Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients

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Abstract

The aim of this study was to assess the efficacy of methadone compared with buprenorphine maintenance therapy in heroin-dependent patients over a treatment period of 18 weeks. Subjects were randomized to receive either methadone or buprenorphine in a comparative double-blind study and consisted of 164 heroin-dependent male patients who met the DSM-IV criteria for heroin dependence and were seeking treatment. The 164 subjects included 41 patients in 1-mg, 41 patients in 3-mg, and 41 patients in 8-mg dosage group of buprenorphine, and also 41 patients in the 30-mg dosage group of methadone. The mean age was 31.4 years for total buprenorphine group and 33.7 years for methadone group (the mean age differences in 4 groups were not statistically significant). Subjects received buprenorphine at a dose of 1, 3, or 8 mg per day or methadone at a dose of 30 mg per day and were treated in an urban outpatient clinic, offering a 1-hour weekly individual counseling session. Days retained in treatment were measured. Completion rates by buprenorphine dosage group were 29.3% for the 1-mg dose group, 46.3% for the 3-mg dose group, 68.3% for the 8-mg dose group, and 61% for the 30-mg methadone dose group. Retention in the 8-mg dose group was significantly better than in the 1-mg dose group \( (p = .00041) \) and in the 3-mg dose group \( (p = .045) \); other comparison (1 mg dose with 3 mg dose) was not significant. Methadone group was significantly better than 1mg buprenorphine dose group \( (p = .004) \), but was not significantly different from 3 mg buprenorphine dose group \( (p = .18) \) or 8 mg buprenorphine dose group \( (p = .49) \). The results support the efficacy of buprenorphine for outpatient treatment of heroin dependence and seem to indicate that the highest dose (8 mg) of buprenorphine was the best of the three doses of buprenorphine, and also support the superiority of 30 mg of methadone compared to 1 mg dose of buprenorphine for Iranian heroin-dependent patients to increase their retention in treatment.

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1. Introduction

Very little has been published on heroin, opium and other substance dependence in Iran. Opium is widely used there for pleasure, as a painkiller, a hypnotic, and for the treatment of premature ejaculation.

Drug abuse remains a crime in Iran, but the authorities are now willing for dependence to be treated as a psychiatric disorder. Substance abusers undergoing treatment are no longer prosecuted, nor are the specialists who are treating 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 (Drug Control Headquarters [DCHQ], 1997). Alcohol is prohibited both by religion and law. Other abused illicit substances include heroin, opium, alcohol, 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 patients. At the present time, there are 12 treatment and rehabilitation centers in Iran, with one center specifically for women. Up until 1999 approximately 25,000 to 30,000 individuals were admitted to these centers (90% of these referrals were ordered by courts). The treatment was residential with the average duration of stay from 2 to 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 buprenorphine or methadone. 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% to 80% according to the duration and site of therapy. Recently self-referral centers have developed across the country, as have also Narcotics Anonymous groups, which now have approximately 5000 members (Razzagh et al., 1999; DCHQ, 2001; Moore, 2001).

At present, the number of substance users in Iran is estimated to be between 1.8 million to 3.3 million, and the number of intravenous drug users between 200,000 and 300,000 of whom 1841 are estimated to be to suffer from HIV infection. Of all those suffering from HIV infection, 74.8% are intravenous drug users (Razzaghi et al., 1999; DCHQ, 2001; Moore, 2001).

As was mentioned before, treatment is generally modeled on detoxification with clonidine and tranquilizers; however, recently drug policy makers accepted treatment with buprenorphine or methadone for opium and heroin-dependent patients.

Methadone or buprenorphine could be used for treatment of opioid-dependent patients. 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 et al., 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, Jaffé, 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 (leva-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 dependants (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 et al., 1988). However, in Iran very little is published about treatment of heroin-dependent patients. Iranian health policy recently recommends that heroin-dependent 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 1, 3, and 8 mg per day doses of buprenorphine, and also compared with 30-mg dose of oral methadone in the maintenance treatment of heroin-dependent patients over an 18-week treatment period. Accordingly, this study is the research in Iran examining multiple doses (1, 3, and 8 mg) of sublingual buprenorphine tablets compared with 30-mg dosage of oral methadone tablets.

2. Materials and methods

2.1. Subjects

One hundred sixty-four (164) consecutive unpaid heroin-dependent male patients (3 buprenorphine groups with 41 patients in each group, and one methadone group with 41 patients as well) seeking treatment from an outpatient clinic in Shiraz city during 2001 were screened for participation. Only males were selected for the study because the rate of opioid abuse is thought to be negligible among females. Patients were matched into treatment groups by level and duration of physical dependence. Both patients and research staff were blind to the medications (when patients needed inductions, a clinician had the information). Research staff consisted of an addiction psychiatrist, a general practitioner, and a psychologist. 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. Prior to each interview, we explained the aims of the research study, guaranteed confidentiality, and discussed informed consent. The interviews and examinations were done on the premises.
of the treatment clinic because it appeared to be a non-threatening and suitable environment. Relatives, family members, or friends accompanied most patients to the clinic; this attendance provided a condition 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 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 0–9) were also excluded.

2.2. Procedure

This research study was a four-group, randomized, double-blind design comparing doses of 1, 3, and 8 mg of buprenorphine tablets to 30 mg of methadone tablets over an 18-week treatment period of 164 heroin-dependent male individuals. Patients were allocated randomly to 4 equal groups and then administered a 1 mg (41 patients), 3 mg (41 patients), or 8 mg (41 patients) sublingual dose of buprenorphine tablet per day, and 30 mg (41 patients) dose of methadone tablet per day as well. Subjects who missed up to 6 consecutive days of dosing were re-induced on buprenorphine or methadone 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 18 weeks. In addition to pharmacotherapy and daily contact with research staff, subjects were offered a weekly 1-hr individual counseling (cognitive behavior therapy) session for their problems. Efficacy was assessed by treatment retention.

Induction onto buprenorphine for the 8-mg group was done by administering 1, 3, and then 8 mg over the first 3 study days and then continuing with 8 mg daily. For the 3-mg group induction onto buprenorphine was done by administering 1, and then 3 mg over the first 2 study days and then continuing with 3 mg daily. For the 1-mg group we started 1 mg the first study day and continued with 1 mg daily. Induction onto methadone was done by administering 10, 20, and then 30 mg over the first 3 study days and then continuing with 30 mg daily. Patients were followed up as long as 18 weeks. Many patients continued to take buprenorphine or methadone and they will be the subject of further followup studies.

2.3. Statistical analysis

Data analysis was carried out by using SPSS (SPSS, Chicago, IL). Chi-square analyses were used to test for differences in 18-week completion rates among the four dosage groups. Two-sided tests were used at 0.05 levels.

3. Results

The data were gathered from 164 male heroin-dependent patients (123 patients whose mean age was 31.43 years (S.D. = 9.37) for buprenorphine groups and 41 patients whose mean age was 33.7 (S.D. = 12.9) for methadone group). The mean age differences in 4 groups were not statistically significant.

Completion rates by dosage group were 29.3% for the 1-mg group, 46.3% for the 3-mg group, and 68.3% for the 8-mg group. The 1-mg group had significantly poorer retention than the 8-mg group ($\chi^2 = 12.5, DF = 1, p = .00041$). Also, the 3-mg group had significantly poorer retention than the 8-mg group ($\chi^2 = 4.04, DF = 1, p = .045$). Comparison of 1-mg group with 3-mg group was not significant ($\chi^2 = 2.54, DF = 1, p = .11$).

Comparison of 1-mg buprenorphine group (29.3%) with 30-mg methadone group (61.0%) was significant ({$\chi^2 = 8.32, DF = 1, p = .004$}). Comparison of 3-mg buprenorphine group (46.3%) with 30-mg methadone group (61.0%) was non-significant ({$\chi^2 = 1.77, DF = 1, p = .18$}). Comparison of 8-mg buprenorphine group (68.3%) with 30-mg methadone group (61.0%) was non significant ($\chi^2 = .48, DF = 1, p = .49$).

4. Discussion

Very little has been published on heroin-dependent individuals in Iran. 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 in Iran.

The results of this study, which is the first experience in Iran comparing 1 mg, 3 mg, and 8 mg dose of buprenorphine with 30 mg dose of methadone, are supportive of the efficacy of both methadone and buprenorphine. There was clear superiority of 30-mg dose of methadone and 8-mg dose of buprenorphine vs. 1 mg dose of buprenorphine in patient retention. About 68.3% of patients in the 8 mg dose group remained in treatment for 18 weeks. In comparison, retention rates of 42% and 44% were reported for an 8 mg dose in an American study over a 17-week treatment period (Johnson et al., 1992). There are several comparisons of buprenorphine with methadone. In a study by Johnson et al.
(1992), buprenorphine at 8 mg per day was superior to methadone 20 mg per day and equivalent to methadone at 60 mg per day. In another study 8 mg of buprenorphine was significantly less effective than 80 mg of methadone (Ling et al., 1994).

Since this research study is the first study in Iran comparing doses of 1, 3, and 8 mg of buprenorphine tablets to 30 mg of methadone tablets, relatively low 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 more psychosocial treatment to address these patients’ problems.

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

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References


