original paper

Controlled trial of maintenance treatment of intravenous buprenorphine dependence

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Abstract

Background Buprenorphine dependence is a relatively novel addiction.

Aims To compare the treatment outcome in three groups over 12-weeks of treatment.

Methods Two hundred and four intravenous (IV)-buprenorphine-dependent patients were randomised into three groups. Subjects received 50mg oral methadone tablet, or 5mg sublingual buprenorphine tablet, or 50mg oral naltrexone, and a weekly 30-minute clinical counselling session.

Results The majority (80%) had a history of opium or heroin dependency before they were introduced to IV buprenorphine. The main source of buprenorphine for misusers was street sale (91%). The mean duration of buprenorphine dependence was 1.9 years and the mean dose per day was 3.9 ampoules (1 ampoule contains 0.3mg of buprenorphine in 1ml). Overall 59% of the patients completed the 12-week study. Retention in the 50mg methadone group was significantly better than the 5mg dose buprenorphine group (p=0.001) and the 50mg dose naltrexone group (p=0.000). Retention in the 5mg buprenorphine group was significantly better than the 50mg naltrexone dose group (p=0.000).

Conclusions These results support the efficacy and safety of oral methadone and sublingual buprenorphine tablets for injection buprenorphine-dependent patients.

Introduction

The opioid-like euphoric effects of buprenorphine may lead to psychic dependence and patients have reported liking the opiate-like effects following its use.[1,2] Misuse of buprenorphine has recently assumed a threatening proportion.[3-8] Although introduced as a safe analgesic, buprenorphine misuse had been reported.[3,9,10] The first reported cases of buprenorphine misuse in India were seen from 1987 onwards,[4] and then its misuse spread rapidly.[6,7]

Buprenorphine is available in Iran as injection ampoules of 1ml containing 0.3mg buprenorphine, which is equianalgesic to 10mg morphine sulphate. It is also available as 2ml ampoules and sublingual tablets. Injectable buprenorphine is misused in Iran, mainly through intravenous route. It is reportedly of Pakistani, Indian and European origin, where it is manufactured under different trade names for detoxification, for opioid withdrawal and as an analgesic. In Iran it is produced for detoxification and to treat opium or heroin-dependent individuals. In recent years, its misuse has shown an upward trend. Although most individuals use buprenorphine injection, some combine it with injectable antihistaminics, diazepam and occasionally pentazocine to increase the quality and duration of action. Other reports of its 'misuse' come from Australia,[11] Bangladesh,[12] France,[13] India[5,8,14] and New Zealand.[15]

We present the results of a controlled trial from Shiraz, Iran, on how the introduction of buprenorphine maintenance therapy has been associated with illicit intravenous misuse. The Iranian experience may be useful for other countries, such as the US, where the Food and Drug Administration is currently considering market approval of buprenorphine for maintenance therapy.

Patients and methods

Subjects

Two hundred and four unpaid male buprenorphine-dependent patients seeking treatment from an outpatient clinic in Shiraz City, Iran (population 1.5million) during 2002 were screened for participation. Patients were randomised into three treatment groups. At screening, patients were examined by a physician to establish eligibility. Prior to each interview, the aims of the research study was explained, confidentiality guaranteed and informed consent discussed. The interviews and examinations were done on the premises of the treatment clinic. 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 injection buprenorphine for at least six months was also a requirement. Patients were excluded from the study if they had serious medical conditions such as severe heart failure, severe liver cirrhosis, or cancer, or had a diagnosis of alcohol dependence, or had been prescribed anticonvulsants, neuroleptics or methadone during the previous month.

Procedure

The 204 intravenous buprenorphine-dependent patients were randomly allocated to three groups. Subjects were assigned onto a 50mg oral methadone tablet (68 patients), 5mg sublingual buprenorphine tablet (68 patients) or 50mg oral naltrexone (68 patients) regimen. Individuals who missed up to six consecutive days of dosing were re-inducted on methadone, buprenorphine or naltrexone using the same schedule as the initial induction, but if they needed more than three re-induction or missed seven or more consecutive doses, they were not continued in the study. Patients were treated for up to 12 weeks. In addition to pharmacotherapy and daily contact with research staff, subjects were offered a weekly 30-minute individual counselling session. Efficacy was evaluated by treatment retention.

Table 1. Mean age and SD of intravenous buprenorphine-dependent patients, n=204

Group	No.	Mean	SD	Min	Max
Methadone	68	31.19	9.66	17	53
Buprenorphine	68	30.97	9.72	17	53
Naltrexone	68	31.48	9.75	18	51
Total	204	31.22	9.67	17	53

Table 2. Frequency distribution of buprenorphine-dependent patients by age, occupational status, educational status and marital status (n=204)

	Number	%
Age (years)		
<20	12	5.9
20-24	47	23
25-29	50	24.5
30-34	32	15.7
35-39	12	5.9
40-44	21	10.3
>44	30	14.7
Occupation		
Unemployed	46	22.5
Private sector job	33	16.2
Labourer	48	23.5
Government employee	35	17.2
Retailer	25	12.3
Truck and taxi driver	14	6.9
Other	3	1.5
Years of education		
1-5	30	14.7
6-12	113	55.4
>12	61	29.9
Marital status		
Single	80	39.2
Married	124	60.8

Table 3. Factors associated with intravenous buprenorphine-dependent patients (n=204)

	No	%
Substances previously used		
Opium	129	63.2
Heroin	35	17.2
No substance	40	19.6
Other substances currently used		
No substance	204	100
Number of ampoules		
1 - 2	67	32.8
3 - 4	87	42.6
5 - 6	25	12.3
7 - 8	16	7.8
>8	9	4.4
* Mean ampoule=3.86 SD=2.61 Minimum=1(ampoule) Maximum=19 (ampoule)		
Duration of misuse		
0.5 - 1 year	94	46.1
1.1 - 2 years	68	33.3
2.1 - 4 years	33	16.2
> 4 years	9	4.4
* Mean duration=1.87 SD=1.74 Minimum=0.5 (year) Maximum=15 (year)		
Causes of misuse		
Pleasurable purposes	73	35.79
For opium/heroin dependency	67	32.84
Release of tension etc.	54	26.47
Other	10	4.90
Source		
Street sale	185	90.69
Drug stores	11	5.39
Other	8	3.92

Induction onto methadone was done by administering 20mg and then 50mg over the first two study days and then continuing with 50mg daily. Induction onto buprenorphine was done by administering 2mg and then 5mg over the first two study days. Induction onto naltrexone was done by administering 20mg and then 50mg methadone over the first two study days, and then tapering off in the next 10 days. Ten days after detoxification, induction onto naltrexone was done by administering 50mg 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. $\chi 2$ analyses were used to test for differences in 12-week completion rates among the three groups, and t test analyses were used to test for differences in means. These were two-sided with significance set at $p<0.05$.

Results

Data were collected from 204 male intravenous buprenorphine-dependent patients. There were no significant differences in the type of substances previously used, number of buprenorphine ampoules injected a day or the mean duration of buprenorphine misuse, between the three groups. Patient characteristics are given in Table 2. There is no difference in mean age between the three groups (see Table 1). Most subjects (80.4%) gave a history of opium or heroin dependency before they were introduced to buprenorphine (see Table 3). The most frequently used previous substance was opium (63.2%). The majority (79.4%) reported using buprenorphine for the past six to 24 months. Only 4.4% reported using it for more than four years. The main source of buprenorphine for the misusers (90.69%) was the street (see Table 3).

They reported that the drug made them feel fresh and energetic and able to function normally. Patients described 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 antihistaminics. A majority reported that cigarettes soaked in buprenorphine had a different, sweet taste. Most patients (75.4%) were using one to four ampoules a day (one ampoule contains 0.3mg of buprenorphine in 1ml).

Table 4. Frequency distribution of completers by group

Group	Completers		Non-completers		Total	
	N	%	N	%	N	%
Methadone	61	89.7	7	10.3	68	100
Buprenorphine	44	64.7	24	35.3	68	100
Naltrexone	16	23.5	52	76.5	68	100
Total	121	59.3	83	40.7	204	100

χ^2=62.92 DF=2 Significance (2-sided)=0.000
Methadone vs. Buprenorphine: χ^2=12.07, DF=1, Significance (2-sided)=0.001
Methadone vs. Naltrexone: χ^2=60..62, DF=1, Significance (2-sided)=0.000
Buprenorphine vs. Naltrexone: χ^2=23.38, DF=1, Significance (2-sided)=0.000

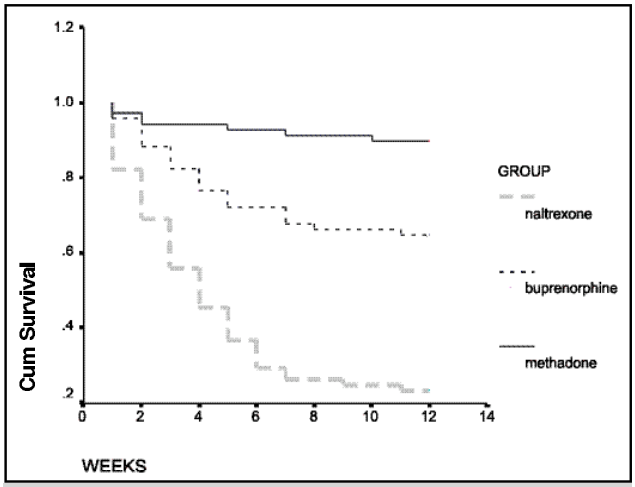

Figure 1. Kaplan-Meier survival analysis of relapses.

Table 4 summarises the frequency distribution of completers by group (methadone group, buprenorphine group and naltrexone group). Figure 1 gives Kaplan-Meier survival analysis of relapses. Overall 121 (59.3%) patients completed the 12-week study. Completion rates by group were 61 (89.7%) for the 50mg methadone group, 44 (64.7%) for the 5mg buprenorphine group and 16 (23.5%) for the 50mg naltrexone group. The naltrexone group had significantly poorer retention than the methadone group (χ2=60.62, df=1, p=0.000). Also, the naltrexone group had significantly poorer retention than the buprenorphine group (χ2=23.38, df=1, p=0.000). Comparison of the methadone group with the buprenorphine group was also significant (χ2=12.07, df=1, p=0.001).

Discussion

This study indicates that the characteristics that make buprenorphine promising for treating opium and heroin dependents also make it appealing on the illegal drug market. Some patients started injecting buprenorphine to suppress the withdrawal symptoms of opium or heroin and to eliminate or decrease their dependence on opioids. There were a variety of reasons why opium-dependent patients wanted to decrease their dependence. Opium became less available and more expensive. Methadone is scarce in Iran and therefore some patients use buprenorphine to self-medicate. Buprenorphine was considered a good alternative to opium because it was cheaper, easy to carry, more available than opium and produced the same effects. The pleasurable effects of buprenorphine helped some patients to have a relatively normal life. Some increased the pleasurable effects of buprenorphine by using it with antihistaminic agents or diazepam.

This study supports the efficacy of oral methadone for treatment of IV buprenorphine dependence. There was a clear superiority of sublingual buprenorphine over naltrexone in patient retention. It is likely that 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 study was limited to IV buprenorphine dependents seeking treatment, therefore it may not be representative of the entire population of buprenorphine-dependent patients. However, it has generated data, which could be useful in understanding and controlling buprenorphine misuse and dependency. Retention in treatment is reasonable on methadone or sublingual buprenorphine but inadequate for the naltrexone group.

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References

1. Bickel WK, Stitzer ML, Bigelow GE et al. A clinical trial with buprenorphine: comparison with methadone in the detoxification of heroin addicts. *Clin Pharmacol Ther* 1988; 43: 72-8.
2. Johnson RE, Cone EJ, Henningfield JE et al. Use of buprenorphine in the treatment of opiate addiction. Physiologic and behavioral effects during a rapid dose induction. *Clin Pharmacol Ther* 1989; 46: 335-43.
3. O'Connor JJ, Maloney E, Travers R et al. Burprenorphine abuse among opiate addicts. *Br J Addiction* 1988; 83: 1085-87.
4. Basu D, Malhotra AK, Varma VK. Buprenorphine dependence: a new addiction in India. *Disabilities and Impairments* 1990; 3: 142-6.
5. Singh RA, Mattoo SK, Malhotra A et al. Cases of buprenorphine abuse in India. *Acta Psychiatrica Scandinavica* 1992; 86: 46-8.
6. Umesh Babu SB, Chaturvedi SK. Changing patterns of opiate abuse with a focus on buprenorphine. *Indian J Psychiat* 1995; 37: (suppl) 23.
7. Kumar MS. A study of buprenorphine abuse in Madras city, India. In exploratory studies on drug abuse in the Asian region; Navaratnam V. Devi V. Eds: International Monograph Series No. 10. University Sains Malaysia: Penang, 1997; 49-69
8. Sharma Y, Matoo SK. Burprenorphine abuse in India: an update. *Indian J Psy* 1999; 41: 154-9.
9. Harper I. Temgesic abuse. *NZ Med J* 1983; 96: 777.
10. Strang J. Abuse of buprenorphine. *Lancet, ii* 1985; 725.
11. Quigly AJ, Bredmeyer DE, Seow SS. A case of buprenorphine abuse. *Med J Aust* 1984; 140: 425-6.
12. Ahmed SK, Ara N. An exploratory study of buprenorphine use in Bangladesh: a note. *Substance use & Misuse* 2001; 36 (8): 1071-83.
13. Obadia Y, Perrin V, Feroni I et al. Injecting misuse of buprenorphine among French drug users. *Addiction* 2001; 96: 267-72.
14. Basu D, Mattoo SK, Malhotra A et al. A longitudinal study of male buprenorphine addicts attending a clinic in India. *Addiction* 2000; 95: 1363-72.
15. Rainey HB. Abuse of buprenorphine. *NZ Med J* 1986; 99: 72.

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