

## Socio-demographic Profile and Help-seeking Behaviour of Buprenorphine Abusers in Singapore

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### Abstract

**Introduction:** The US Food and Drug Administration (FDA) approved buprenorphine or Subutex for the treatment of opiate dependence in October 2002. Buprenorphine is a partial agonist of the mu-opioid receptor; although initial animal research suggested a low abuse potential for buprenorphine, it was subsequently shown to have an abuse potential similar to that of morphine or hydromorphone. The objectives of this study were to establish the socio-demographic profile and help-seeking behaviour of buprenorphine abusers attending the de-addiction treatment clinics of the Community Addictions Management Programme. **Materials and Methods:** One hundred and twenty subjects, all buprenorphine abusers fulfilling the diagnostic criteria for opiate dependence, who consented to the study, completed an interviewer-administered questionnaire. **Results:** The mean age of those participating in the study was 39.2 [standard deviation (SD) 8.0] years. The majority of the participants were male (90%), 52.5% were currently employed and 98% had at least primary education. A family history of drug abuse was reported by 27% of the subjects. Illicit drug abuse occurred at an early age with mean age of onset of illicit drug abuse being 16.9 (SD 4.8) years with gateway drugs like marijuana and glue. **Conclusions:** It is vital for our medical profession to be aware of the trend in the local population to move from the abuse of illicit substances, to the abuse of prescriptive medications. It makes it necessary to increase the understanding of addictions both amongst our practising medical fraternity, and amongst those training to enter the profession. At the hospital level, it necessitates a higher level of vigilance among our emergency room physicians and those treating infectious diseases.

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### Introduction

Opiate dependence is a major health and social concern in many countries across the world. The burden of disease is considerable, with surveys indicating that up to 2% of the population had used opiates for non-medicinal reasons.<sup>1,2</sup> Other concerns include mortality, human immunodeficiency virus (HIV) and hepatitis B and C transmission, tuberculosis, healthcare costs, law enforcement costs as well as lost productivity.<sup>3</sup> Treatment is central to the improvement of both individual and society and withdrawal remains the first step in many long-term treatments.<sup>4</sup> For many years, this consisted of suppressing withdrawal symptoms with

methadone and gradually reducing the methadone dose.<sup>4</sup> The development of an addiction and tolerance to methadone can, however, be problematic for individual patients.<sup>5,6</sup>

The US Food and Drug Administration (FDA) first approved the use of buprenorphine or Subutex for opiate dependence in October 2002. Health Science Authority has approved the use of buprenorphine as treatment for opiate dependence and it has been available since 2002 in Singapore. Buprenorphine is a semi-synthetic opiate derivative synthesised from thebaine. It is a partial agonist of the mu-opioid receptor, i.e., it combines both agonistic and antagonistic properties but has low intrinsic activity

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compared to pure agonists.<sup>7</sup> It thus produces typical opioid-associated subjective and physiological effects but to a lesser extent than those produced by full mu-agonists, and exhibits a “ceiling” effect at which further dose increases produces no additional effects.<sup>8</sup> Buprenorphine is provided as a sublingual tablet, because the drug, when taken orally, undergoes first-pass metabolism in the liver and small intestine, resulting in the bioavailability of half that taken as a sublingual dose.<sup>9</sup> However, the sublingual tablet takes approximately 3 to 7 minutes to disintegrate, depending on the person and the dose,<sup>10</sup> making supervised administration difficult. Although initial animal research suggested a low abuse potential for buprenorphine,<sup>7</sup> subsequent work showed the abuse potential to be similar to that of morphine or hydromorphone in heroin users and non-opiate-dependent volunteers.<sup>11,12</sup>

However, buprenorphine offers several advantages in the treatment of heroin addiction. A recent meta-analysis<sup>13</sup> showed that as maintenance treatment, buprenorphine is effective, but not more effective than methadone. In the management of opioid withdrawal, buprenorphine may be better tolerated than clonidine or methadone. A recent study conducted in the USA by Sullivan et al<sup>14</sup> concluded that office-based buprenorphine holds the promise of bringing patients who have never received pharmacotherapy into treatment. In a cross-sectional and longitudinal analysis, they compared the clinical characteristics and treatment outcomes of patients on a clinical trial of office-based buprenorphine/naloxone treatment with those enrolled in a methadone maintenance programme during the same time period. Subjects on buprenorphine were more likely to be male, employed full-time, have no history of methadone treatment, have fewer years of opioid dependence, and have lower rates of injection drug use as compared to those on the methadone maintenance programme. Kakko et al<sup>15</sup> assessed the 1-year efficacy of buprenorphine in combination with intensive psychosocial therapy for the treatment of heroin dependence and concluded that the combination of buprenorphine and intensive psychosocial treatment is safe and highly efficacious, and should be added to the treatment options available for individuals who are dependent on heroin.

A number of countries have reported buprenorphine abuse following the introduction of buprenorphine as an analgesic. Lavelle et al<sup>16</sup> reported that in interviews with 78 clients of Glasgow drug agencies during 1989 to 1990, buprenorphine was found to be more widely and frequently misused than heroin or other opiates. Fifty-eight per cent of buprenorphine users used 6 to 7 days weekly. O'Connor et al<sup>17</sup> reported that the proportion who reported buprenorphine abuse went from 0% to 80% in a 12-month period in a study of opiate users presenting for treatment in a centre in Ireland.

Following its use as a substitution treatment for opiate addictions, studies from France and Australia have reported the disturbing trend of buprenorphine abuse in the population. In a cross-sectional study in France, Obadia et al<sup>18</sup> found that out of 343 intravenous drug addicts, 57% had used buprenorphine at least once in the last 6 months and that among patients who had received buprenorphine as substitution therapy, at least 70.5% had used it intravenously in the past 6 months. Vidal-Trecan et al<sup>19</sup> conducted a cross-sectional survey on subjects on buprenorphine maintenance therapy and identified buprenorphine diversion and injection as a significant problem, with about half (46.5%) of the subjects ever injecting buprenorphine; 67.2% of this subgroup had since used both injected and sublingual buprenorphine. Reports of complications include cases of acute hand-ischaemia following intra-arterial injection of buprenorphine suspension,<sup>20</sup> acute hepatitis in patients infected with hepatitis C virus<sup>21</sup> and fatalities<sup>22</sup> associated with the concomitant intake of psychotropics.

A recent study by Jenkinson et al<sup>23</sup> examined the indicators of buprenorphine diversion and injection among injecting drug users in Melbourne, Australia. They found that one-third of their study sample had injected buprenorphine in their lifetime, almost half of those who reported recent buprenorphine injection reported obtaining the drug illicitly at least once during that time.

The objectives of this study were to establish the socio-demographic and help-seeking profiles of buprenorphine abusers attending the de-addiction treatment clinics of the Community Addictions Management Programme (CAMP).

## Materials and Methods

In 2001, the Ministry of Health started CAMP as a 5-year pilot programme to treat eligible patients suffering from addiction problems. In the early years, the vast majority of those seeking help were using legal drugs like tobacco, alcohol or had problems with gambling or gaming. The current trend now reflects that of other countries, with many more of those seeking help doing so for the abuse of or dependence on prescriptive drugs. CAMP is currently the only avenue of comprehensive addiction treatment in Singapore, with emphasis on training, prevention and public education initiatives.

The study was approved by the Institution Review Board and a written informed consent was taken from all patients who expressed their willingness to participate in the study. Recruitment for this cross-sectional study was done from February 2005 to January 2006. All patients abusing buprenorphine who met the DSM-IV criteria for opiate dependence, attending CAMP's inpatient and outpatient treatment clinics, were invited to join the study. Only 4 of the 124 patients invited to participate in the study declined

to take part in the study, giving a response rate of 97%.

Eligibility criteria for the study were all buprenorphine abusers fulfilling the diagnostic criteria for opiate or dependence; those with serious medical illness requiring prescription of buprenorphine for analgesic purposes were excluded from the study. One hundred and twenty subjects, who consented to the study, completed an interviewer-administered questionnaire. The questionnaire comprised mainly closed-ended questions covering demographic characteristics, drug use history, drug use trends, crime and health behaviour.

Statistical analysis was carried out using SPSS for Windows, version 10.1. Standard descriptive statistics were used to analyse the characteristics of participants. Chi-square test and Mann-Whitney U test were used to test for significant differences between groups. A stepwise logistic regression was performed using IV abuse as the dependent variable and gender, marital status, age and years of buprenorphine abuse as the covariates.

## Results

### *Characteristics of the Study Sample*

The demographic characteristics of the sample are shown in Table 1. The age of the 120 subjects ranged from 20 years to 64 years, with a mean age of 39.2 (SD 8.0) years. The majority of the participants were male (90%), 52.5% were currently employed and 98% had at least primary education. About a third had debts (34.2%) and 55.8% reported a monthly income of less than \$500. Many of them (89.2%) had undergone rehabilitation in Drug Rehabilitation Centres (DRCs) for abuse and 79.2% had a past history of imprisonment. Those incarcerated had spent an average of 6 (4.2) years in DRCs and 3.7 (3.3) years in prison. Twenty-seven per cent of the subjects reported a family history of drug abuse. It was interesting to note that illicit drug abuse occurred at an early age, with the mean age of onset of illicit drug abuse being 16.9 (SD 4.8) years, with gateway drugs like marijuana and glue. The mean age at which they first started intravenous abuse of any drug was found to be 31.2 [standard deviation (SD) 10.5] years.

### *Perceptions and Patterns of Buprenorphine in the Study Sample*

Sixty-four of the subjects (53.3%) reported buprenorphine as the first drug they had abused intravenously. The mean age at which they first abused buprenorphine was 37.3 (7.7) years. The average quantity of daily use was 7.7 (4.8) mg and the average length of buprenorphine abuse was 1.7 (0.9) years and 99.2% were abusing it daily during their participation in the study. While 39.2% subjects initiated buprenorphine use to stop heroin abuse, 32.5% did so out of curiosity. Before initiating the use of buprenorphine,

Table 1. Demographic Characteristics of Survey Group

| Variable                      | Study group<br>n = 120 |
|-------------------------------|------------------------|
| Age (y) — mean (SD)           | 39.2 (8.0)             |
| Onset age of illicit drug use | 16.9 (4.8)             |
| Onset age of IV drug abuse    | 31.4 (7.7)             |
| Gender — no. (%)              |                        |
| Female                        | 11 (9.2%)              |
| Male                          | 109 (90.8%)            |
| Race — no. (%)                |                        |
| Chinese                       | 58 (48.3%)             |
| Malay                         | 36 (30%)               |
| Indian                        | 15 (12.5%)             |
| Others                        | 11 (9.2%)              |
| Marital status — no. (%)      |                        |
| Single                        | 69 (57.5%)             |
| Married                       | 24 (20%)               |
| Divorced, Separated, Widowed  | 27 (22.5%)             |
| Education — no. (%)           |                        |
| No education                  | 2 (1.7%)               |
| Primary school                | 47 (39.2%)             |
| Secondary school              | 52 (43.3%)             |
| Tertiary education            | 3 (2.5%)               |
| Vocational institute          | 10 (8.3%)              |
| Others                        | 6 (5%)                 |
| Accommodation — no. (%)       |                        |
| Living alone                  | 16 (13.4%)             |
| Living with family            | 96 (80%)               |
| Living with friends           | 7 (5.8%)               |
| Homeless                      | 1 (0.8%)               |

SD: standard deviation

only 24.2% of the subjects were aware of its abuse/dependence potential. Reasons for switching to IV use of buprenorphine were stated as mainly, “to get an extra high” (33.3%) and “pressure by peers who IV” (15.8%). Polysubstance abuse was reported by 81.7% of the subjects, with buprenorphine being used in combination mainly with short-acting benzodiazepines. We examined the differences between the injectors and the non-injectors. Chi-square tests revealed significant differences in IV abuse by those aged 45 years or more as compared to those below it ( $P = 0.002$ ,  $\chi^2 = 9.4$ ). There were no other significant differences between these 2 groups. Logistic regression using IV abuse as the dependent variable and gender, marital status, age and years of buprenorphine abuse as the covariates revealed age <45 years to be a significant predictor of IV buprenorphine abuse ( $P = 0.022$ ).

Table 2. Patterns of Buprenorphine Abuse

| Reasons for initiating buprenorphine abuse           |    |         |
|------------------------------------------------------|----|---------|
| To stop heroin use                                   | 47 | (39.2%) |
| Curiosity                                            | 39 | (32.5%) |
| To reduce stress                                     | 12 | (10%)   |
| To manage opiate dependence                          | 10 | (8.3%)  |
| Others                                               | 12 | (10%)   |
| Main reason for switching to IV use of buprenorphine |    |         |
| To get extra high                                    | 40 | (33.3%) |
| To get a rush feeling                                | 16 | (13.3%) |
| Curiosity                                            | 19 | (15.8%) |
| Reduce intake of Subutex                             | 8  | (6.7%)  |
| Pressure by peers who IV                             | 19 | (15.8%) |
| Others                                               | 12 | (10%)   |
| Reasons for polysubstance abuse                      |    |         |
| To increase euphoria                                 | 66 | (55%)   |
| To make effect last longer                           | 19 | (15.8%) |
| Overcome withdrawal                                  | 2  | (1.7%)  |
| Save money                                           | 4  | (3.3%)  |
| Others                                               | 8  | (6.7%)  |

About 61% of the patients reported the primary source of obtaining buprenorphine to be through general practitioner (GP) prescriptions, while 22.5% had obtained it from the black market and 16.7% cited their friends as their source of buprenorphine. Of the respondents, 21.7% of the subjects had sought treatment for medical conditions associated with buprenorphine abuse in various restructured hospitals in Singapore. These data were obtained from patients report; corroborating evidence was gathered from discharge summaries or treatment sheets given to the patients. While all the treatment teams were aware of the IV abuse, we could not determine whether this was apparent at first diagnosis or during the subsequent treatment. Only 1 subject reported overdose with buprenorphine. Table 3 lists these complications.

#### *Help-seeking Behaviour of Study Sample*

The average time taken by subjects to realise that they were unable to carry out their daily activities without buprenorphine was reported as 5.8 (11.6) weeks, with a median of 3 weeks. However, the average time before seeking treatment for abuse/dependence was 1.5 (1.2) years. Of the patients, 50.8% had attended some form of de-addiction programmes (Narcotics Anonymous, halfway homes, etc) before seeking treatment for buprenorphine dependence in CAMP. Among the respondents, 61.7% had tried to quit on their own at some point, with the majority going cold turkey or substituting benzodiazepines for buprenorphine. The main reasons for seeking treatment

Table 3. Medical Conditions Requiring Hospitalisation Related to Buprenorphine Abuse

| Medical condition                               | Frequency (%) |
|-------------------------------------------------|---------------|
| Skin and soft tissue infections                 | 14 (58.3%)    |
| Gangrene                                        | 2 (8.3%)      |
| Thrombophlebitis                                | 1 (4.2%)      |
| Acute hepatitis                                 | 1 (4.2%)      |
| Septicaemia with endocarditis                   | 1 (4.2%)      |
| Multiple lung abscesses                         | 1 (4.2%)      |
| Withdrawal management                           | 2 (8.3%)      |
| Removal of embedded foreign body (needle parts) | 2 (8.3%)      |

were a desire to quit (32.5%), family pressure (19.3%) and an awareness of health risks (18.3%). The majority of the patients preferred inpatient detoxification (84.2%) as compared to outpatient detoxification.

#### **Discussion**

This study is significant as it looks at an important group, i.e., opiate-dependent patients who are generally large consumers of healthcare resources and have the potential to consume even more resources in the future if the healthcare community is not galvanised into action. Until the 1990s, the primary illicit drug abused in Singapore and most of Southeast Asia was heroin. To stem the tide of increasing abuse and recidivism among heroin-dependent persons, the Singapore government took drastic measures in amending the Misuse of Drugs Act (MDA). The effect of this hardening of legislation against drug abuse was a fairly dramatic drop in illicit drug abuse in Singapore. Unfortunately, it also appears to have led to opiate-dependent persons seeking legal alternatives like prescription drugs to appease their cravings and addictions.

The long and chronic nature of drug dependence is seen by the fact that most respondents started their illicit drug use at the age of 16.9 years, but the average age of the study participants was 39.2 years. Most (90%) of the individuals on buprenorphine had, had a previous stint in a DRC and almost 80% had also served a prison sentence before. The introduction of newer medications like buprenorphine to treat opiate dependence has therefore seen a rapid and massive take-up rate, without the psychosocial treatment components and other means of monitoring compliance and avoiding diversion and abuse.

While 60% of those taking buprenorphine obtained it from doctors, 40% obtained it from “friends” or the black market. This is an indication of fairly large-scale diversion and abuse, in part because the medical profession is not familiar enough with the treatment of chronic opiate dependent patients, especially those with long histories of multiple incarcerations and with antisocial behaviours and

personalities. Our study also showed that 53.3% of our study population only started intravenous drug use (IVDU) after the introduction of buprenorphine. Since it is well documented that the injection of medications designed for oral consumption puts the abuser at a risk of harm from the rapid onset of drug effect, local injury and vascular injury,<sup>24</sup> these findings are of concern, as buprenorphine is meant only for sublingual use. A recent study from Singapore highlighted 4 cases of parenteral abuse of Subutex resulting in severe upper limb complications.<sup>25</sup> The medical fraternity has to learn that intravenous drug abuse is a serious strain on medical resources, and needs to be dealt with in a coordinated and urgent manner.

Polysubstance abuse is common in this population, with 81.7% of respondents admitting to injecting a cocktail of drugs and not buprenorphine alone. Ninety-eight (81.7%) patients were using benzodiazepines concomitantly, of these 60% were using it intravenously with buprenorphine. Midazolam was the most commonly used benzodiazepines, alone or in combination with other benzodiazepines. The primary reasons for injecting drug use were to obtain a rush or extra high sensation (46.6%). This was also reflected in the reasons for polysubstance abuse, where 55% responded that it increased their euphoria, while 15.8% stated that it made the effects last longer. This is unfortunate and indicative of the fact that respondents still have little insight into their disorder, and what it takes to get well. This lack of understanding of real recovery is dangerous in that this population is vulnerable to diverting and abusing prescription medications, with potentially fatal outcomes. While buprenorphine alone is generally not fatal in overdose, the combination with benzodiazepines, especially midazolam, which seems to be the drug of choice, has been shown to cause profound and rapid respiratory depression in animals.<sup>26</sup>

In summary, this study starkly exposes a trend in our local population in moving from the abuse of illicit substances, to that of prescriptive medications to obtain their euphoric fix. It is vital that our medical profession is aware of this trend that is not only local but also a growing phenomenon worldwide.<sup>27</sup> Thus, it is necessary to increase the understanding of addictions both amongst our practicing medical fraternity and amongst those training to enter the profession. At the hospital level, it also necessitates a higher level of vigilance amongst those treating infectious diseases, and the emergency room physicians. Many studies actually recommend that all intravenous drug users with a fever of more than 38.1°C should be admitted, as the final diagnosis is often more than trivial and can include illnesses like infective endocarditis, pneumonia and septicaemia.<sup>28</sup>

For those actually treating patients with chronic opiate dependence, it is important not to mix medications with

abuse potential, especially midazolam and short-acting hypnotics. It is also vital for the attending doctor to search for IVDU tracks and, if they are evident, to put the patient on supervised daily dosing, or refer them to a tertiary treatment provider. Studies conducted in Australia and USA<sup>29,30</sup> suggest that buprenorphine-naloxone combination tablet (Suboxone) is practical and safe for use in diverse community settings. The tablet has been designed to deter diversion and intravenous misuse, and may be suitable for unsupervised administration. This study was done before the Ministry of Health implemented the clinical practice guidelines for opiate dependence,<sup>31</sup> and the Central Addiction Registry for Drugs, Singapore (CARDS), which helps doctors to track if their patients are “doctor-hopping”. While this may have closed a large loophole in the availability of buprenorphine on the black market, the authors recommend that buprenorphine be made a controlled drug, as this would enable the authorities to take action against black-market sales. It would also allow those who genuinely want to recover from their opiate dependence to do so without being vulnerable to diversion and abuse of their medication.

In summary, this study gives valuable insights into the issue of buprenorphine abuse in difficult patients seen from an institutional perspective. More research is needed into both basic pharmacokinetic studies of the doses needed in our Asian patients, as well as health services research to monitor overall quality of life benefits and problems associated with maintenance use in community settings.

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