist at the mu receptor (Lewis, 1985; Martin, Eades, Thompson, Huppler, & Gilbert, 1976). Since it is a partial agonist, there is a ceiling on its ability to cause respiratory depression; thus use of buprenorphine is less likely to result in an overdose. Its use results in less physical dependence, so that it may be easier to detoxify from buprenorphine than methadone (Jasinski, Pevnick, & Griffith, 1978).

Buprenorphine is poorly absorbed after oral administration, but well absorbed after sublingual administration, reaching 60%–70% of the plasma concentration achieved by parenteral routes (Jasinski, Fudala, & Johnson, 1989). Buprenorphine has been under intensive research for the treatment of opioid dependence since the late 1970s (Jasinski, Pevnick, & Griffith, 1978). Results from random assignment trials in the United States, comparing buprenorphine with methadone for the maintenance treatment of opioid dependence, indicate the safety and efficacy of buprenorphine compared with methadone (Ling et al., 1998; Ling, Rawson, & Compton, 1994; Strain, Stitzer, Liebson, & Bigelow, 1994). For example, Johnson, Jaffe, and Fudala (1992) showed that a daily sublingual dose of 8 mg of buprenorphine was comparable to 60 mg of methadone in terms of retention rate and opiate negative urinalysis.

Some new synthetic oral opioids, such as buprenorphine, slow release morphine, methadone, and LAAM (levo-alpha-acetyl-methadol) were assessed as potential treatment options for opiate addicts (Fischer et al., 1999; Lange, Fudala, Dax, & Johnson, 1990; Patricio & Miguel, 1994). Many surveys have shown that methadone maintenance therapy leads to a decrease in illegal substance consumption, improved rehabilitation of intravenous opiate dependents, a decrease in HIV infection and also a decrease in criminal and antisocial behavior (Newman, 1987; Plomp, Van Der Hek & Ader, 1996; Schottenfeld & Kleber, 1995).

Although methadone maintenance therapy has been successful overall, it is associated with a number of problems, including limited community and patient acceptance, thus methadone is not ideal for all opioid dependents (Kolar, Brown, Weddington & Ball, 1990; Schottenfeld & Kleber, 1995). Methadone, LAAM and slow-release morphine are full mu-receptor agonists, whereas buprenorphine is a partial mu-receptor agonist and a kappa-receptor antagonist. Buprenorphine has low bioavailability after oral ingestion as a result of its high rate of metabolism by the liver, but could

be administered sublingually. (Bullingham, McQuay, Porter, Allen & Moore, 1982).

Withdrawal symptoms following the discontinuation or slow reduction of buprenorphine are relatively mild in contrast with methadone (Bickel, Stitzer, Bigelow, Liebson, Jasinski & Johnson, 1988). However, in Iran very little is published about treatment of heroin-dependent patients. Iranian health policy recently recommends that heroin-addicted individuals could be treated with clonidine or with opioid agonists, such as buprenorphine, methadone, or LAAM.

The goal of this study was to evaluate the efficacy of methadone compared with buprenorphine over a treatment period of 12 weeks. As a secondary objective, the results were determined concurrently for subjects treated with naltrexone.

Materials and Methods

Subjects

Ninety-three (93) consecutive unpaid heroin dependent males (3 equal groups with 31 patients in each group) seeking treatment from an outpatient clinic in Shiraz city during 2001 and 2002 were screened for participation. Only males were selected for the study because the rate of opioid abuse is thought to be negligible among females. Shiraz is the capital city of the Fars Province with a population of about 1.5 million and is located in the southern part of Iran. At screening, patients were examined by a physician to establish eligibility and to discuss the informed consent. Subjects had to meet Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria for opioid dependence (American Psychiatric Association, 1994). Daily use of heroin for at least 6 months was also a requirement. Patients were excluded from the research study if they had another serious medical condition (e.g., cancer, severe liver cirrhosis, or severe heart failure) a diagnosis of alcohol dependence, or had been prescribed anticonvulsants, neuroleptics, or methadone during the previous month. Patients with a score of 7 or higher on the interviewer severity rating of the psychiatric problem scale of the Addiction Severity Index (range, 0 to 9) were also excluded.

Treatment

This research study was a three group, randomized design comparing 60 mg dose of oral methadone tablet to 6 mg dose of sublingual buprenorphine tablet and 50 mg dose of oral naltrexone over a 12-week treatment period of 93 heroin dependent males. Patients were assigned randomly to groups and then administered a 60 mg (31 patients) oral dose of methadone tablet, or 6 mg (31 patients) sublingual dose of buprenorphine tablet, or 50 mg (31 patients) oral dose of naltrexone per day. Subjects who missed up to 6 consecutive days of dosing were re-inducted on methadone or buprenorphine or naltrexone with the use of the same schedule as the

initial induction, but if they needed more than 3 re-inductions or missed 7 or more consecutive doses, they were not continued in the study. Patients were treated for up to 12 weeks. Efficacy was assessed by treatment retention.

Induction onto methadone was done by administering 20 mg, 40 mg, and then 60 mg over the first 3 study days and then continuing with 60 mg daily. Induction onto buprenorphine was done by administering 2 mg, 4 mg, and then 6 mg over the first 3 study days. Induction onto naltrexone was done by administering 20 mg, 40 mg, and then 60 mg methadone over the first 3 study days, and then tapering in 10 days. Ten days after detoxification, induction onto naltrexone was done by administering 50 mg daily. 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-square analyses were used to test for differences in 12-week completion rates among the 3 groups, and t-tests were used to test for differences in means. These were two-sided with significance set at $p < 0.05$.

Results

The data were gathered from 93 male heroin-dependent patients, 31 patients whose mean age was 31.23 (SD = 9.68) for the methadone group, 31 patients whose mean age was 32.26 years (SD = 8.95) for the buprenorphine group, and 31 patients whose mean age was 30.94 (SD = 8.67) for the naltrexone group, $F = 0.180$; $df = 2$; $P = 0.835$ (Table 1).

Table 2 shows frequency distribution of patients by age, occupational, educational, and marital status. Table 3 indicates dose and duration of heroin use.

Completion rates by group were 93.5% for the 60 mg dose methadone group, 67.7% for the 6 mg dose buprenorphine group, and 41.9% for the 50 mg dose naltrexone group ($X^2 = 18.9$, $df = 2$, $p < 0.0001$). Retention in the 60 mg methadone group was significantly better than in the 6 mg buprenorphine group ($X^2 = 6.60$, $df = 1$, $p = 0.01$), and in the 50 mg naltrexone group ($X^2 = 18.90$, $df = 1$, $p < 0.0001$). Buprenorphine group was significantly better than 50 mg naltrexone group ($X^2 = 4.17$, $df = 1$, $P = 0.04$) (Table 4).

Table 1. Mean Age of Heroin-Dependent Patients (N=93; F=0.180; DF=2, 90, p=0.835). CI = Confidence Interval

Treatment	N	Mean (SD)	Range	95% CI
Methadone	31	31.2 (SD 9.68)	17-56	27.7-34.8
Buprenorphine	31	32.3 (SD 8.95)	19-53	29.0-35.5
Naltrexone	31	31.0 (SD 8.67)	18-54	27.8-34.1
Total	93	31.5 (SD 9.03)	17-56	29.6-33.3

Table 2. Sample Characteristics: Age and Occupational, Educational and Marital Status (N=93)

	N	%
Age (years)		
<20	7	7.5
20-24	10	10.8
25-29	31	33.3
30-34	23	24.7
35-39	5	5.4
40-44	8	8.6
45-49	3	3.2
>50	6	6.5
Occupation		
Unemployed	30	32.3
Private sector job	25	26.9
Laborer	13	14
Government employee	12	12.9
Retailer	13	14
Years of education		
Illiterate	4	4.3
Primary	9	9.7
Guidance & High school	64	68.8
Higher education	16	17.2
Marital Status		
Single	42	45.2
Married	51	54.8

Table 3. Dose and Duration of Heroin Abuse (N=93)

Heroin Dose per day/gr.*	N	%
1.0 - 2.0	60	64.5
2.1 - 3.0	19	20.4
3.1 - 4.0	14	15.1
Duration of heroin use**		
0.5 - 1.0 year	37	39.8
1.1 - 2.0 years	21	22.6
2.1 - 4.0 years	12	12.9
> 4.0 years	23	24.7

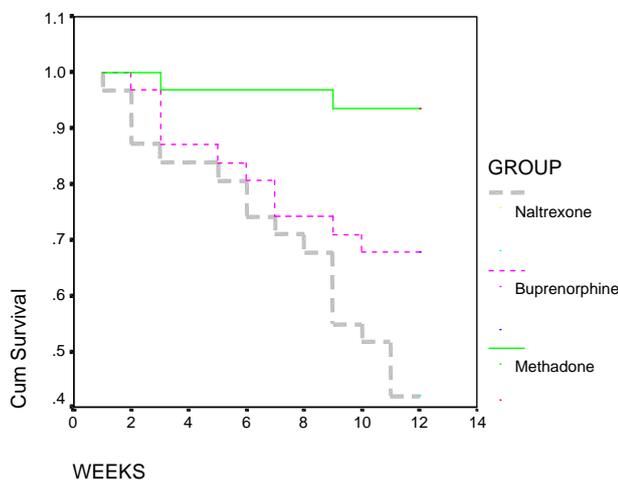
*Mean dose, 1.98 gr. (SD=1.02); range, 1-4

**Mean duration, 2.8 (SD=3.1) years; range, 0.5.-15

Table 4. Frequency distribution of completers by group

Group	Reten- tion rate		Re- lapse rate		Total N
	N	%	N	%	
Methadone	29	93.5	2	6.5	31
Buprenorphine	21	67.7	10	32.3	31
Naltrexone	13	41.9	18	58.1	31
Total	64	68.8	30	31.2	93

$X^2=18.9$; $df=2$; $p<0.0001$. Methadone vs. buprenorphine : $X^2=6.60$; $df=1$; $p=0.01$. Methadone vs. naltrexone: $X^2=18.90$; $df=1$; $p<0.0001$: Buprenorphine vs. naltrexone: $X^2=4.17$; $df=1$; $p=0.041$

Figure 1. Kaplan-Meier Survival Analysis of Relapse Rate

Discussion

Very little is known about Iranian heroin dependent individuals. They are usually detoxified and treated with clonidine and recently with methadone or buprenorphine. Iranian drug policy states that if individuals are found to be in possession and using illegal substances, such as heroin, opium, morphine, cannabis, LSD, hallucinogens, stimulants, cocaine, and alcohol, they should be arrested and may be imprisoned (tobacco products are legal). If addicted-patients refer to private clinics or treatment centers, they are not arrested (even if they relapse); therefore, this sample appears to be representative of the population of heroin users who voluntarily seek treatment.

The results of this study are supportive of the efficacy of methadone, buprenorphine and naltrexone. There was clear superiority of 60 mg dose of methadone and 6 mg dose of buprenorphine versus 50 mg dose of naltrexone in patient retention.

About 67.5% of patients in the 6 mg dose of buprenorphine group remained in treatment for 12 weeks. In comparison, retention rates of 42% and 44% were reported for an 8 mg dose of buprenorphine in an American study over a 17-week treatment period (Johnson, Jaffe, & Fudala, 1992). There are several comparisons of buprenorphine with methadone. In a study, buprenorphine at 8 mg per day was superior to methadone 20 mg per day and equivalent to methadone at 60 mg per day (Johnson, Jaffe, & Fudala, 1992). In another study 8 mg of buprenorphine was significantly less effective than 80 mg of methadone (Ling, Rawson, & Compton, 1994).

Since in this research study relatively moderate doses of buprenorphine and methadone were considered, it is likely that even greater benefits would have been achieved with higher doses of buprenorphine and methadone, or if there had been psychosocial treatment to address these patients' problems.

Conclusions

Although no real outcome measures other than the 'process' measure of retention are warranted, it appears that naltrexone, methadone or buprenorphine is a useful drug for the outpatient maintenance treatment of Iranian heroin dependent patients. Although not systematically compared here, our clinical impression is that treatment with methadone or buprenorphine or naltrexone also seems to be much better than traditional methods, such as abrupt cessation without any medication or slow decrease in dose of heroin use. Continued investigation of opioid agonists and partial agonists, especially methadone or buprenorphine and also antagonists, especially naltrexone, is strongly recommended to improve Iranian treatment options for opioid abuse.

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