A Randomized, Clinical Trial of Buprenorphine Maintenance Treatment for Iranian Patients With Opioid Dependency

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Abstract
Objectives: This study assessed the effect of a 4-mg/d sublingual dosage of buprenorphine in the maintenance treatment of Iranian patients with opioid dependency by comparison with a 1-mg/d dosage over a 24-week treatment period. As a secondary objective, results were determined concurrently for patients treated with a 2-mg/d dosage.

Methods: Patients were randomized to three dosage groups. The participants included 420 consecutive patients (407 men and 13 women) with opioid dependency who met the criteria for opioid dependence of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and were seeking treatment. Patients received a 1-, 2-, or 4-mg/d dosage of buprenorphine and were treated in an outpatient clinic (in Shiraz, Iran, with a population of approximately 1.5 million), including a 1-hour weekly clinical counseling session. Measurements included Addiction Severity Index, retention in treatment, and illegal opioid use as determined by random urine toxicology.

Results: The mean age was 36.3 years (SD, 11.3; range, 16–72). Overall, 237 (56.4%) of the patients completed the 24-week study. Completion rates by dosage group were 45.7% for the 1-mg group, 55.7% for the 2-mg group, and 62.9% for the 4-mg group ($\chi^2 = 14.0, \text{df} = 2, P < 0.001$). No sex difference was observed ($\chi^2 = 0.04, \text{df} = 1, P = 0.84$).

Conclusions: The results support the efficacy and safety of buprenorphine for opioid dependence and suggest that an adequate dosage of buprenorphine is strongly recommended for Iranian patients with opioid dependence to increase their success rate.

Key Words: Buprenorphine, Iranian, maintenance treatment, opioid dependence.

Buprenorphine is a partial agonist at the $\mu$ receptor and a weak antagonist at the $\kappa$ receptor.$^{1,2}$ Buprenorphine is poorly absorbed after oral administration but well-absorbed after sublingual administration, reaching 60 to 70% of the plasma concentration achieved by parenteral routes.$^3$ Buprenorphine has been under intensive research for the treatment of opioid dependence since the late 1970s.$^4$ 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.$^5$ Johnson et al.$^8$ showed that a daily sublingual dose of 8 mg buprenorphine was comparable with 60 mg methadone in terms of retention rate and opiate negative urinalysis.

Some new synthetic oral opioids, such as buprenorphine, slow-release morphine, and leva-$\alpha$-acetyl-methadol, are currently being assessed as potential treatment options for patients with opiate addiction.$^{9–11}$

Little is known about treatment of patients with opioid dependency in Iran. Patients with heroin and opium addictions are usually treated with clonidine and not with opioid agonists, such as buprenorphine, methadone, or leva-$\alpha$-acetyl-methadol.

This article presents data obtained using buprenorphine (1, 2, and 4 mg) for Iranian patients with opioid dependency. The primary goal of the current study was to assess the efficacy of a 4-mg/d sublingual dosage of buprenorphine in the maintenance treatment of patients with opioid dependency in comparison with a 1-mg/d dosage over a 24-week treatment period. Because it was believed that
outcomes with other dosages could be useful, data were also collected for a 2-mg/d dosage.

**Methods and Materials**

**Subjects**

Four hundred twenty unpaid, consecutive patients with opioid addiction (407 men and 13 women) who sought treatment from an outpatient clinic in Shiraz, Iran, were screened for participation in 2000 and 2001. Shiraz is the capital city of the Fars province with a population of approximately 1.5 million and is located in southern part of Iran. Subjects were examined to establish eligibility and to discuss informed consent. Subjects had to meet the criteria for opioid dependence of the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition.* Daily use of opioid at least for 6 months was a requirement. Patients were excluded from the study if they had a diagnosis of a medical condition (such as liver cirrhosis, cancer, or severe congestive heart failure), had alcohol dependency, or were using anticonvulsants, neuroleptics, or methadone. Patients with a need for psychological or psychiatric treatment as determined by an Addiction Severity Index score of 7 or higher (range, 0–9) at the interview were excluded.

**Procedure**

Patients were randomly assigned to treatment with one of three medication dosages. Subjects were inducted to 1, 2, or 4 mg sublingual buprenorphine per day. Subjects who missed up to 6 consecutive days of dosing were reinducted to buprenorphine using the same schedule as in the initial induction, but if they needed more than three reinductions or missed seven or more consecutive doses, the treatment was considered to be a failure. Patients were treated for up to 24 weeks. In addition to pharmacotherapy and daily contact with research staff, subjects were offered a 1-hour weekly counseling session about their problems. To assess efficacy, retention in treatment was evaluated by random urine testing. Some of the patients missed visits, and after seven consecutively missed visits, their treatments were considered to be failures. Random urine samples were tested weekly for opioids.

**Analysis**

Data analysis was performed using SPSS (SPSS, Chicago, IL). χ² Analyses were used to test for differences in dosage groups.

**Results**

Data were gathered from 420 patients with opioid dependency whose mean age was 36.25 years (SD, 11.34; range, 16–72). Subjects included 407 (96.9%) men and 13 (3.1%) women who were assigned to one of three groups of equal size (each group included 140 patients).

Table 1 summarizes age distribution of these subjects. Sixty-two (14.8%) were in the range of 20 to 24 years, 68 (16.2%) were in the range of 25 to 29 years, and 78 (18.6%) were in the range of 30 to 34 years. Only 6 (1.4%) were younger than 20 years, and 60 (14.3%) were older than 50 years.

Table 2 shows occupational status of the subjects. One hundred seventeen (27.9%) were employed in the private sector job.
45.7 24-week study. Completion rates by dosage group were school education.

62.9 The majority, 304 (72.4 88 (21

8 mg bu-

methadone. In another study, 8 mg buprenorphine at 60 mg/d was

treatment problems.

There is psychosocial treatment addressed toward patients

period.8,13 Higher retention rates could be achieved if

8-mg dose in two other studies over a 17-week treatment

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Iran, are supportive of the efficacy of buprenorphine. The

voluntarily seeking treatment.

If individuals with addiction refer them-

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be imprisoned. If individuals with addiction refer them-

themselves voluntarily to private clinics or government outpa-

tient clinics, they are not arrested. Therefore, this sample

could be representative of the population of opioid users

mentally) methods, such as abrupt cessation without any medi-

cation or slow decrease in dosage of heroin use. Use of

opioid agonists, especially buprenorphine, is strongly rec-

ommended for Iranian patients with opioid addiction to

increase treatment success rate.

Discussion

Little is known about patients with opioid dependency in

Iran. They are usually detoxified and treated with cloni-
dine, rarely with methadone. Iranian drug policy states that

if an individual is found to be in possession of and using an

illegal substance, such as heroin, opium, morphine, can-
nabis, LSD, hallucinogens, stimulants, cocaine, or alcohol

(tobacco products are legal), he or she is arrested and may

be imprisoned. If individuals with addiction refer them-

selves voluntarily to private clinics or government outpa-

tient clinics, they are not arrested. Therefore, this sample

could be representative of the population of opioid users

voluntarily seeking treatment.

The results of this study, which is the first of its kind in

Iran, are supportive of the efficacy of buprenorphine. The

4-mg/d dosage was superior compared with the 1-mg/d

dosage. Approximately 63% of the patients in the 4-mg

group remained in treatment for 24 weeks. This is com-

parable to retention rates of 42 and 44% reported for the

8-mg dose in two other studies over a 17-week treatment

period.8,13 Higher retention rates could be achieved if

there is psychosocial treatment addressed toward patients’

problems.

There are several comparisons of buprenorphine with

methadone. In one study, buprenorphine at 8 mg/d was

superior to methadone at 20 mg/d and equivalent to

methadone at 60 mg/d.8 In another study, 8 mg bu-

prenorphine was significantly less effective than 80 mg

methadone.13

Conclusions

It can be concluded that buprenorphine is a useful and safe

drug for maintenance treatment for Iranian opioid users

and is also much better than clonidine and traditional (cul-
tural) methods, such as abrupt cessation without any medici-

ation or slow decrease in dosage of heroin use. Use of

opioid agonists, especially buprenorphine, is strongly rec-

ommended for Iranian patients with opioid addiction to

increase treatment success rate.

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