

## Concomitant Use of Midazolam and Buprenorphine and its Implications Among Drug Users in Singapore<sup>†</sup>

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### Abstract

**Introduction:** The aim of this study was to determine the prevalence and characteristics of benzodiazepine (BZD) abuse among intravenous opioid users in Singapore. **Materials and Methods:** Eligibility criteria for inclusion in this study were all intravenous buprenorphine abusers, who presented to the Community Addictions Management Programme (CAMP) over a 1-year period from February 2005 to January 2006. One hundred and twenty subjects, who consented to the study, completed an interviewer-administered questionnaire and underwent blood test for blood-borne viral infections. **Results:** The age of the 120 subjects ranged from 20 to 64 years, with a mean age of 39.0 (SD 8.0) years. The majority of the participants were male (90.0%); 48.3% were Chinese. Ninety-eight (81.7%) patients were using BZDs concomitantly. Midazolam was the most commonly used BZD. Buprenorphine abusers who were concomitantly using BZDs were significantly younger and reported an earlier age of onset of illicit drug abuse as compared to those not using BZDs. Those abusing BZDs were more likely to share syringes ( $\chi^2=5.8, P=0.02$ ), and were more likely to be seropositive for hepatitis C virus ( $\chi^2=4.3, P=0.04$ ). **Conclusions:** This study highlights the extreme caution that needs to be exercised in prescribing BZDs to all patients in general and patients with injecting drug use or histories of drug abuse in particular. At a public health level, general practitioners (GPs) who prescribe buprenorphine should have compulsory training which highlights the potential dangers of abuse and concomitant abuse of BZDs.

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**Key words:** Benzodiazepine, Intravenous drug use, Needle sharing, Singapore

### Introduction

Benzodiazepines (BDZs) (commonly known as “sleeping pills”) are routinely and successfully used in the treatment of sleep and anxiety disorders. However, studies have indicated that BZD use among injecting drug users (IDUs) constitutes a major clinical and public health problem. Misuse has been linked to higher rates of risk-taking behaviour (such as needle sharing) psychopathology, reduced health and social functioning and a greater risk of opiate overdose.<sup>1</sup> Studies conducted in the United States, Europe and Australia indicate that BZD use is extremely common among IDUs.<sup>2-4</sup> Klee et al<sup>2</sup> found the use of temazepam to be associated with more needle sharing in the preceding 6 months, while van den Hoek et al<sup>5</sup> reported BZD use to be a predictor of hepatitis C seropositivity in a Dutch study of IDUs. Studies have also suggested a link between BZD use and human immunodeficiency virus (HIV) risk-taking among IDUs.<sup>6</sup> BZD dependence is a global phenomenon in heroin-abusing populations and in

patients undergoing methadone maintenance treatment (MMT), with lifetime prevalence reported as 61% to 94%.<sup>4,7</sup> BZD use in MMT patients has been associated with higher risk-taking behaviour,<sup>8</sup> a higher risk for infectious diseases,<sup>9</sup> and an 8-fold likelihood of death when compared to patients on MMT who are not abusing BZDs.<sup>10</sup>

Buprenorphine is a semi-synthetic opiate derivative synthesised from thebaine. It is a partial agonist of the mu-opioid receptor in that it combines both agonistic and antagonistic properties but has a low intrinsic activity compared to pure agonists.<sup>11</sup> It thus produces typical opioid subjective and physiological effects but these are less than those produced by full mu-agonists, and exhibits a “ceiling” effect at which further increases in dosage produce no additional effects.<sup>12</sup> The withdrawal syndrome produced if the treatment is suddenly discontinued appears to be less rapid and less intense than with pure agonists like methadone.<sup>13</sup> Following its use as a substitute treatment for opiate addictions, studies from France and Australia have

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Table 1. Socio-demographic and Clinical Characteristics of Benzodiazepine (BZD) Abusers

Variable	Concomitant BZD use Mean $\pm$ SD (n = 98)	No concomitant BZD use Mean $\pm$ SD (n = 22)
Age (y)*	38.4 $\pm$ 8.0	43.2 $\pm$ 6.8
Age of onset of illicit drug use (y)*	16.3 $\pm$ 3.8	19.8 $\pm$ 7.6
Mean daily dose of buprenorphine (mg)	7.4 $\pm$ 4.4	9.0 $\pm$ 6.0
	n (%)	n (%)
Gender		
Male	87 (88.7)	22 (100)
Female	11 (11.3)	0
Ethnicity		
Chinese	46 (46.9)	12 (54.5)
Malay	30 (30.6)	6 (27.3)
Indian	13 (13.3)	2 (9.1)
Others	9 (9.2)	2 (9.1)
Employment status		
Employed	51 (52.6)	12 (54.5)
Unemployed	46 (47.4)	10(45.5)
Needle sharing*		
Yes	50 (51)	5 (22.7)
No	48 (49)	17 (77.3)
Hepatitis C virus seropositivity*		
Yes	41 (47.1)	4 (21.1)
No	46 (52.9)	15 (78.9)
Any one blood-borne infection*		
Yes	46 (54.1)	4 (21.1)
No	39 (45.9)	15 (78.9)

SD: standard deviation; \* $P < 0.05$

reported the disturbing trend of buprenorphine abuse in the population. In a cross-sectional study in France, Obadia et al<sup>14</sup> found that out of 343 intravenous drug addicts, 57% had used buprenorphine at least once in the last 6 months and that in patients who had received buprenorphine as substitution therapy, at least 70.5% had used it intravenously during the past 6 months. A report by Reynaud et al<sup>15</sup> linked 6 deaths to the concomitant use of buprenorphine and BZDs. Post-mortem analyses strongly implicated the concomitant use of BZD in buprenorphine overdose. While a “ceiling effect” of buprenorphine is documented,<sup>16</sup> the associated use with central nervous system depressants is liable to modify this property, and concomitant administration of BZD therefore prolongs respiratory depression in humans and experimental animals.<sup>17,18</sup>

Table 2. Reasons for Concomitant Benzodiazepine (BZD) Use

Reasons for BZD use	n (%)
To increase euphoria	66 (55)
To make the effect of buprenorphine last longer	19 (15.8)
To save money	4 (3.3)
To overcome withdrawal	2 (1.7)
Others	8 (6.7)

In Singapore, buprenorphine was available in the general medical practice as a substitute treatment for opiate addiction, but it was recommended that the prescribing physician regularly collaborate with addiction physicians in the Community Addictions Management Programme (CAMP), a specialised addiction treatment centre, for the management of patients. In Singapore, a few cases of buprenorphine abuse have been reported<sup>19-22</sup> and a growing number of cases have been noticed among patients attending our clinics. The misuse of buprenorphine was mainly via 2 practices: 1) the improper use of the tablet form for intravenous injection or 2) the association of buprenorphine in tablet or injectable form with other drugs, mainly BZDs. This study was undertaken to determine the prevalence and characteristics of BZD abuse among intravenous opioid users in Singapore and to explore whether these patients differed from intravenous opioid users who were not abusing BZDs.

## Materials and Methods

This study is part of a larger study profiling buprenorphine abusers in Singapore.<sup>20</sup> The study was conducted under CAMP in Singapore. CAMP is currently the major provider of addiction treatment in Singapore, and all patients seeking in-patient treatment are referred to this programme.

The study was approved by the Institution Review Board and a written informed consent was taken from all the patients who expressed their willingness to participate in the study. Recruitment for this cross-sectional study was done from February 2005 to January 2006. Those eligible for the study were intravenous buprenorphine abusers fulfilling the diagnostic criteria for opioid dependence; those with serious medical illness requiring prescription of buprenorphine for analgesic purposes were excluded from the study. All subjects completed an interviewer-administered questionnaire covering demographic characteristics, drug use history, drug use trends, criminal justice and health behaviour. Data on concomitant BZD use collected included information on the type of BZD being abused, route of administration and reasons for concomitant use.

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 in categorical and quantitative variables respectively.

## Results

The age of the 120 subjects ranged from 20 to 64 years, with a mean age of 39.0 (SD 8.0) years. The majority of the participants were male (90.0%), 48.3% were Chinese, 30% were Malays, 12.5% were Indians and 9.2% belonged to other ethnic groups. Ninety-eight (81.7%) patients had been using BZDs concomitantly with buprenorphine (Table 1), of these 26 (21.7%) had been taking it orally while 72 (60%) had been using it intravenously. Only 3 (2%) patients had used BZDs as the first drug of intravenous abuse. Most of the patients reported having used it concomitantly; with midazolam being the most commonly used BZD, alone or in combination with other BZDs (73.4%); followed by Domi (the street name for generic midazolam) (19.1%), 2.5% of patients were using other drugs like valium and codeine. The reasons for concomitant BZD use were stated as “for increasing euphoria” (55%) and for making “the effects of buprenorphine last longer” (16%).

Buprenorphine abusers who were concomitantly using BZDs were significantly younger and reported an earlier age of onset of illicit drug abuse as compared to those not using BZDs. Those abusing BZDs were more likely to be intravenous abusers ( $P = 0.001$ , Fisher’s exact test), share syringes ( $\chi^2 = 5.8$ ,  $P = 0.02$ ), and were more likely to be seropositive for hepatitis C virus ( $\chi^2 = 4.3$ ,  $P = 0.04$ ). The incidence of any one blood-borne infection, i.e., hepatitis B, hepatitis C or HIV, in those abusing BZDs was also significantly higher than in those not abusing BZDs concomitantly. 22.4% of those abusing BZD, as compared to 9.2% of those not abusing BZD, developed medical complications secondary to injecting drug abuse. However, this difference was not statistically significant.

## Discussion

Midazolam is the BZD of choice in our study sample either singly or in combination with other BZDs. It is probably preferred because of its high potency and quick onset of action. The reasons for concomitant BZD use varied in this group. While the most common reason stated by the patients was “for increasing euphoria” (Table 2), other factors included subjects minimising the addictive nature of BZD as compared to opiate use and a failure to recognise polydrug use as a serious problem. A few of our subjects described the concomitant use of BZD as a “cost cutting measure” to reduce the amount of buprenorphine needed to prevent cravings, as the cost of 1 tablet of midazolam is about 6 times less than a standard 8-mg tablet

of buprenorphine. A common misconception amongst users is that the use of “lesser” drugs i.e., prescriptive drugs, at a lower cost with no legal sanctions are “safer” and “less problematic”. BZDs are easily available through general practitioners (GPs) and medical personnel, and the widespread abuse suggests doctor hopping and the use of creative story telling to physicians to obtain the medication. A number of other studies have suggested that most addicts take BZD in order to feel high.<sup>23,24</sup> Other reasons for BZD abuse such as emotional self-medication, treating sleep disturbances or suppressing opiate withdrawal have been less commonly reported.<sup>23,24</sup>

The history of BZD misuse seems shorter when compared to opiate misuse and fewer studies are available for comparison. There are no prevalence data available in Singapore yet. Pirnay et al<sup>25</sup> also found that BZDs are found in the highest composition in urine/blood samples of buprenorphine- and methadone-associated deaths, as compared to other substances like ethanol, cannabis, antidepressants, cocaine, paracetamol and antipsychotics. Kintz<sup>26</sup> performed a study on the toxic concentration in both buprenorphine- and methadone-associated deaths in France from 1996 to 2000, and found that buprenorphine levels were usually within the therapeutic range, implying that BZD plays the determining role in the mortality.

Our study also noted that BZD-abusing patients were significantly younger and had an earlier age of onset of drug abuse. These patients were more likely to share syringes and had a higher prevalence of antibodies to hepatitis C virus. These findings are similar to those reported by Bleich et al<sup>27</sup> in patients undergoing MMT who were abusing BZDs. Their study also found that BZD-abusing individuals had higher psychopathology scores and were more depressive than non-abusing patients, which supports a self-medication hypothesis. Unfortunately, we did not assess levels of psychopathology in our study.

This study highlights the extreme caution that needs to be exercised in prescribing BZDs to all patients in general, and patients with IDUs or histories of drug abuse in particular. In prescribing BZDs, even for detoxification from drugs, the prescribing physician must be aware of the potential for abuse. A few authors suggest that if BZDs are prescribed, the less popular, slow-onset drugs should be prescribed.<sup>23</sup> At a public health level, GPs who prescribe buprenorphine should have compulsory training highlighting the potential dangers of the concomitant abuse of BZDs. Once polysubstance abuse, especially intravenous BZD abuse, is present, there is a greater risk of local and systemic infections or even death from the combinations. A recent study on buprenorphine-associated deaths showed that BZDs were present in 44 out of 50 of the reported deaths.<sup>28</sup>

This study has limitations as it was conducted in a tertiary care hospital and the population may therefore not be representative of those in the community on maintenance buprenorphine therapy. Despite this, it is clear that there is a high level of concomitant BZD abuse among drug-dependent patients in Singapore. It has even more significance with regard to the classification of buprenorphine as a class A drug under the Misuse of Drugs Act, as many may attempt to turn to using combinations of other prescription and non-prescription drugs. Doctors at all levels should be aware of this phenomenon, and err on the side of caution when prescribing potentially abusable and addictive medications like BZDs. It is recommended that we do countrywide studies on BZD use and abuse to plan regulatory and preventive measures for the future. Ongoing monitoring is needed to understand the health needs as well as health impact of the abuse on the group of patients who are poly-drug abusers especially those concomitantly abusing BZD since they are likely to be heavy users of health resources both for obtaining the medication as well as for issues caused by harm related to use.

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