

# THE USE OF BUPRENORPHINE IN THE TREATMENT OF HEROIN ADDICTION IN CHINA : A REVIEW

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## SUMMARY

Buprenorphine hydrochloride, a partial opioid agonist with low abuse potential, is a promising agent for opiate addiction. The experience and clinical trials from China were reviewed here. The detoxification programs with buprenorphine monotherapy or combined with other medications were different from those in western countries. Future directions were also discussed.

**Key words:** buprenorphine, opiate addiction, detoxification, Chinese

## INTRODUCTION

Though China was once the biggest victim of opium smoking in the history, the re-emergence of heroin addiction is a relatively new phenomenon to the public as well as medical professionals. Recently, China has found itself again in the midst of a wave of drug trafficking and addiction. China has approximately 300 or more treatment centers mainly run by health authorities or the Justice Department. The number of registered opioid addicts rose to 520 000 by the end of 1995.

The efforts made by Chinese medical professionals in recent years has been mainly oriented toward detoxification and other short-term pharmacotherapeutic interventions. Most of these methods have been well known in the literature. Due to a number of reasons, at present there are no maintenance treatment programs with methadone and other opioid agonists (Ministry of Health, 1995).

Buprenorphine (Bup), an analgesic developed in 1970s, is usually classified as a mixed agonist-antagonist opioid. In recent years, its efficacy in suppressing opiate withdrawal syndrome has been well recognized (e.g. Kosten and Kleber 1988). Clinical studies have also suggested that Bup produce feelings of warmth and some comfort, but it does not induce heroin-like rush or euphoric effects in human subjects. The withdrawal of Bup is substantially less difficult than that of methadone. Therefore, Bup is considered a promising agent in the treatment of opioid dependence (e.g. Zheng Jiwang and Zhang Kaigao 1992).

## CURRENT STATUS OF BUP IN CHINA

Injectable Bup has been manufactured by China Qinghai Pharmaceutical Factory since the late 1980s. In China, Bup is on the List of Psychotropic Drugs, with the same regulatory status as benzodiazepines. It is currently used in general hospitals (mainly surgical wards) and in institutions specialized for the treatment of drug abuse. Since its introduction to the market, almost a dozen trials on detoxification of heroin abusers with Bup have been conducted in various parts of China.

Currently Bup is widely employed across China particularly in south China's Guangdong province. Many clinicians prefer Bup to methadone or clonidine both in compulsory and non-compulsory settings.

Bup abuse has been occasionally observed and illegal trade of the substance has also been reported.

## DETOXIFICATION PROGRAMS WITH BUP IN CHINA

At present, only injectable Bup is available in China, whereas sublingual Bup is undergoing evaluation. Though influenced by the literature, Chinese investigators made their own treatment recommendations for the use of Bup. For example, most Chinese studies last about 2 weeks instead of the 2-17 weeks proposed by the literature and the recommended daily dose of Bup is also lower than recommended by the National Institute on Drug Abuse (NIDA). These considerations may be based on the fact that the majority of Chinese drug abusers have a relatively short history of drug abuse and their body weight and metabolism are different from their Caucasian counterparts.

In detoxification Bup can be used alone or in combination with other agents. As all the detoxification programs in China are short-term, they employ similar dose schedules. The initial dose of Bup is individualized depending on the severity of opiate withdrawal syndrome, the history of drug abuse and the patient's somatic condition. The initial dose will be reduced within a few days and eventually discontinued in 1-2 weeks.

## INJECTABLE PREPARATION

### Detoxification Programs with Bup

#### (A) RESULTS OF A CONTROLLED TRIAL

The first controlled study was conducted by Li Jianhua et al. (1993) in southwest China's Yunnan Province, which is heavily afflicted by opiate addiction. Eighty-four heroin addicts were randomly divided into a Bup group of 42 subjects (26 male, 16 female) and methadone control group having also 42 subjects (27 male, 15 female). The average length of drug abuse was 1-3 years. All cases underwent at least a 12- or 21-day trial for Bup and methadone respectively.

The outcome was measured by the modified Himmelsbach's Opiate Withdrawal Scale which showed that Bup was effective in controlling opiate withdrawal syndrome (OWS). In general, it was easier to withdraw opiates by Bup than methadone. Bup treatment was also shorter than treatment with methadone. However, the data also showed that the OWS in Bup group was more severe in the first 3 days and lasted longer than in the methadone group. The authors suggested that Bup should be administered at least 15 hours after the last dose of heroin unless the antagonistic effect emerged into otherwise the opiate withdrawal will be precipitated.

#### (B) OPEN LABEL STUDIES

Zheng Hongbo et al (1992) examined the efficiency of Bup in 55 heroin abusers in a psychiatric hospital in Guangzhou. The length of drug abuse ranged from 9.5 months to 8 years. 50 addicts completed the 10 day trial. The dose range was 0.3 - 1.2 mg/day. These investigators also used the 25-item modified Himmelsbach's Opiate Withdrawal Scale. The results supported Li Jianhua's findings; total scores dropped from 26.9±13.4 (day 1) to 17.1±13.0 (day 4) to 13.6±15.1 (day 7). Bup was effective in controlling such symptoms as craving, anxiety, yawning, sweating, lacrimation, rhinorrhea, drowsiness, chilling, bone and muscle pain, anorexia and insomnia, but had little effect on nausea, diarrhoea and vomiting. Five patients were withdrawn from the study at day 2 or day 3 because of the unsatisfactory therapeutic effect of Bup.

More recently, Tan Shaoqiang et al (1996) reported their observations in 631 heroin addicts treated with intramuscular Bup for 8-10 days. Eighty-seven percent of the patients were successfully detoxicated while 13 % of the subjects interrupted the treatment. The investigators opined that Bup could control opiate withdrawal syndrome if dose reduction was carefully executed. No patients reported euphoria and excitement after the administration of Bup. Bup appeared to be non-addictive. In conclusion, on the basis of the aforementioned studies, Bup seems to be a useful addition to the treatment of heroine withdrawal.

#### **Bup combined with other agents**

##### (A) COMBINATION WITH DIHYDROETORPHINE (DHE)

DHE was developed as a high-potency analgesic in the late 1970s. In recent years DHE has been tried in the treatment of opiate addiction (Wang Shufan et al, 1992, Jiang Zuoning et al, 1992). More recently, DHE was used together with Bup in some detoxification programs.

In Su Mujin et al's (1994) comparative study, 95 addicts were randomly allocated into 3 groups ; Group A : Bup + DHE ( 57 subjects; 52 male, 5 female) ; Group B : DHE alone (20 subjects; 16 male, 4 female) ; Group C : Bup alone (20 subjects; 18 male, 2 female). In the 10-day trial, patients in Group A had the following treatment schedule :

- day 1-2 : DHE 180-240ug/d iv. drip
- day 3-9 : Bup 1.2-0.15mg/day
- day 10 : Bup 0

In group A, OWS were well under control in the first 6 days, but some symptoms rebounded slightly after termination and lasted for a long period. Generally speaking, the curve of

severity of OWS over time in group A was smoother than that in Groups B and C. The authors suggested that the combination of DHE + Bup could be a better alternative than Bup or DHE alone.

Wang Peiyu et al (1993) observed 100 heroin addicts (89 male, 11 female) who received a 10-day treatment with DHE + Bup. The dose schedule was as follows ;

Day 1-3 : DHE 740-1180ug/day iv. drip,

Day 4-7 : Bup was administered im. and titrated individually, while DHE 60-80 ug(SL) was allowed on a prn basis. The investigators felt that DHE + Bup was more effective than DHE(SL). This conclusion, however, was not supported by another study (Lin Hui et al. 1994) which was conducted in a center for non-compulsory admissions. One hundred and forty-three addicts underwent a 7-day treatment program with DHE (Group A, 36 subjects), Bup (Group B, 51 subjects) or both agents in combination (Group C, 46 subjects). The length of treatment was 10.3±5.3, 11.3±4.1 and 14.3±10.1 days in Groups A, B and C respectively. The results suggested that Bup alone was better than DHE+Bup, while the combination treatment was more effective than DHE alone.

##### (B) COMBINATION WITH CLONIDINE

The use of clonidine in the opiate detoxification has been well established in China (Jiang Zuoning et al, 1991; Wang Xiaoping, 1992). It is also an officially recommended program by central health authorities. (Ministry of Health, 1992). However, it has its own shortcomings including side effects particularly hypotension and oversedation and insufficient control of OWS, especially in the first 3 days. In addition, some patients cannot tolerate clonidine treatment at all. For these reasons, therefore, the use of clonidine in opiate withdrawal is limited.

In order to facilitate the use of clonidine, some clinician (Yang Zheng et al, 1996) tried to combine Bup with clonidine. The dose schedule was as follows ;

Day 1-3 : Bup 1.2 - 0.9 mg/day im,

Day 3-9 : clonidine: 0.3 - 1.2/day

Day 10 : discontinuation of drug treatment.

In a non-compulsory inpatient setting more than 80 % addicts completed the 7-12 day long treatment program which produced less side effects than clonidine treatment. In fact, some addicts preferred the combination of clonidine with Bup when several other programs were offered to them.

##### (C) THE USE OF BUP IN GRADED DETOXIFICATION PROGRAMS

Graded detoxification programs using several medications have been developed by Qin Boyi and his colleagues (Yang Zheng et al. 1996). Introducing naltrexone, these investigators wanted to facilitate the process of detoxification. In the aforementioned study the sequence of agents was as follows : high-potency opioid agonist (DHE) - agonist (methadone) - partial agonist (buprenorphine) - non-opioid agent (clonidine) - antagonist (naltrexone) - drug free state. Clinicians could chose 2 or more agents in one program depending on the condition of the patients and the availability of different agents.

## SUBLINGUAL BUP

Currently, sublingual Bup has not yet been approved by the health authorities in China although studies advocated its use in the treatment of opiate addiction. Luo Xiaoyun et al (1994) conducted a clinical trial involving 81 addicts (77 male, 4 female) in a non-compulsory closed unit. Based on the severity of OWS and the length of drug abuse, doses were carefully titrated until maximum effect was achieved. The maximum daily dose was 3.0-7.0 mg for the first 4 days ; after that the dose was reduced gradually on day 5-9 and eventually sublingual Bup was discontinued. All subjects were rated by using the 11-item Clinical Institute Narcotic Assessment (CINA) and the Inventory of Adverse Drug Reaction developed by the authors.

The authors concluded that (1) sublingual Bup is effective in suppressing OWS; (2) Bup can control most symptoms of OWS; (3) When Bup is given in a dose of less than 8 mg/day, it is safe and causes less side effects; (4) sublingual administration is more convenient than im or iv route; (5) sublingual Bup treatment is recommended in regions where addictology is relatively underdeveloped.

## SIDE EFFECTS OF BUP

Some studies reported side effects of Bup but further analysis suggested that these were, in fact, part of OWS. For example, nausea and vomiting could be side effects of treatment, but more probably they are symptoms of OWS. In 57 patients treated with DHE + Bup, the frequency of side effects were : dizziness 8, drowsiness 22, nausea 6, vomiting 5 and sweating in 3 cases (Su Mujin et al 1994). In 18 subjects treated only with Bup, 6 cases had nausea and vomiting, 5 suffered from drowsiness, 3 had dizziness and 1 patient had an increase of serum GPT.

## CONCLUSIONS

To sum up, Bup is a promising agent in the treatment of heroin addiction. Some investigators even suggested that it might be the first agent to be evaluated in a pilot study of long-term (1-6 months) treatment program in China. At present, however, strict regulations and control regarding its use are necessary. More research work is warranted concerning its optimal dose, side effect profile, the possibility of combining Bup with other agents and the impact of concurrent medication on its efficiency.

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