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Evaluation on drug dependence of buprenorphine[1]

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ABSTRACT

AIM: To survey and assess the drug dependence and abuse potential liability of buprenorphine among opiate abusers. **METHODS:** Subjects of opiate dependence with history of buprenorphine use for 3 d at least were surveyed by interview. Physical dependence of buprenorphine was assessed using 30 items opiate withdrawal scale (OWS), which composed of 30 symptoms/signs. A 4-point scale was used to rate each symptoms/signs: zero (0), mild (1), moderate (2), and severe (3). Subjects were asked to rate their symptoms according to severity of previous experienced buprenorphine withdrawal. The estimate of the degree of subjective euphoria for buprenorphine was assessed using visual analogue scale (VAS). **RESULTS:** Subjects 1235 who met the research criteria cases completed this survey in multi-detoxification treatment centers. The main initial purposes of buprenorphine use were detoxification (77.4 %) and protracted abstinence treated (26.6 %) respectively. The scores of OWS of buprenorphine were between 0.2 to 1.3; The mean scores of OWS in 3 different categories of frequency of buprenorphine use on "continuous use", "un-continuous use", and "sometimes continuous, sometimes un-continuous" were 0.9±0.9, 0.4±0.5, and 0.7±0.4, respectively (F=70.846, P<0.05). The degree of subjective euphoria for buprenorphine was slight to sub-moderate (mean score of VAS was 27 mm ±24 mm). The mean scores of VAS in different routes of buprenorphine administration of sublingual and injection were (24±23) mm and (27 ±24) mm, respectively. No significant difference was found between sublingual and injection use of buprenorphine (u=1.516, P>0.05). **CONCLUSION**: Both physical and psychic dependence of buprenorphine were low.

INTRODUCTION

As a mixed opiate agonist-antagonist, buprenorphine is a relative new treatment agent for heroin addiction of detoxification in China. Buprenorphine has been well evaluated in clinical trial in China as a form of detoxification for heroin addicts[1,2]. However, one of key issue is that we lack the systematic data for its drug dependent potential. In order to evaluate drug dependence and abuse potential of buprenorphine, a multi-center study was carried out by State Drug Administration in 2000 to 2001.

SUBJECTS AND METHODS

Subjects were from multi-area and multi-detoxification centers. Subjects 1235 who met research criteria cases completed this survey in 17 detoxification treatment centers of Beijing (348 cases), Haerbin (50 cases), Shanghai (115 cases), Chongqing (112 cases), Wuhan (268 cases), Nanning (101 cases), and Guangdong (241

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cases) areas. The subjects were 71.3 % male, 94.2 % Han, and 39.1 % married, with a mean age (30±6) years (ranging in age from 17 to 41 years). Most cases were primary and secondary education level (94.0 %), unemployed (45.7 %), and private business persons (32.7 %). All subjects met diagnostic criteria for opiate dependence on the structured clinical interview for DSM-III-R[3], with history of buprenorphine use at least 3 d, and with the experience of buprenorphine discontinuance. Subjects with major mental disorders were not permitted to participate in this study. The frequency of buprenorphine use was divided into three patterns: "continuous use", "un-continuous use", and "sometimes continuous, sometimes un-continuous use". "Continuous use" was defined as "those who had used buprenorphine 20 d or more in a month"; "un-continuous use" was defined as "those who had used buprenorphine 3 d at least, but less than 20 d in a month"; and "sometimes continuous, sometimes un-continuous use" was defined as on this condition between "continuous use" and "un-continuous use".

Subjects provided basic demographic data and were also asked a structured questionnaire that included the drug history and the purposes of using buprenorphine. The questionnaire was administered by trained clinicians. The same method which priority evaluated drug dependence of dihydroetorphine and tramadol was used in this study[4,5]. The degree of opiate-like withdrawal symptoms (physical dependence) of buprenorphine was measured using modified opiate withdrawal scale (OWS)[6]. The modified OWS consisted of 30 typical opiate withdrawal signs/symptoms. A 4-point scale of zero (0), mild (1), moderate (2), and severe (3) was used to rate the intensity of each signs/symptoms of buprenorphine withdrawal. Subjects were asked to rate their symptoms according to severity of previous experienced buprenorphine withdrawal. The subjective euphoria (psychic dependence) of buprenorphine was rated by visual analogue scale (VAS)[7]. This is a line of 100 mm in length, which left end represented no euphoria, while the other end represented maximal euphoria of buprenorphine. Subjects made a mark on the line to represent the degree of euphoria experienced for buprenorphine. The subjective euphoria of different routes of buprenorphine administration was also compared using VAS. The tolerance of buprenorphine was evaluated by differences of dose and frequency between initial and last time of buprenorphine use. All the interviews and assessments were conducted by trained clinicians (psychiatrists or medical doctors). All subjects' answers were required to be clear. Original data input and data analysis were by EPI-INFO[8]. The unpaired *t*-test, *u*-test, and analysis of variance (ANOVA) were used. A 95 % significance threshold was applied in tests.

RESULTS

Opiate (heroin) was the main abused drug. The mean time of opiate abuse was (26±20) months. The purposes of buprenorphine use were divided into 5 factors: pain relief, detoxification of opiate addiction, "protracted abstinence treatment" after detoxification, seeking euphoria of buprenorphine, and other purposes. The results showed that 77.4 % of subjects were for the purpose of detoxification treatment; 26.6 % of subjects for "protracted abstinence treatment", and only 2.5 % of subjects for seeking euphoria from buprenorphine (Tab 1).

Tab 1. Main purposes for buprenorphine use (multi-choice answer, n=1235).

Purposes	*n*	%
Medical purpose (as a pain relief)	32	2.6
Detoxification treatment	956	77.4
"Protracted abstinence" treatment (avoidance of physical discomfort after detoxification)	328	26.6
Seeking euphoria (for enjoyment of effect from buprenorphine)	31	2.5
Other purposes	5	0.4

The mean cumulative frequency of buprenorphine use was (60±63) times. The average single doses and frequency between initial and last time of buprenorphine use are presented in Tab 2.

The withdrawal signs/syndromes of buprenorphine appeared (8±8) h after last drug administration. The degree of buprenorphine physical dependence was mild according to OWS (the range of mean scores of withdrawal signs/symptoms were 0.2 to 1.3). The mean gross scores of OWS in three different categories of frequency of buprenorphine use on "continuous use", "un-continuous use", and "sometimes continuous, some times un-continuous" were 0.9±0.9, 0.4±0.5, and 0.7±0.4, respectively. The result of ANOVA was F=70.846,

Tab 2. The average single dose and frequency of buprenorphine use. Mean±SD. [b]*P*<0.05 *vs* average single dose of sublingual route of initial use, *t* =-7.008, df=154; [e]*P*<0.05 *vs* frequency of sublingual route of initial use, *t* =-10.37, df=155; [h]*P*<0.05 *vs* average single dose of injection route of initial use, *t* =-3.134, df=927; [k]*P*<0.05 *vs* frequency of injection route of initial use, *t* =-8.724, df=948.

Routes of administration	Initial use		Last time of use	
	Average single dose/ mg per time	Frequency/ times per day	Average single dose/ mg per time	Frequency/ times per day
Sublingual	1.2±1.1	2.0±1.0	2.1±2.2[b]	2.8±0.8[e]
Injection	0.5±2.3	2.0±1.1	0.8±0.6[h]	2.8±1.4[k]

[a]*P*<0.05. Tab 3 was presented the signs/symptoms of distribution of buprenorphine withdrawal.

Subjective euphoria of buprenorphine measured by VAS showed that buprenorphine produced the degree of "slight" to "sub-moderate" euphoria experience (mean VAS value=27 mm±24 mm). No significant differences were found between the different routes of sublingual and injection use of buprenorphine (the VAS value of sublingual use=24 mm±23 mm; the VAS value of injection=27 mm±24 mm, u=1.516, P>0.05).

DISCUSSION

In the survey, subjects were asked about the main purposes of buprenorphine use. From the information

Tab 3. Buprenorphine withdrawal and mean scores of signs/symptoms. Mean±SD.

Signs/symptoms	Respondents	Intensity of withdrawal 0	1	2	3	OWS factors
		n %	*n* %	*n* %	*n* %	
Insomnia	1089	302 (27.7)	313 (28.7)	352 (32.3)	122 (11.2)	1.3±1.0
Ache and pain	1073	333 (31.0)	355 (33.1)	273 (25.4)	112 (10.4)	1.2±1.0
Restlessness	1078	349 (32.4)	416 (38.6)	240 (22.3)	73 (6.8)	1.0±0.9
Weakness	1075	350 (32.6)	471 (43.8)	189 (17.6)	65 (6.0)	1.0±0.9
Feeling sick	1075	368 (34.2)	488 (45.4)	171 (15.9)	48 (4.5)	0.9±0.8
Increased sweating	1071	427 (39.9)	445 (41.5)	155 (14.5)	44 (4.1)	0.8±0.8
Poor appetite	1074	439 (40.9)	444 (41.3)	127 (11.8)	64 (6.0)	0.8±0.9
Stiffness of arms or legs	1081	497 (46.0)	331 (30.6)	206 (19.1)	47 (4.3)	0.8±0.9
Gooseflesh	1076	442 (41.1)	474 (44.1)	125 (11.6)	35 (3.3)	0.8±0.8
Yawning	1061	461 (43.4)	441 (41.6)	123 (11.6)	36 (3.4)	0.8±0.8
Runny eyes	1073	489 (45.6)	417 (38.9)	133 (12.4)	34 (3.2)	0.7±0.8
Fatigue and tiredness	1066	496 (46.5)	422 (39.6)	95 (8.9)	53 (5.0)	0.7±0.8
Runny nose	1066	550 (51.6)	379 (35.6)	110 (10.3)	27 (2.5)	0.6±0.8
Hot and cold flushes	1062	581 (54.7)	321 (30.2)	119 (11.2)	41 (3.9)	0.6±0.8
Heart pounding	1066	631 (59.2)	308 (28.9)	89 (8.3)	38 (3.6)	0.6±0.8
Headache	1072	628 (58.6)	317 (2936)	98 (9.1)	29 (2.7)	0.6±0.8
Depression	1072	674 (62.9)	275 (25.7)	91 (8.5)	32 (3.0)	0.5±0.8
Feeling cold	1061	659 (62.1)	304 (28.7)	72 (6.8)	26 (2.5)	0.5±0.7
Dizziness or giddiness	1057	718 (67.9)	248 (23.5)	62 (5.9)	29 (2.7)	0.4±0.7
Dry mouth	1064	734 (69.0)	225 (21.1)	82 (7.7)	23 (2.2)	0.4±0.7
Vomiting	1070	781 (73.0)	195 (18.2)	72 (6.7)	22 (2.1)	0.4±0.7
Stomach cramps	1065	786 (73.8)	198 (18.6)	59 (5.5)	22 (2.1)	0.4±0.7
Diarrhea	1064	846 (75.8)	185 (17.4)	51 (4.8)	22 (2.1)	0.3±0.7
Trembling hands	1063	797 (75.0)	202 (19.0)	52 (4.9)	12 (1.1)	0.3±0.6
Muscular tension	1050	797 (75.9)	193 (18.4)	47 (4.5)	13 (1.2)	0.3±0.6
Drowsiness	1061	879 (82.8)	119 (11.2)	36 (3.4)	27 (2.5)	0.3±0.6
Trouble in starting urination	1062	875 (82.4)	129 (12.1)	45 (4.2)	13 (1.2)	0.2±0.6
Spontaneous twitching of muscles	1060	874 (82.5)	143 (13.5)	34 (3.2)	9 (0.8)	0.2±0.5
Eyes sensitive to light	1057	899 (85.1)	116 (11.0)	32 (3.0)	10 (0.9)	0.2±0.5
Others	336	293 (87.2)	18 (5.4)	13 (3.9)	12 (3.6)	0.2±0.7

provided by subjects, 77.4 % of subjects were for the purpose of detoxification treatment; 26.6 % of subjects for "protracted abstinence" treatment; and only 2.5 % of subjects for seeking euphoria from buprenorphine. It demonstrated that the most of subjects were the therapeutic purpose use of buprenorphine.

Main finding in this survey was that buprenorphine produced low dependent potential, not only physical dependence, but psychic dependence. The physical and psychic dependence is the critical aspect in assessing the impact of drug abuse potential[9]. Theoretically, almost all the compounds that have affinity to opioid receptor (primarily the μ receptor such as morphine, methadone, and heroin) produce drug dependent potential and other adverse drug reactions including respiratory depression which can be fatal. This study supports this postulate that buprenorphine as a partial agonist at the μ-opioid receptor, unlike morphine and methadone which are all full agonists at this receptor, had a unique pharmacological profile, and a significantly lesser drug dependent potential (both physical and psychic) than morphine and methadone.

Pharmacotherapies for heroin addicts are based on two key clinical features of opiate dependence, acute withdrawal (detoxification) and "protracted abstinence syndrome" after detoxification[10]. Main three categories of medicine for detoxification of opiate addiction are currently available: clonidine, methadone, and buprenorphine. Clonidine is an alpha-adrenergic agonist drug that acts on the locus coeruleus, suppressing the withdrawal overactivity of noradrenergic neurones and therefore reducing the release of noradrenaline. Thus it suppresses some of the autonomic signs/symptoms of opiate withdrawal, but is less effective at suppressing the subjective discomfort of withdrawal, and has undesirable side effects of hypotension and sedation. It is the causes of detoxification failure or discontinue detoxification therapy[11]. Methadone is an efficacy drug for heroin addiction not only by relief of acute withdrawal, but also by treatment of protracted abstinence and maintenance. However, methadone has some limitations: It can produce lethal overdose[12-14]; It can produce moderate to sub-severe withdrawal syndromes when stopped and difficulties with discontinuation from methadone treatment to a drug-free state[15]; It has abuse potential and illicit diversion[16]. In contrast, buprenorphine appears to be a very promising treatment alternative for heroin addicts, not only it has good treatment retention, but has low drug dependent potential due to its partial agonist properties resulting in a ceiling effect on euphoria[10]. The result of OWS suggested that the withdrawal of buprenorphine produced a symptom/sign that was qualitatively similar to that of opiate agonist, but the intense was considerably less. Theoretically, buprenorphine is a high affinity, mu opiate partial agonist, with kappa antagonist action. This unique combination of pharmacological properties confers potential advantages, including enhanced safety over existing medications for treating opiate dependence[17,18].

In conclusion, the results suggest that buprenorphine produces low drug dependent potential because of its unique pharmacological properties.

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