Indian J Physiol Pharmacol 2008; 52 (1): 53–63

ASSESSMENT OF DIFFERENTIAL DOSES OF BUPRENORPHINE FOR LONG TERM PHARMACOTHERAPY AMONG OPIATE DEPENDENT SUBJECTS

SHANTANU DE, RAKA JAIN*, RAJAT RAY, ANJU DHAWAN AND SUNNY T. VARGHESE

National Drug Dependence Centre,
Department of Psychiatry,
All India Institute of Medical Sciences,
New Delhi – 110 029

(Received on July 23, 2007)

Abstract : The aim of the present study was to evaluate, two different doses of sublingual buprenorphine (2 mg and 4 mg) among patients on maintenance treatment and to assess the relationship of steady state plasma level with craving.

Twenty three male opioid dependent (ICD-10 DCR) subjects, were assigned to double blind randomized controlled trial of 2 and 4 mg/day doses of buprenorphine in an inpatient setting. They were evaluated thrice (2nd, 7th and 14th day) in 2 weeks for withdrawal symptoms (acute and protracted), sedation, euphoria, craving, side effects, global rating of well being and for measurement of plasma levels of buprenorphine. The data showed that there were no significant difference in scores of euphoria and sedation, protracted withdrawal symptoms and side effects, craving and overall well being and plasma level of buprenorphine among the subjects. However, both the groups had significant difference in score on almost all the measurements on final observation in comparison to initial observation.

Both 2 mg/day and 4 mg/day dose of buprenorphine were effective in long term pharmacotherapy of opioid dependence without significant difference as compared by different measures used in the study.

Key words : buprenorphine craving maintenance treatment plasma level

INTRODUCTION

Reports from the various de-addiction centers in India indicate that a majority of the patients utilizing the services are dependent on opioid drugs. The period prevalence rate (use in last one month) of heroin use among adult males in India is around 0.2–1.3% (1).

Maintenance therapy aims at reducing the need for illicit drugs by prescribing

*Corresponding Author : Tel. No. : 91-011-26593236, 26593595; Fax : 91-011-26588663, 26588641; E-mail : rakajain2001@yahoo.com

medication (agonist or antagonist) on a regular basis to the dependent patients. Buprenorphine as a long-term maintenance agent has emerged as an alternative to the widely used methadone (2, 3). It has a limited euphoric effect, wide safety margin and a ceiling effect on respiratory depression (4). Several western studies have used doses ranging between 2–32 mg (sublingual) per day comparing it with methadone and have shown its efficacy. It has been reported that 8 mg/day of buprenorphine is equal in efficacy to methadone as a maintenance agent though the difference between 4 mg and 8 mg was marginal (5, 6, 7). The optimal dose for maintenance therapy in Indian subjects is not known. This dose may be lower due to the lower habit size, decreased purity of heroin available, and the lower body weight among Indians. Similar observations have been made regarding antipsychotic medications in Asian subjects who require lower doses of neuroleptics to control their psychotic symptoms (8).

The present study compared the effectiveness of 4 mg/day of buprenorphine against 2 mg/day over a period of 2 weeks in a controlled experimental environment in heroin dependent patients who were stabilized on 2 mg or less of buprenorphine.

METHODS

Subjects of the study

The study sample included twenty male opioid dependent subjects aged between 25–50 years who satisfied the DSM IV TR criteria for opioid dependence. These subjects were receiving 2 mg or less of buprenorphine, as a maintenance treatment for at least 1 month before the study. These subjects were chosen from the out patient department and the community clinic of the National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi. Informed consent was obtained from all the subjects before including in the study. Subjects who were totally abstinent from opioids while receiving 2 mg or less of buprenorphine and who were dependent on any other psychotropic drug (except nicotine) in previous month were excluded from the study. The study got approved by an Institutional Ethics Committee and was in compliance with the ethical standards of the Committee on Human Experimentation of the institution.

Study design

The subjects were admitted to the ward and divided into two groups (Group-1 and Group-2) using random allocation table. Group-1 subjects were given 2 mg buprenorphine and Group-2 subjects were given 4 mg buprenorphine in a double blind manner.

Administration of the tablets

Subjects in Group 1 received one tablet of buprenorphine (2 mg) and one tablet of placebo in the morning and 1 tablet of placebo in the evening. Subjects in Group 2 received 2 tablets of 2 mg buprenorphine in the morning and 1 tablet of placebo in the evening. All the tablets (both placebo and active compound) were administered sublingually.

Instruction to the patients

Patients were informed that they would receive daily medicines at 7 am and 7 pm and assessment would be done at 10 am on the 2nd, 7th and 14th day of admission. No medicines other than Loperamide and Zopiclone were permissible. Opioid withdrawal (acute and protracted), euphoria, sedation, craving and overall status were assessed using the appropriate tools.

Urine samples were screened by thin layer chromatography on the day of admission to assess presence of illicit opioid and other drug of abuse (9). In addition, two random urine samples were also screened to ensure that the subjects were free from exogenous opioid use other than the prescription medicine.

Blood samples were drawn, on the day of admission and on the 14th day, 3 hours after the morning dose of medicine (10 am) and the plasma level of buprenorphine was estimated. The quantitative assessment was done by gas liquid chromatography (GLC), using Hewlett Packard 5890 series II equipment. The samples were injected on to the GLC column in split mode and modified conditions were set to ascertain the steady state plasma levels (10).

Assessment

Signs and symptoms of opiate withdrawal were rated using subjective opiate withdrawal scale (SOWS) and the objective opiate withdrawal scale (OOWS) (11). Assessment of euphoria and sedation were done using Morphine Benzedrine Group scale (MBG) and Pentobarbital Chlorpromazine Alcohol Group scale (PCAG) (12). A checklist of protracted withdrawal symptoms commonly reported in literature was prepared (Jasinski, 1978) and the patient rated each symptom (13). A list of common side effects of buprenorphine was prepared and assessed. Craving was assessed by Visual Analog scale (VAS) (14), following exposure to the drug related cues in the form of color slides showing drug use paraphernalia, simulated drug purchase, consumption (inhaling heroin or injecting drugs) and withdrawal symptoms. A total of six slides were shown to each subject and subjects were exposed to each slide for 3 minutes and description of the situation depicted in the slide was narrated in a lucid manner in order to elicit craving. The peak rating was assessed on three parameters of desire to consume drug, difficulty in resisting drug consumption and uneasiness. Global rating scale was used to assess the physical state of the patient and overall well being at the end of the study.

Administration of the scales

All the scales except the global rating scale were administered on the 2nd, 7th and 14th day after admission. SOWS, OOWS and Cue Exposure were assessed as “here and now” basis. Assessment on other items was based on the following time frames—previous one month during the first assessment (Day 2), for the previous 5 days during the second assessment (Day 7) and for the previous 7 days during the third assessment (Day 14). During assessment, scales were presented in the sequence as described above.

Data analysis

Socio-demographic data of both the groups were compared using Chi-square test with Yates correction and unpaired t test. Both the groups were compared on scores of all the scales on day 2, 7 and 14 (inter-group comparison) using unpaired t test. The scores of all the scales were compared within the same subjects in a group on day 2, 7 and 14 (intra-group comparison) by Friedmans two way analysis of variance. The relationship of steady state plasma level to buprenorphine dose was assessed using Mann-Whitney test. Spearmann correlation coefficient test was used for studying the relationship of plasma level with MBG and VAS.

RESULTS

Forty-five patients with opioid dependence, fulfilling the ICD-10 DCR criteria were screened for the study. Twenty-three subjects participated in the study and twenty-two subjects stayed in the treatment for the entire duration of the study. One subject dropped out on the third day of the study. Demographic profile and drug use history of the subjects is shown in Table I. The socio-demographic profile of the subjects did not reveal any baseline differences between the two groups. The mean age of the subjects was 36 ± 5.5 years and they had a mean duration of 7 years of education. The subjects in both the groups had similar age of onset of initiation, duration and frequency of non prescription opioid use. In spite of being on prescription buprenorphine (dose between 1.2–2 mg/day) over last one month, subjects continued using illicit heroin and non-prescription buprenorphine. Median number of days of heroin use in last one month was 9 days for subjects in group 1 and 18 days for subjects in group 2.

TABLE I: Use of non-prescription opioid in the subjects.

	Group 1 (2 mg, n=11) Mean (±S.D.)	*Group 2 (4 mg, n=12) Mean (±S.D.)*	*Signi-ficance (2 tailed)*
Age of initiation of heroin use (years)	25.6 (4.3)	24.1 (5.0)	0.43
Duration of daily use (years)	12.0 (4.3)	9.9 (5.8)	0.35
Frequency of heroin use in last 1 month (days)	11.0 (10.5)	17.8 (11.4)	0.15
Frequency of buprenorphine use in last 1 month (days)	6.3 (10.4)	4.7 (10.9)	0.72
Last use (before admission) (no. of days)	1.3 (1.6)	3.6 (6.6)	0.26

Unpaired t test applied.

Six subjects used only ‘Street heroin’ while rest of them combined it with either buprenorphine (non prescription) or pentazocine injection. Few of them were also using alcohol, cannabis, chlorpheniramine maleate and benzodiazepine concurrently, in a non dependent fashion. Though they had no difference as regards alcohol, cannabis and benzodiazepine use, more subjects in group 1 reported using chlorpheniramine maleate use as compared to subjects in group 2. Before inclusion in the study, subjects of both the groups received mean buprenorphine dose of about 1.8 mg/day. The duration of therapy was variable. The median duration was 5 months in group 1 and 3 months in group 2.

Opiate withdrawal measures

The mean subjective (Table II) and objective (Table III) opioid withdrawal scores between the groups did not reveal any significant difference. In both the groups, scores reduced more on 7th day in comparison to baseline than on 14th day. The comparison of mean SOWS scores among the subjects of group 1 revealed that differences between scores on 2nd day and 7th day, 2nd day and 14th day reached significance. There was no significant difference between scores of the 7th and 14th day.

The intra-group comparison of SOWS score in group 2 showed statistically significant decrease of scores on the 14th day when compared with the 2nd day. Statistically significant difference was not observed between the scores on the 2nd and 7th day as well as between the 7th and 14th day. The OOWS scores, declined and significant difference was observed between 2nd day and 7th day as well as between 2nd and 14th day in both the groups (multiple range test).

Measurement of protracted withdrawal symptoms

The comparative protracted withdrawal scores reveal that on 7th day, the difference between the scores of both the groups were significant (Table IV). The reduction of scores was more in group 1 than the group 2 when compared to baseline, although the difference was not statistically significant. On comparing within the groups (multiple range test), the mean scores of the subjects showed that both the groups had significant reduction in protracted withdrawal symptom scores on 7th day and 14th day as compared

TABLE II: Intragroup comparison of SOWS scores.

	Group 1 (2 mg)			*Group 2 (4 mg)*		
	2nd day (n=11)	*7th day (n=10)*	*14th day (n=10)*	*2nd day (n=12)*	*7th day (n=12)*	*14th day (n=12)*
Mean±SD	12.8±4.9	3.9±3.6	1.2±1.1	12.5±8.3	5.1±4.5	2.1±3.7
Significance	0.00*			0.00*		

Friedman's two way analysis of variance. *P≤0.05.

TABLE III: Intragroup comparison of OOWS scores.

	Group 1 (2 mg)			*Group 2 (4 mg)*		
	2nd day (n=11)	*7th day (n=10)*	*14th day (n=10)*	*2nd day (n=12)*	*7th day (n=12)*	*14th day (n=12)*
Mean±SD	4.4±1.7	0.7±0.9	0.1±0.3	5.3±1.4	0.7±0.8	0.08±0.3
Significance	0.00*			0.00*		

Friedman's two way analysis of variance. *P≤0.05.

to scores on 2nd day (baseline).

Measurement of euphoria and sedation

Euphoria and sedation were also measured among these subjects using Morphine Benzedrine Group scale (MBG) and Pentobarbital, Chlorpromazine, Alcohol Group scale (PCAG), respectively. As shown in Table V and Table VI that there was no significant difference in the MBG and PCAG scores on 2nd day, 7th day and 14th day in both the groups respectively. However, the increase or decline from baseline of MBG and PCAG scores respectively is significant on day 7 and day 14 but the changes between mean score of day 7 and day 14 are not significant.

Assessment of craving

As shown in Table VII, the mean VAS score yielded no significant difference between the subjects in the two groups on the 2nd, 7th and 14th day but the mean baseline score was lower among subjects

TABLE IV: Intra-group comparison of protracted withdrawal symptoms scores.

	Group 1 (2 mg)			*Group 2 (4 mg)*		
	2nd day (n=11)	*7th day (n=10)*	*14th day (n=10)*	*2nd day (n=12)*	*7th day (n=12)*	*14th day (n=12)*
Mean±SD	18.4±6.3	7.4±5.5	4.4±3.9	16.3±4.3	11.3±5.5	7.3±6.8
Significance	0.00*			0.00*		

Friedman's two way analysis of variance. *P≤0.05.

TABLE V: Intra-group comparison of MBG scores and PCAG scores in patients receiving 2 mg.

	MBG Score			*PCAG Score*		
	2nd day (n=11)	*7th day (n=10)*	*14th day (n=10)*	*2nd day (n=11)*	*7th day (n=10)*	*14th day (n=10)*
Mean±SD	5.7±3.7	10.6±2.4	12.0±1.5	10.0±2.2	5.1±2.9	4.2±2.6
Significance	0.00*			0.00*		

Friedman's two way analysis of variance. *P≤0.05.

TABLE VI: Comparison of MBG scores and PCAG scores in patients receiving 4 mg (n=12).

	MBG Score			*PCAG Score*		
	2nd day	*7th day*	*14th day*	*2nd day*	*7th day*	*14th day*
Mean±SD	6.6±3.2	10.8±3.0	11.2±3.6	8.8±3.1	5.7±2.9	4.6±2.5
Significance	0.01*			0.00*		

Friedman's two way analysis of variance. *P≤0.05.

TABLE VII: Comparison of mean Visual Analog Scale (VAS) scores on different days between patients receiving 2 mg and 4 mg buprenorphine.

Days after admission	*Group 1 (2 mg) Mean (±S.D.)*	*Group 2 (4 mg) Mean (±S.D.)*	*Significance (single tailed)*	*95% C.I. of mean*	
				Lower	*Upper*
2nd	37.3 (28.3) (n=11)	42.5 (27.7) (n=12)	0.32	–29.5	19.1
7th	17.0 (20.6) (n=10)	28.3 (22.1) (n=12)	0.11	–30.5	7.8
14th	11.0 (16.6) (n=10)	15.0 (19.3) (n=12)	0.30	–20.2	12.2

Minimum Score = 0, Maximum Score + 100.
C.I. = Confidence interval, Unpaired t test applied. *P≤0.05.

TABLE VIII: Intra-group comparison of Visual Analog Scale (VAS) scores.

	Group 1 (2 mg)			*Group 2 (4 mg)*		
	2nd day (n=11)	*7th day (n=10)*	*14th day (n=10)*	*2nd day (n=12)*	*7th day (n=12)*	*14th day (n=12)*
Mean±SD	37.3±28.3	17.0±20.6	11.0±16.6	42.5±27.7	28.3±22.1	15.0±19.3
Significance	0.00*			0.06		

Friedman's two way analysis of variance. *P≤0.05.

receiving 2 mg than 4 mg buprenorphine.

On comparison of VAS scores within subjects of these two groups (intra-group) on these days, it appears that the decline from scores of 2nd day to scores of 7th day and 14th day in group 1 was more overt (Table VIII). But significant change was not observed in the decline between 7th and 14th day (multiple range test). The decline on VAS score in group 2 was not significant when compared among the subjects on these days (multiple range test).

Measurement of blood level of buprenorphine

As shown in Table IX, the blood levels of buprenorphine on the day of admission (while being on outpatient therapy) in both the groups were below the cut off level for detection. After stabilization on the above doses, blood level of buprenorphine on 14th day was variable in two groups. Subjects receiving 4 mg had higher blood level though the difference was not statistically significant.

TABLE IX: Comparison of blood level of 14th day among subjects receiving 2 mg and 4 mg buprenorphine.

	Blood level (ng/ml) Mean (±S.D.)	*Signi-ficance (single tailed)*	*95% C.I. of mean*	
			Lower	*Upper*
Group 1 (2 mg)	16.9 (9.3)		–28.1	0.3
Group 2 (4 mg)	30.8 (19.7)	0.06	–27.5	–0.3

Mann-Whitney test; C.I. = Confidence interval.

Correlation between VAS score and blood level

The correlation between VAS scores and blood levels on day 14 was not significant in group 1 ($r = 0.50$, $P = 0.14$) and group 2 ($r = 0.12$, $P = 0.7$).

Measures of overall well being

All the subjects (n = 22) reported that they felt better in their overall well being following the completion of the study as compared to before the study.

Urinary opioids

During the 2 week study, urine samples were screened by thin layer chromatography for illicit opioids. In group 1, 7 patients (63.6%) and in group 2, 8 patients (66.7%) had samples positive for morphine on the day of admission but the subsequent samples collected for urinary opioids during the study were negative for morphine.

DISCUSSION

Long-term pharmacotherapy for drug dependence is important and adequate doses can control withdrawal related discomfort and craving. These drugs not only reduce the illicit opioid use and criminal behavior but also improve the socio-economic function as well. Superiority of a particular drug or a certain dose (of a medication) over another dose in long term pharmacotherapy can be assessed by its ability to reduce craving and withdrawal symptoms (acute and protracted) in an experimental situation. The current study conducted in the inpatient setting did not resemble naturalistic setting, but compliance to the prescribed medicine and cessation of illicit/non-prescription use of opioids and other drugs were ensured.

Outpatient studies have been conducted “by comparing different doses of buprenorphine to doses of methadone. The studies comparing two or more different doses of buprenorphine or comparing doses of buprenorphine with methadone had a variable sample size (40–225) and the subjects were followed up for variable duration (6–52 weeks) (15, 16, 17). These studies had taken treatment retention, illicit opioid and cocaine use, urinary opioid detection, criminal behavior and arrest, HIV seroconversion, socially productive behavior i.e. employment and social functioning, as some of the outcome measures (18). In the current study, the effectiveness of two doses of buprenorphine was assessed in an inpatient setting by comparing their ability to suppress acute and protracted withdrawal symptoms (by Subjective and Objective Withdrawal Scale and Protracted Withdrawal Symptom check list) and craving (Visual Analog Scale). Side effects like euphoria and sedation were assessed by MBG or PCAG scale respectively and other side effects were checked with the help of a checklist of common adverse effects of buprenorphine. The subjects enrolled in the study were already on 2 mg or less of buprenorphine on an outpatient basis and were consuming illicit opioid drugs. This could have been due to poor control of withdrawal symptoms and craving, sub therapeutic blood level and disturbing side effects leading to poor compliance. It has been proposed that plasma level of methadone could be correlated well with remission of withdrawal discomfort (19). As no psychosocial intervention was initiated in this study, the difference between the two groups could be attributable only to pharmacotherapy.

The randomization was effective as evident from the fact that no significant difference was observed in pretreatment variables. Subjects in both the groups were assessed and scores in all the scales decreased on day 7 as compared to baseline

except MBG score (which increased from base level). The Subjective and Objective Opioid Withdrawal Scores in both the groups reduced significantly between 2nd day (baseline) and 7th or 14th day. Similar observation was made in the measurement of protracted withdrawal symptoms also. As the buprenorphine level in the blood reached a steady state after 4 days, the effect of the drug showed that the subjects had a lower score on 7th day in comparison to 2nd day. Following achievement of steady state blood level, scores did not reduce much from day 7 to day 14. In the baseline assessment (2nd day), higher scores on withdrawal symptoms were due to initial lower blood level of drug on account of lower dose of buprenorphine. High scores on withdrawal symptoms as evidenced at baseline, could have been due to stoppage of illicit drug use resulting in the appearance of opioid withdrawal symptoms.

The MBG score increased and PCAG score reduced over two weeks. The euphoria (MBG score) increased in the subjects (following regular compliance and increased dose) on 7th day, as the drug level increased but did not increase further on 14th day as steady state plasma level had already been reached. The sedative effect of buprenorphine (PCAG score) in both the groups reduced on day 7 steeply in comparison to day 2 and remained so till day 14. This could be a manifestation of development of tolerance to the sedative properties of buprenorphine. The tolerance to different effects of a drug develops at different rate (20). The subjects probably developed tolerance to sedation more quickly than euphoria. The high initial scoring on PCAG scale on day 2 (prior to onset of treatment as per study schedule) might also be due to co-prescription of benzodiazepine along with buprenorphine at the preceding night before the baseline (day 2) evaluation.

Craving is a significant factor in opiate addiction that is associated with drug dependence and in relapse to drug use after treatment. Craving could be elicited following verbal description of a situation in which subjects experienced a strong craving and subjects rated it on a visual analog scale (VAS) at the end of two week detoxification from opioids (21). In this study, craving was assessed by VAS to compare the desire for psychoactive substance between both the groups. Craving was assessed following cue exposure of photographs depicting drug purchase and consumption situations. The simulated drug use situations aroused craving which were measured subjectively by VAS. The measurement of craving (VAS score) showed that the craving decreases on day 7 as euphoria increases in both the groups, which could be explained by attainment of steady state level of drug in blood and cue exposure induced extinction of conditioned craving (22, 23), of stimuli through repeated sessions was not considered as a possibility in a 2 week inpatient study in which weekly test sessions were conducted following an initial practice session with different scales (VAS, PCAG, MBG among others). In the current study, craving subsided on day 7 and day 14 following regular use of buprenorphine. Thus, it can be inferred that buprenorphine could successfully suppress or attenuate craving.

The inter-group comparison between the two groups did not reveal any significant difference of scores on SOWS, OOWS, MBG, PCAG and VAS, but showed significant difference in the scores of Protracted

Withdrawal Symptom checklist on day 7. The high initial scores could be due to the depletion of blood level of buprenorphine, despite being on maintenance medication, due to dispensing of the medicine after 12–13 hours (following the last dose) and completion of initial assessment leading to withdrawal related discomfort.

The plasma levels of buprenorphine were not detected in most of the subjects (except three who had level of < 4 ng/ml) on the day of admission, which reflects low dose prescription from outpatient setting. The plasma levels on 14th day in the two groups showed wide variation, which was also reported by Chawarski, Schottenfeld, O'Connor and Pakes, (1999), signifying differences in the pharmacokinetic and pharmacodynamic process among the subjects of the same population group (24). In general, higher doses of buprenorphine resulted in higher overall plasma concentrations at 14th day, although the difference was not significant. As the plasma level of buprenorphine increased, both the SOWS and OOWS scores decreased. This was similar to reduction of subjective and objective symptoms in relation to increased plasma methadone concentrations (19). As observed from the visual analog score and plasma level of buprenorphine, the craving decreased as plasma level of buprenorphine increased.

The side effect profile comparison showed that the percentage of patients reporting side effects is less on day 14 than on day 2. This could be due to living in a controlled environment, having better nutrition and exaggeration of problem on initial days in anticipation to get higher dose of buprenorphine and other medications.

Overall, the results indicated that the effectiveness of 2 mg/day and 4 mg/day dose of buprenorphine were almost equal. The study findings revealed that there were no difference of effect as measured in this study between the subjects receiving 2 mg and 4 mg buprenorphine. However both the doses caused significant reduction of scores at the end of the study in comparison to baseline. Essentially the doses were equally effective to reduce withdrawal symptoms and craving. The findings when compared with previous studies (4, 25), suggest that the difference between the two groups in current study may not have reached significance with chosen assessment parameters as two marginally different doses of 2 mg or 4 mg were compared for a shorter duration. It may also be due to the small sample size.

The findings from this 14 day study may not be readily applicable to the patient population in an open naturalistic setting where patients encounter drug related cues, consume illicit opioids and are influenced by various psychological factors. The study documented that prescribing 4 mg/day dose would not be hazardous for the subjects as comparable side effects emphasized it as safe as 2 mg/day dose. This study should be followed up with further studies of long term follow up in outpatient setting.

In conclusion, some opioid addict subjects do perform better with higher doses and cautious clinical judgment is necessary before concluding about a particular dose from the results of this study. Apart from pharmacotherapy, long-term treatment of opioid dependence should consist of psychosocial intervention like counselling, rehabilitation and measures for relapse prevention.

REFERENCES

1. Ray R. South Asia drug demand reduction report. UNDCP, ROSA: New Delhi. 2000.
2. Oreskovich MR, Saxon AJ, Ellis ML, Malte CA, Reoux JP, Knox PC. A double-blind, double-dummy, randomized, prospective pilot study of the partial mu opiate agonist, buprenorphine, for acute detoxification from heroin. *Drug and Alcohol Dependence* 2005; 77: 71–79.
3. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clinical Pharmacology and Therapeutics* 1994; 55: 569–580.
4. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives of General Psychiatry* 1997: 54: 713–720.
5. Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Archives of General Psychiatry* 1996; 53: 401–407.
6. Ling W, Charuvastra C, Collins JF, Batki S, Brown Jr LS, Kintaudi P, Wesson DR, McNicholas L, Tussel DJ, Malkernekar U, Renner JR, Santos E, Casadonte P, Fye C, Stine S, Wang RIH, Segal D. Buprenorphine maintenance treatment of opioid dependence: amulticentre randomized clinical trial. *Addiction* 1998; 93: 475–486.
7. Fischer G, Gombas W, Eder H, Jagsch R, Peternell A, Stuhlinger G, Pezawas L, Aschauer HN, Kasper H. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction* 1999; 94: 1337–1347.
8. Lin KM, Finder E. Neuroleptic dosage for Asians. *American Journal of Psychiatry* 1983; 140: 490–491.
9. Jain R. *Detection of drugs of abuse in body fluids – a manual for laboratory personnel*. National Drug Dependence Treatment Centre, AIIMS: New Delhi. 1990.
10. Martinez D, Jurado MC, Ropetto M. Analysis of buprenorphine in plasma and urine by gas chromatography. *Journal of Chromatography* 1990; 528: 459–463.
11. Handelsman L, Cochrane KJ, Aronson JM, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *American Journal of Drug Abuse* 1987; 13: 293–308.
12. Haertzen CA, Hickey JE. Addiction Research Centre Inventory (ARCI): measurement of euphoria and other drug effects. In: *Methods of assessing the reinforcing properties of abused drugs*. Bozarth MA (Ed). Springer Verlag: New York USA 1987; 489–524.
13. Jasinski DR Opiate withdrawal syndrome: acute and protracted aspects. *Annals of New York Academy of Science* 1978; 363: 183–186.
14. Folstein MF, Luria R. Reliability, validity and clinical application of the visual analog scale. *Psychological Medicine* 1973; 3: 479–486.
15. Gerra G, Borella F, Zaimovic A, Moi G, Bussandri M, Bubici C, Bertacca S. Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug and Alcohol Dependence* 2004; 15: 37–45.
16. Strain EC, Stitzer ML, Liebson LA, Bigelow GE. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *American Journal of Psychiatry* 1994; 151: 1025–1030.
17. Ahmadi J. Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients. *Journal of Substance Abuse Treatment* 2003; 24: 217–220.
18. Simoens S, Matheson C, Bond C, Inkster K, Ludbrook A. The effectiveness of community maintenance with methadone or buprenorphine for treating opiate dependence. *British Journal of General Practice* 2005; 55: 139–146.
19. Hiltunen AJ, Lafolie P, Martel J, Ottosson EC, Boreus LO, Beck O, Borg O, Hjemdahl P. Subjective and objective symptoms in relation to plasma methadone concentration in methadone patients. *Psychopharmacology* 1995; 118: 122–136.
20. Smith CM. The pharmacology of sedative/hypnotics, alcohol and anaesthetics. In: Martin RW (Ed). Drug Addiction. Vol. 1, Springer-Verlag, Berlin Heidelberg New York, 1977.
21. Weinstein A, Wilson S, Bailey J, Myles J, Nutt D. Imagery of craving in opiate addicts undergoing detoxification. *Drug and Alcohol Dependence* 1997; 48: 25–31.
22. Childress AR, McLellan AT, O'Brien CP. Abstinent opiate abusers exhibit conditioned craving, conditioned withdrawal and reductions in both through extinction. *British Journal of Addiction* 1986; 81: 655–660.
23. Marlatt GA. Cue exposure and relapse prevention in the treatment of addictive behaviours. *Addictive Behaviors* 1990; 15: 395–399.
24. Chawarski MC, Schottenfeld RS, O'Connor PG, Pakes J. Plasma concentrations of buprenorphine 24 to 72 hours after dosing. *Drug and Alcohol Dependence* 1999; 55: 157–163.
25. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. *Journal of Nervous and Mental Disorders* 1993; 181: 358–364.