Brief article

Twelve-month maintenance treatment of opium-dependent patients

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Abstract

The goal of this study was to compare the effects of 1, 3 and 8 mg per day doses of buprenorphine in the maintenance treatment of opium-dependent subjects in Iran over a treatment period of 12 months. Participants were randomized to three equal groups (171 subjects per group) of opium-dependent individuals who met the DSM-IV criteria for opioid dependence and were seeking treatment. They were treated in an urban outpatient clinic, offering a 1-hour weekly individual counseling session. Overall, 282 subjects (55%) completed the 12 months study. Completion rates by dosage group were 46 (26.9%) for the 1 mg dose group, 102 (59.6%) for the 3 mg dose group, and 134 (78.4%) for the 8 mg dose group ($p = .000$). These findings are consistent with previous reports of effective buprenorphine use in western countries as a suitable maintenance treatment for opium dependence. © 2004 Elsevier Inc. All rights reserved.

Keywords: Buprenorphine; Opium dependence; Retention in treatment

1. Introduction

Very little has been published on opium dependence in Iran. Opium is widely used there for pleasure, as a pain-killer, a hypnotic, and for the treatment of premature ejaculation. Iranian society was able to contain the problem through well-defined contexts for this usage, and also by traditional methods of social control.

While morphine, codeine, and heroin can be used by injection intravenously, intramuscularly, or subcutaneously, opium itself cannot be used by injection because it contains a large proportion of insoluble material. Oral consumption mainly includes the drinking of liquid extracts used medicinally, and also a brewed mixture of opium poppy heads, known as poppy tea (Steenotf, Kaa, & Worm, 1988; Unniathan & Stang, 1993).

Opium contains morphine and codeine, which are poorly absorbed in the stomach but well absorbed in the small intestine; therefore the onset of action is delayed after oral ingestion. In contrast, vaporized morphine produced by smoking of opium is rapidly absorbed across the lungs into the blood stream, and within a few seconds is available at the brain. Hence the onset of action is more rapid after smoking; however, the duration of action is longer after oral ingestion (Jaffe & Martin, 1985).

A rare route of opium use is sniffing of powdered opium into the nose (Westermeyer & Neider, 1982). Sniffing has the advantage that absorption of the morphine starts quickly (like smoking) without substantial loss of morphine that happens through escaped smoke; and because there is no smoke odor, the opium user is not as readily detected.

Buprenorphine is a partial agonist at the mu receptor (Lewis, 1985; Martin, Eades, Thompson, Huppler, & Gilbert, 1976). Buprenorphine has several potential advantages. 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 is 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, indicated 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.

Buprenorphine has low bioavailability after oral ingestion as a result of its high rate of metabolism by the liver, but can 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 known about treatment of opium-dependent individuals, especially with buprenorphine.

Thus the goal of this study was to evaluate the efficacy of 1-, 3-, and 8-mg per day doses of buprenorphine in the maintenance treatment of opium-dependent subjects over a 12-month treatment period. Accordingly, this study is one of the first research studies in Iran examining multiple doses (1 mg, 3 mg, and 8 mg) of sublingual tablet form of buprenorphine for treatment of opium-dependent individuals for a period of 12 months.

2. Materials and methods

2.1. Subjects

Five hundred thirteen unpaid opium-dependent individuals (three groups with 171 subjects in each group) seeking treatment from one outpatient clinic in the center of Shiraz city during 2000 and 2001 were screened for participation. Shiraz has a population of about 1.5 million and is one of the Iranian cities with the highest rates of opioid dependence. At screening, individuals were examined by a physician to establish eligibility and to discuss the informed consent. Participants had to meet Diagnostic and Statistical Manual of Mental Disorders (4th ed.) criteria for opioid dependence (American Psychiatric Association, 1994). Participants were excluded from the research study if they:

- were 18 years or younger, or 85 years or older
- had a serious medical condition such as cancer, severe liver cirrhosis, or severe heart failure
- met diagnostic criteria for alcohol dependence
- had been prescribed anticonvulsants, neuroleptics, or methadone during the previous month
- had 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)

2.2. Procedure

The present research was a double blind study. Groups of 171 subjects each were assigned randomly and then inducted onto a 1 mg, 3 mg, or 8 mg sublingual dose of buprenorphine tablet per day.

For the 8 mg dose group, induction onto buprenorphine was done by administering 1, 3, and 8 mg over the first 3 study days and then continuing with 8 mg daily. For the 3-mg dose group, induction was done by administering 1 and 3 mg over the first 2 study days and then continuing

Fig. 1. Kaplan-Meier survival analysis of relapses.
with 3 mg daily. For the 1-mg dose group, 1 mg was administered continuously from the first day. After induction, subjects who missed 6 consecutive days of dosing were re-induced (by a clinician who was aware of their dose and schedule). Subjects who needed more than three re-inductions were not continued in the study. Successfully inducted subjects were eligible for treatment for up to 12 months. In addition to pharmacotherapy and daily contact with research staff, subjects were offered a weekly 1-hr individual counseling session for their problems.

There were no biological measures of drug use taken during the course of treatment. Efficacy for the purposes of this project was assessed by treatment retention and we measured patient drop out prior to 12 months. Since it is likely that not all clients who left treatment had poor outcomes, we believe this is a reasonably conservative estimate of performance.

We hypothesized that 8 mg per day of buprenorphine would be more effective than 3 mg, which would be more effective than 1 mg per day in maintaining patient participation. Note: doses of over 8 mg per day are currently not permitted in Iran.

### 2.3. Statistical analysis

Analyses were done (using SPSS Version 10, SPSS, Chicago, IL) comparing all groups on baseline characteristics using analysis of variance for continuous variables and chi-square analyses for categorical variables. Retention rates in the three groups was compared using Kaplan-Meier survival analyses for weeks of remissions and relapse. Two-sided tests were used at alpha = .05.

### 3. Results

The data were gathered from 513 opium-dependent individuals (493 men and 20 women). Their mean age was 37.64 years (SD = 11.29; range, 19 to 82). The majority 351 (68.4%) had education at the level of secondary or high school. Seventy-nine subjects (15.4%) had higher education; 74 (14.4%) had education at the level of primary school and 9 (1.8%) were illiterate. Four hundred fifteen subjects (80.9%) were married and only 98 (19.1%) were single.

Fig. 1 (Kaplan-Meier curve) indicates the distribution of completers by group. Overall, 282 (55%) of the subjects completed the 12-months study. Twelve-month completion rates by dosage group were 46 (26.9%) for the 1 mg group, 102 (59.6%) for the 3 mg group, and 134 (78.4%) for the 8 mg group. All groups differed from each other at p < .001.

Table 1 reports the odds ratio of completing 12 months of treatment for the 3 and 8 mg per day dose groups relative to the 1 mg group.

#### Table 1

<table>
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<th>Group</th>
<th>Odds</th>
<th>Significance</th>
<th>95% Confidence interval for mean</th>
<th>Significance</th>
<th>Lower bound</th>
<th>Upper bound</th>
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### 4. Discussion

Very little has been published about opium dependence and its treatment in Iran. Opioid-dependent individuals are usually detoxified and treated with clonidine and rarely with methadone. Iranian drug policy states that if individuals are found to be in possession or 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 substance-dependent individuals refer themselves voluntarily to private clinics or treatment centers, they are not arrested; therefore, this sample could be representative of the population of opium users who voluntarily seek treatment in Iran.

The results of this study, comparing 1 mg, 3 mg, and 8 mg doses of buprenorphine, are supportive of the efficacy of higher doses of buprenorphine for treatment of opium dependence. There was clear superiority of the 3 mg dose over the 1 mg dose and the 8 mg dose over the 3 mg dose, at least in our treatment retention measure. Approximately 78.4% of subjects in the 8 mg dose group remained in treatment for 12 months. It is likely that even higher retention rates could have been achieved if there had been more psychosocial treatment to address the problems afflicting these subjects. In comparison, retention rates of 42% and 44% were reported for an 8-mg dose in two American studies over a 17-week treatment period (Johnson et al., 1992).

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### References


