Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment

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ABSTRACT

Aims To examine concurrent buprenorphine and benzodiazepine consumption and to compare opioid toxicity symptoms induced by methadone and buprenorphine, examining factors associated with the reporting of these symptoms.

Design Self-report cross-sectional survey.

Setting Five needle syringe programmes and five opioid substitution treatment services in Melbourne, Australia.

Participants A total of 250 people who had experience with methadone or buprenorphine. Eligibility criteria were current or previous methadone or buprenorphine use.

Measurements Structured questionnaire covering: demographic characteristics; current treatment and drug use; concurrent use of buprenorphine and benzodiazepines, including route of administration and source of medications; and opioid toxicity symptoms reported in association with methadone and buprenorphine consumption.

Findings Of those reporting buprenorphine use, two-thirds reported concurrent benzodiazepine use, with a median dose reported of 30 mg diazepam equivalents. A greater number of opioid toxicity symptoms were reported in relation to methadone consumption compared with buprenorphine. Those reporting opioid toxicity with buprenorphine were more likely to report intravenous use compared with those reporting opioid toxicity with methadone.

Conclusions The risk of opioid toxicity appeared greater with methadone compared with buprenorphine, despite high levels of benzodiazepine consumption and injection being reported in relation to buprenorphine use. The prevalence of buprenorphine injection and the normalization of methadone-induced sedation are two findings that merit further investigation. Establishing recommendations as to the safest and most effective way to manage benzodiazepine-using people in opioid substitution treatment is necessary for the optimization of treatment for opioid dependence in polydrug-using individuals.

Keywords Benzodiazepine, buprenorphine, methadone, opioid toxicity.

INTRODUCTION

Methadone has been the main opioid substitution treatment (OST) for heroin dependence since the 1960s. Buprenorphine is now considered an effective alternative to methadone [1], with increasing uptake internationally. While the benefits of OST are well established, safety remains an important issue, especially as co-consumption with other psychoactive substances is often reported [2,3]. The safety profile of buprenorphine is considered a key benefit in comparison to other medications, primarily because of the ceiling on its pharmacological effects [4].

As central nervous system (CNS) depressants, benzodiazepines have been shown to act synergistically with opioids to reduce respiratory function [5], thereby increasing the risk of fatal and non-fatal overdose with opioids such as methadone and heroin [6–10]. The situation in relation to partial opioid agonists such as buprenorphine is less clear. It is known that in relation to respiratory function, the ceiling effect for buprenorphine is observed only when it is used in the absence of other psychoactive drugs. For example, buprenorphine and benzodiazepines, used together peri-operatively, have been reported to cause severe respiratory depression in opioid-naïve individuals [11,12]. Further, a series of
coroners’ reports have also implicated the combination of buprenorphine and benzodiazepines as potentially fatal [13–16]. These findings are consistent with animal studies that have shown that, while buprenorphine may cause less respiratory depression than methadone, when combined with benzodiazepines the ceiling effect on respiratory depression is no longer evident [17]. In this context there is a need to understand more clearly the safety profile of buprenorphine as used in OST, where it is likely that many clients will use other drugs.

Although benzodiazepine use in methadone-maintained individuals has been well described [18–20], concomitant use of benzodiazepines in high-dose buprenorphine treatment is not well documented. Further, few studies have made direct comparisons between the CNS depression induced by methadone and buprenorphine, especially where polydrug use is involved. While subjects in clinical trials have reported that buprenorphine is less sedating than methadone [21], the effect on the safety profile of buprenorphine when used in ‘real life’ conditions (including unsanctioned intravenous use and use with other co-intoxicants) has not been examined.

In order to address these issues, this study investigates two aspects of opioid substitution pharmacotherapy treatment. First, co-consumption of buprenorphine and benzodiazepines is examined. Secondly, self-reported opioid toxicity symptoms by individuals who have taken methadone and buprenorphine were investigated to allow a comparison of safety to be made between methadone and buprenorphine. Demographic and behavioural factors reported in association with buprenorphine or methadone toxicity were also investigated.

**METHOD**

**Participants**

A sample of 250 volunteers who had been prescribed methadone or buprenorphine previously, or were currently on an opioid substitution treatment, were recruited. Participants were recruited from five needle and syringe programmes (NSPs) and five sites where methadone and buprenorphine was prescribed and/or dispensed (treatment-orientated sites, TS) in metropolitan Melbourne between November 2004 and July 2005. Recruitment sites were selected across the geographical spread of the key drug-using areas in Melbourne. The two types of recruitment sites were used to capture a broad demographic range of people who had experience with methadone and buprenorphine. Participants responded either to flyers advertising the study or were referred to the study by service staff.

**Measures**

A survey instrument, consisting of 35 questions, was developed for self-completion by participants. These questions covered general demographics such as age, gender, employment and education. Past and current pharmacotherapy treatments were recorded. Participants were asked to report about frequency (daily, weekly, occasionally or never) of other drug use over the previous 12 months for a series of illicit and prescription medications. Occasional use was defined as less than weekly use.

Simultaneous buprenorphine and benzodiazepine consumption was examined in those who reported taking benzodiazepines at the same time as buprenorphine. This examination included the dose of benzodiazepine taken (indexed by name, strength and number of tablets) and the source and route of administration for both benzodiazepines and buprenorphine. The maximum number of benzodiazepine tablets taken normally at the same time as buprenorphine was recorded. Benzodiazepine type was verified by confirming brand name and appearance where there was uncertainty.

Self-reported opioid toxicity experienced in relation to buprenorphine and methadone consumption was examined. Participants were asked whether they had experienced three symptoms from taking methadone: (1) extreme drowsiness (operationally defined as very difficult to rouse, or of concern to an observer); (2) unconsciousness; or (3) an overdose attended by a doctor or ambulance from taking methadone; and then questioned about the same symptoms from taking buprenorphine.

If toxicity from methadone or buprenorphine was reported participants were asked about the source of the drug, route of administration and any other drug or medication taken at the same time.

**Procedure**

Volunteers were eligible if they were currently, or had previously been in methadone or buprenorphine treatment. Regular users of illicit buprenorphine were considered eligible. Staff at study sites identified participants that fitted into this latter category.

The survey was voluntary, anonymous and confidential. Surveys were either self-completed or completed with assistance, with all surveys completed in the presence of a researcher (to clarify questions and/or assist when required). The survey took approximately 15 minutes to complete and participants were reimbursed AUD$10 for their time. All aspects of this study were approved by the Human Research Ethics Committees of the Victorian Department of Human Services, Monash University, Salvation Army and Peninsula Health.
Data analysis

All benzodiazepines were converted to diazepam equivalents on the basis of the name, strength and number of tablets taken according to accepted clinical practice guidelines that were also used to define therapeutic doses [22].

Descriptive statistics were used in describing the major characteristics of the sample, with odds ratios (ORs) generated to compare these between recruitment sites.

Examination of opioid toxicity symptoms was undertaken only with participants who reported having used both methadone and buprenorphine. ORs were used to compare the frequency of reported toxicity symptoms between drug types (using a matched analysis). Additional analysis was undertaken to examine factors reported in association with reported opioid toxicity symptoms between drug types, using ORs generated with 95% confidence intervals (CIs) adjusted for clustering for those who reported symptoms for both methadone and buprenorphine. Binary logistic regression was used to analyse factors associated with toxicity with methadone and buprenorphine independently. All analyses were undertaken using SPSS for Windows version 11.5 or STATA version 9.

RESULTS

Characteristics of the sample

Of the 250 participants, 64% were male and 84% were born in Australia. Twenty per cent of the sample were aged between 18 and 25 years, 44% between 26 and 35 years and the remaining 37% were aged above 35 years.

Eighty per cent were unemployed. Participants had completed a mean of 10.7 ± 2.3 years of school, with 46% completing no further education after secondary school.

Drug treatment history

Seventy-seven per cent of participants reported having ever received buprenorphine pharmacotherapy, with 44% in buprenorphine treatment at the time of study; 78% of participants reported having ever received methadone with 31% in methadone treatment at the time of the survey (see Table 1). Around two-thirds of the sample (66%) had experienced both methadone and buprenorphine at some point in time. Eight participants were identified as being current daily users of intravenous buprenorphine but not currently in pharmacotherapy treatment.

Participants were asked about other drug use and frequency of drug use over the previous 12 months. The most common substances reported to be used daily were benzodiazepines (36%) and antidepressants (33%). The majority of participants (81%) reported using benzodiazepines at least occasionally over the last 12 months. Amphetamine use was reported frequently among this sample. While only 5% reported daily use, 65% reported using amphetamines at least occasionally. Less than 2% of the sample reported use of prescription opioids (including tramadol, oxycodone, morphine and codeine) or cocaine in the previous 12 months.

Recruitment site differences

There were a number of differences between the participants recruited from the two types of sites. While age, years of school completed and employment did not vary significantly between samples, participants in the NSP sample were more likely to be male (73% for NSPs versus 55% for TS, OR = 2.24, 95% CI = 1.33–3.82) and less likely to be in treatment currently (64% at NSPs versus 90% at TS, OR = 0.21, 95% CI = 0.10–0.40). Participants in the NSP sample were more likely to report illicit buprenorphine use (22% at NSP versus 11% at TS, OR = 2.29, 95% CI = 1.14–4.56) or illicit methadone use (12% at NSP versus 4% at TS, OR = 3.27, 95% CI = 1.15–9.30). While participants in the NSP sample were more likely to report signs of buprenorphine toxicity (33% at NSP versus 21% at TS, OR = 1.86, 95% CI = 1.05–3.29), there was no association between type of recruitment site and reporting of methadone toxicity (38% at NSP versus 43% at TS, OR = 0.82, 95% CI = 0.49–1.36).

Buprenorphine and benzodiazepines consumption

Buprenorphine-experienced participants were asked if they had ever taken benzodiazepines at the same time as buprenorphine. The majority of buprenorphine-experienced participants had taken benzodiazepines concurrently (67%, n = 138), with 37% reporting taking

<table>
<thead>
<tr>
<th>Table 1 Profile of opioid pharmacotherapy treatment of the sample.</th>
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</thead>
<tbody>
<tr>
<td>Opioid substitution treatment</td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Methadone</td>
</tr>
<tr>
<td>Buprenorphine</td>
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<tr>
<td>Naltrexone</td>
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<tr>
<td>Suboxone (buprenorphine/naloxone combination)</td>
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<td>LAAM</td>
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</table>
benzodiazepines with buprenorphine daily and an additional 18% reporting taking the combination most days.

The median benzodiazepine dose reported as being taken with buprenorphine was 30 mg of diazepam equivalents (some large outliers making the distribution non-normal). Almost half the sample reported doses that exceeded therapeutic doses, with several doses of over 500 mg of diazepam equivalents reported (maximum 1350 mg). Neither the mean nor median doses of reported diazepam equivalents differed between the two types of recruitment site.

Participants reporting concurrent buprenorphine and benzodiazepines use were asked where they usually obtained their benzodiazepines. In just over a third of the cases (35%), participants reported that they only received benzodiazepines via a prescription from the medical practitioner that prescribed their buprenorphine. A further 28% reported acquiring benzodiazepines from other prescribers in addition to, or instead of acquiring them from their buprenorphine prescriber. A further 17% of those reporting concurrent buprenorphine and benzodiazepines use were asked where they usually obtained their benzodiazepines. In just over a third of the cases (35%), participants reported that they only received benzodiazepines via a prescription from the medical practitioner that prescribed their buprenorphine. A further 28% reported acquiring benzodiazepines from other prescribers in addition to, or instead of acquiring them from their buprenorphine prescriber. Seventeen percent reported acquiring benzodiazepines from other prescribers in addition to, or instead of acquiring them from their buprenorphine prescriber. Seventeen percent of the subset reported acquiring benzodiazepines from an illicit source.

Of those reporting concurrent buprenorphine and benzodiazepines use, the majority indicated that their buprenorphine supply was from a licit pharmacotherapy source (84%). The remainder of this subset reported acquiring buprenorphine from an illicit source.

While 36% of concurrent buprenorphine and benzodiazepines users usually reported injecting their buprenorphine, a smaller number reported usually injecting benzodiazepines (8%). Only 4% reported usually injecting both buprenorphine and benzodiazepines.

**Opioid toxicity symptoms**

Participants were asked if they had ever experienced one or more of three signs or symptoms of opioid toxicity (extreme drowsiness, unconsciousness and overdose) in association with methadone and/or buprenorphine consumption (Table 2). Analysis was undertaken only for the subset that had taken methadone and buprenorphine (n = 164) in order to compare between their experiences of opioid toxicity from both medications.

<table>
<thead>
<tr>
<th>Toxicity symptom</th>
<th>Methadone (%)</th>
<th>Buprenorphine (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme drowsiness</td>
<td>42.1</td>
<td>24.3</td>
<td>2.71 (1.55–4.72)</td>
</tr>
<tr>
<td>Unconsciousness</td>
<td>7.3</td>
<td>3.0</td>
<td>2.40 (0.86–7.58)</td>
</tr>
<tr>
<td>Overdose</td>
<td>6.7</td>
<td>1.2</td>
<td>10.00 (1.68–218.90)</td>
</tr>
</tbody>
</table>

Participants were more likely to report opioid toxicity in relation to methadone compared with buprenorphine across all the symptoms examined. While the difference in reporting of unconsciousness failed to reach significance, participants were 10 times more likely to report overdose (OR = 10.00, 95% CI = 1.67–218.90), and 2.7 times more likely to report extreme drowsiness (OR = 2.71, 95% CI = 1.55–4.72), in association with methadone consumption compared with buprenorphine.

**Factors associated with reporting opioid toxicity**

When participants reported an opioid toxicity symptom in relation to methadone or buprenorphine consumption they were asked how they took the opioid, where the opioid came from on that occasion and other drugs or medications (including benzodiazepines) taken at that time (Table 3).

Table 3 shows that those reporting opioid toxicity from buprenorphine were four times more likely to have injected it at the time compared with those reporting opioid toxicity with methadone (OR = 0.25, 95% CI = 0.12–0.52). While co-consumption of heroin was almost four times more likely to be reported with methadone toxicity symptoms (OR = 3.93, 95% CI = 1.69–9.14) than with buprenorphine toxicity symptoms, there was little variation between the two pharmacotherapy treatments in reported concurrent benzodiazepine consumption on occasions where toxicity was reported.

Logistic regression was undertaken to examine whether other drug use or demographic characteristics predicted signs of toxicity for both methadone and buprenorphine independently. The only effect found for methadone was that those reporting daily benzodiazepine use were significantly more likely to report side effects with methadone (OR = 2.17, 95% CI = 1.11–4.23) after adjusting for age, gender, employment and illicit drug use. After adjusting for these variables in the model, this association was only marginally significant for buprenorphine (OR = 2.08, 95% CI = 1.00–4.37), but age was significantly associated with reporting of buprenorphine toxicity (with those less than 25 being more than twice as likely to report buprenorphine toxicity, OR = 2.37, 95% CI 1.01–5.57).
DISCUSSION

This study investigated two aspects of pharmacotherapy treatment: concurrent buprenorphine and benzodiazepine use, and opioid toxicity symptoms associated with methadone and buprenorphine.

Concurrent buprenorphine and benzodiazepine use

Concurrent buprenorphine and benzodiazepine use was reported by two-thirds of buprenorphine-experienced participants, consistent with benzodiazepine use reported previously in methadone maintenance treatment [18,19]. The median (30 mg) and maximum (1350 mg) diazepam equivalent doses reported by those using concomitant buprenorphine and benzodiazepines were comparable to doses reported in other methadone maintenance studies [19,20]. Two groups of benzodiazepine users were identified, a minority reporting using benzodiazepines prescribed only from their buprenorphine prescriber and the majority who reported acquiring benzodiazepines from other sources, including illicit sources. The fact that the majority of the sample reported using multiple doctors and illicit sources to obtain their benzodiazepines is concerning. This means that, for the pharmacotherapy prescriber in particular, it is difficult to ascertain how many benzodiazepines clients are consuming. As a consequence there may be difficulties in assessing and advising on associated risks of additional drug use by the prescriber.

As indicated, the minority (around one-third) of the sample reported using benzodiazepines supplied only by their buprenorphine prescriber. This finding may suggest that prescribers themselves may be unaware or unconcerned about the risk of toxicity associated with opioid and benzodiazepine co-consumption.

Methadone and buprenorphine toxicity

This research was also designed to examine opioid toxicity in relation to methadone and buprenorphine consumption. Among those who had had experience with both methadone and buprenorphine, signs of opioid toxicity were more likely to be reported in relation to methadone consumption. This was despite the reporting of high-risk practices relating to buprenorphine such as injecting, illicit use and co-consumption of high doses of benzodiazepines.

These findings are consistent with previous reports comparing toxicity attributed to methadone and buprenorphine, indicating that some toxicity occurs with buprenorphine, but at a lower rate than methadone [23,24]. One possible explanation is that buprenorphine may cause less CNS depressant effects than methadone, even when combined with other CNS depressants such as benzodiazepines. Despite pre-clinical studies demonstrating that the ceiling on pharmacological effects is not observed when benzodiazepines are given with buprenorphine [17], the toxicity reported with buprenorphine in this study was still less than that seen with methadone.

In this study there was an association with daily benzodiazepine use and opioid toxicity symptoms being reported, which was significant for methadone toxicity, and marginally significant for buprenorphine toxicity (the failure to reach significance possibly being an artefact of the smaller numbers reporting opioid toxicity in association with buprenorphine). The daily benzodiazepine users identified may represent a group with higher levels of psychiatric comorbidity [25,26], who may be at elevated risk of drug-related adverse events. Further work is needed to clarify the links between use of multiple substances and overdose, and develop recommendations as to the safest and most effective treatment for polysubstance-abusing individuals in order to reduce risks associated with currently available treatments.

Half those reporting buprenorphine toxicity in this study reported intravenous buprenorphine use at that time. Despite this seemingly strong association of intravenous use and buprenorphine toxicity, the level of intravenous buprenorphine use reported by those that experienced toxicity reflect the level of buprenorphine injection seen in drug users in this jurisdiction (e.g. 43%)

### Table 3: Reported factors involved in side-effect reported.

<table>
<thead>
<tr>
<th></th>
<th>Reported methadone toxicity</th>
<th>Reported buprenorphine toxicity</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking dose supervised (i.e. in pharmacy)</td>
<td>67.5</td>
<td>62.8</td>
<td>1.23 (0.65–2.35)</td>
</tr>
<tr>
<td>Injected opioid substitution treatment</td>
<td>20.8</td>
<td>51.1</td>
<td>0.25 (0.12–0.52)</td>
</tr>
<tr>
<td>No other drugs taken at the same time</td>
<td>23.4</td>
<td>13.9</td>
<td>1.88 (0.73–4.85)</td>
</tr>
<tr>
<td>Taken heroin at the same time</td>
<td>38.9</td>
<td>13.9</td>
<td>3.93 (1.69–9.14)</td>
</tr>
<tr>
<td>Consumed alcohol at same time</td>
<td>14.3</td>
<td>9.3</td>
<td>1.63 (0.47–5.68)</td>
</tr>
<tr>
<td>Taken benzodiazepine at the same time</td>
<td>40.3</td>
<td>39.5</td>
<td>1.03 (0.52–2.05)</td>
</tr>
</tbody>
</table>
of the sample in the Melbourne Illicit Drug Reporting System survey [27]. This means that it is possible those injecting buprenorphine may not be over-represented in those reporting opioid toxicity.

In the context of the high prevalence of intravenous buprenorphine use seen in this and other studies (e.g. [28]), it may be appropriate to consider some alternative strategies for buprenorphine delivery. The provision of injectable buprenorphine as a treatment option may reduce the harms from injecting buprenorphine tablets. This treatment may also provide an opportunity to attract a new population into treatment (those currently injecting illicitly obtained buprenorphine), thereby providing the social and health gains that are offered by opioid substitution treatment to a wider population.

Other findings

Anecdotal reports elicited during this study suggested that experiences of extreme drowsiness, unconsciousness and even overdose when being initiated onto methadone treatment are often normalized among participants. Participants reported that being unable to remain awake or causing distress to family members or others by their state of consciousness was not considered abnormal when taking methadone. Indeed, a number of participants termed this experience ‘having a methadone sleep’ or ‘methadone nap’ by a number of participants. These experiences warrant further investigation, as they seem to occur during a high-risk period when tolerance to methadone is not established [9]. One way to investigate these issues would be to conduct studies during the induction into pharmacotherapy treatment of high-risk individuals (such as those who use multiple substances) who are often excluded from clinical trials.

Limitations of the study

We were unable to collect information as to participants’ dose of methadone and buprenorphine. This means that it was not possible to determine if dose of opioid was associated with reporting of opioid toxicity symptoms. However, in cases of fatal opioid toxicity blood opioid levels are often found within the therapeutic range [29,30], suggesting that factors other than dose, such as benzodiazepine consumption, are important contributing factors. The sample was not selected randomly, meaning that the results may not reflect the wider populations of interest. However, the demographic characteristics of the sample were similar to both usual treatment populations and other drug-using samples seen in similar research in this jurisdiction [27,31]. Finally, the use of self-report introduces the possibility of bias. However, self-report in non-coercive circumstances by this population is generally accepted as a reliable and valid form of evidence [32,33].

CONCLUSIONS

In this sample, a high prevalence of concomitant buprenorphine and benzodiazepine use was observed at levels similar to those that have been reported previously in relation to methadone maintenance treatment. While the use of this combination of medications was prevalent in this sample, the reporting of overdose-related side effects from buprenorphine was significantly less than that seen with methadone. Further laboratory studies observing the interaction under controlled conditions are needed to confirm these findings and address some of the limitations of this study. However, despite these limitations, this study suggests that in such ‘real life’ conditions buprenorphine maintains a favourable safety profile and in some circumstances appears to offer a safer alternative to methadone.

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