Brief article

Methadone- and buprenorphine-related ambulance attendances: A population-based indicator of adverse events

Suzanne Nielsen, (B.Pharm.B.Pharm.Sci.(Hons))\textsuperscript{a,b,*}, Paul Dietze, (Ph.D.)\textsuperscript{a,b,d}, Kate Cantwell, (M.Epi.)\textsuperscript{c}, Nicole Lee, (Ph.D.)\textsuperscript{a}, David Taylor, (Ph.D.)\textsuperscript{b}

\textsuperscript{a}Turning Point Alcohol and Drug Centre, Victoria, Australia\textsuperscript{b}Monash University, Victorian College of Pharmacy, Melbourne, Australia\textsuperscript{c}Metropolitan Ambulance Service, Melbourne, Australia\textsuperscript{d}Macfarlane Burnet Institute for Medical Research and Public Health, Melbourne, Australia

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Abstract

This study examined the nature and extent of methadone- and buprenorphine-related morbidity through a retrospective analysis of ambulance service records ($N = 243$) in Melbourne, Australia. Cases in which methadone and buprenorphine were implicated are examined. Demographic and presenting characteristics, transport outcomes, and other substance use were explored. There were 84 buprenorphine-related attendances and 159 methadone-related attendances recorded on the database over the 4-year period. Presenting signs (respiratory rate and Glasgow Coma Scale score) were lower in the methadone-related attendances. Most of the attendances resulted in transport to hospital. Most presentations did not involve traditional signs of opioid overdose, a finding that warrants further investigation. This is the first article to describe characteristics of methadone- and buprenorphine-related ambulance attendances, with results suggesting this may be a useful way to monitor harms associated with these medications in the future. © 2008 Elsevier Inc. All rights reserved.

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1. Introduction

Methadone and buprenorphine are recognized as effective substitution treatments for heroin dependence (Mattick, Kimber, Breen & Davoli, 2004), reducing morbidity and mortality for those in treatment (Caplehorn, Dalton, Haldar, Petrenas & Nisbet, 1996). The safety profile of these pharmacotherapies is much improved compared with illicit opioids, such as heroin, as a result of known dosage and primarily oral administration (although it should be noted that intravenous use has been reported with both methadone and buprenorphine; Darke, Topp, & Ross, 2002; Jenkinson, Clark, Fry, & Dobbin, 2005). Nevertheless, although numerous benefits have been documented for illicit opioid users, methadone and buprenorphine are potent opioids and have also been associated with some mortality (Caplehorn & Drummer, 2002; Kintz, 2001; Tracqui, Kintz & Ludes, 1998; Zador & Sunjic, 2000).

Although both methadone- and buprenorphine-related fatalities have been reported, unlike methadone, buprenorphine has not been routinely screened for in coronial settings in some jurisdictions, such as Victoria (Prof O. Drummer, Victorian Coroners Office, personal communication, April 16, 2007), meaning that the nature and extent of buprenorphine-related harms such as mortality may be poorly understood. Importantly, aside from mortality, there are few other sources of information available on buprenorphine-related harms.

In Melbourne, a unique database has been established that collects information on all substances implicated in nonfatal ambulance attendances. Although previous work has shown...
that ambulance attendance data are a useful indicator of heroin-related harm (Dietze, Cvetkovski, Rumbold & Miller, 2000), the database has not been examined for other opioids such as methadone and buprenorphine. In this article, we present the first examination of this novel indicator of the harms associated with methadone and buprenorphine. The main aim of this article is to compare the characteristics of these methadone- and buprenorphine-implicated cases observed during the period that buprenorphine treatment for heroin dependence has been available in Victoria.

2. Methods

Data were extracted from a database developed for examining nonfatal drug-related ambulance attendances in the Melbourne metropolitan area (Dietze et al., 2000). This database is a compilation of patient care records (PCRs) that are completed by paramedics for each ambulance attendance. Paramedics document medications that are considered to be involved in the presentations, and PCRs are selected by trained data extraction clerks who then pass them on to trained data coders who enter PCR details onto a Microsoft ACCESS database specifically designed for surveillance purposes. As such, cases were included in this database where methadone and/or buprenorphine had a causal role in the patients’ presentation, as determined through paramedic assessment. Details included presenting characteristics of cases (including demographic and clinical signs), treatments provided, and transportation outcomes. For this study, cases were extracted where methadone or buprenorphine involvement was recorded on the case record for the period November 2001 to October 2005 inclusive. As a consequence of paramedic industrial action, data were unavailable from October 2002 to February 2003 inclusive and June to July 2004 inclusive.

A total of 246 cases involving methadone or buprenorphine were extracted from the database. Cases where both methadone and buprenorphine were recorded were excluded \((n = 3)\) due to difficulties presented in analyzing these cases, resulting in a final sample of 243 cases for analysis. It was possible for an individual to present more than once; these 243 cases represented 228 unique client codes.

Cases were examined for clinical signs recorded. These clinical signs included the Glasgow Coma Score (GCS), a clinical scale for assessing consciousness (where \(3 = \text{unconscious}\); \(15 = \text{fully conscious}\)), respiration rate (normal range is between 12 and 20 in adults), pupil size (coded by paramedics as pinpoint, normal, or dilated), demographic characteristics of the presenting individual, attendance setting characteristics (public/private location, others present, police coattendance), and other medications implicated in the attendance.

Comparisons between pharmacotherapy types were undertaken using odds ratios (ORs) for dichotomous outcomes and \(t\) tests for continuous variables. All analyses were undertaken using SPSS V14 or Stata/SE V9 statistical packages.

3. Results

There were 84 buprenorphine-related attendances and 159 methadone-related attendances recorded on the database over the 4-year period.

3.1. Demographics and attendance characteristics

The age and gender of persons attended did not vary between the methadone- and buprenorphine-related attendances (see Table 1). Further, other attendance characteristics such as attendance location, presence of others, and police involvement varied little between groups.

3.2. Clinical indicators of presentation severity

Most attendances had a presenting GCS of 10 or higher (see Table 1). Individuals who attended in methadone-related attendances were five times more likely than buprenorphine-related attendances to be classified as unconscious based on their GCS (GCS = 3). Although the proportion presenting with pinpoint pupils did not differ between the groups, presenting respiration rate was lower for the methadone-related attendances \((t(234) = 2.58, p = .011)\).

In addition to differences in attendance by pharmacotherapy category, there were differences in attendances according to GCS category. Although case setting and case demographics showed little variation by GCS, those presenting with a GCS <10 (unconscious or severely affected) were more likely to also have pinpoint pupils \((\text{OR} = 11.66; 95\% \text{ confidence interval [CI]} = 3.52–51.89)\), and a lower respiratory rate \((t(241) = 4.87, p < .001)\), consistent with typical signs of opioid toxicity.

Most methadone-related (76%) and buprenorphine-related (83%) attendances resulted in transport to hospital, meaning that almost all cases were considered to require further care (Table 1).

3.3. Attendances with GCS of 15

Approximately half of all methadone- and buprenorphine-related attendances involved persons assessed with a presenting GCS of 15 (conscious). Most of these cases were still transported to hospital (80% for buprenorphine and 75% for methadone). Some 33% of these buprenorphine-related attendances with a GCS of 15 were noted as related to the injection of buprenorphine (including arm pain and swelling, withdrawal symptoms, and vomiting).

3.4. Polydrug use

Table 1 shows that documented benzodiazepine use was around three times more likely for the methadone-related
attendances than the buprenorphine-related attendances and that any other drug mention was also three times as likely for the methadone-related attendances (most buprenorphine cases involving reports of buprenorphine alone). Cocaine, ecstasy, or gamma hydroxybutyrate were not reported for any of these cases; levels of reported alcohol and cannabis use were the same in both groups.

4. Discussion

In this article, we have shown that reports of buprenorphine and methadone involvement in ambulance attendance in Melbourne are relatively uncommon. The less than 250 attendances over the 4-year period examined contrasts with up to 460 heroin-related attendances a month recorded in the same jurisdiction (Dietze, Jolley, & Cvetkovski, 2003).

Clinical characteristics indicate most of the buprenorphine and methadone cases present with GCS \( \leq 10 \) and result in transport to hospital. This finding may suggest that most of these attendances represent morbidity other than overdose. One possible explanation for the buprenorphine-related attendances with normal respiration rate, conscious state, and absence of pinpoint pupils could be that some of these presentations represent cases of precipitated withdrawal by the partial opioid agonist buprenorphine. In addition, a number of injection injuries were related to buprenorphine injection in those that had a GCS of 15, suggesting the need for further care to address these injuries. Severe complication from buprenorphine injection has also been reported elsewhere in relation to the intravenous use of the sublingual tablet formulation (Loo, Yam, Tan, Peng & Teoh, 2005; Simonnet et al., 2004). In the period this study investigated, the main buprenorphine product available was the buprenorphine–mono product; however, in 2006, a buprenorphine–naloxone product became widely available in Australia. The impact of this combination product on the level of unsanctioned intravenous use is currently under examination, and a future investigation of this database may provide additional information as to whether harms association with buprenorphine is reduced as a result of the introduction of this combination product.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Buprenorphine (n = 84)</th>
<th>Methadone (n = 159)</th>
<th>OR (95% CI) or p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>30.02 (9.07)</td>
<td>29.79 (9.39)</td>
<td>ns</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>66</td>
<td>55</td>
<td>1.53 (0.88–2.66)</td>
</tr>
<tr>
<td>Location: private/public space (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>52</td>
<td>54</td>
<td>0.91 (0.53–1.57)</td>
</tr>
<tr>
<td>Others present (%)</td>
<td>77</td>
<td>73</td>
<td>1.12 (0.37–3.77)</td>
</tr>
<tr>
<td>Clinical indicators</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (unconscious)</td>
<td>2</td>
<td>11</td>
<td>0.19 (0.03–0.74)</td>
</tr>
<tr>
<td>4–9 (severely affected)</td>
<td>8</td>
<td>6</td>
<td>0.35 (0.46–3.74)</td>
</tr>
<tr>
<td>10–14 (moderately affected)</td>
<td>35</td>
<td>37</td>
<td>0.89 (0.51–1.55)</td>
</tr>
<tr>
<td>15 (conscious)</td>
<td>55</td>
<td>45</td>
<td>1.46 (0.86–2.30)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinpoint pupils (%)</td>
<td>30</td>
<td>36</td>
<td>0.76 (0.43–1.34)</td>
</tr>
<tr>
<td>Respiration rate, mean (SD)</td>
<td>16.2 (5.4)</td>
<td>14.3 (5.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>Naloxone administered (%)</td>
<td>11</td>
<td>19</td>
<td>0.59 (0.25–1.29)</td>
</tr>
<tr>
<td>Other substances involved (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>7</td>
<td>15</td>
<td>0.43 (0.16–1.07)</td>
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<tr>
<td>Benzodiazepines</td>
<td>21</td>
<td>44</td>
<td>0.35 (0.19–0.63)</td>
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<tr>
<td>Alcohol</td>
<td>17</td>
<td>17</td>
<td>0.98 (0.47–1.98)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>8</td>
<td>8</td>
<td>1.02 (0.37–2.65)</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>8</td>
<td>4</td>
<td>1.97 (0.64–6.06)</td>
</tr>
<tr>
<td>Transport to hospital, n (%)</td>
<td>83</td>
<td>76</td>
<td>1.55 (0.78–3.06)</td>
</tr>
</tbody>
</table>
phine-related attendances with a significantly higher number of methadone-related attendances appearing unconscious. This is consistent with the stronger opioid effects associated with a full opioid agonist like methadone and the ceiling on pharmacological effects (including respiratory depression and sedation), which has been shown in buprenorphine (Gustein & Akil, 2006; Walsh et al., 1995). The response to naloxone was lower in the buprenorphine group as compared with methadone; the failure to reach significance was probably due to a lack of statistical power with a small number of cases where naloxone was used. This highlights a possible difference in the management of buprenorphine overdose compared with methadone, as higher doses of naloxone are reported to be required to achieve a reversal of respiratory depression due to the greater binding affinity of buprenorphine compared with naloxone at the opioid receptor (Gal, 1989).

Despite the generally reduced severity of clinical indicators seen in these cases compared with typical heroin overdose presentations, over three quarters were transported to hospital, compared with <20% typically found for heroin overdose (Dietze et al., 2000). The high transportation rate may be a consequence of the more cautious treatment of patients where opioids with longer half-lives are involved (requiring longer periods of observation) or may suggest that some other condition requiring further medical attention may be present.

Pol drug use was identified in most methadone-related attendances, consistent with findings in studies of mortality (Zador & Sunjic, 2000); however, in contrast, buprenorphine was the sole substance documented in more than half of all buprenorphine-related cases. These findings related to morbidity are contradictory to other studies of buprenorphine-related harm, which found that buprenorphine-related mortality occurs almost exclusively in the presence of other concomitant psychoactive substance use (Kintz, 2001; Lai, Yao, & Lo, 2006). This discrepancy may further add support to the suggestion that some buprenorphine-related presentations represent morbidity other than overdose.

The data presented here are limited to the extent that they rely on paramedic judgement and the consistency with which details are recorded on PCRs. This means that the use of other substances may be underrepresented, and this may bias our assessment of other drug involvement. Because the individual involved was conscious in most of the cases, it is likely that they would have been able to self-report the substances involved in their presentations, suggesting that in most of the cases, the documentation of methadone and buprenorphine involvement and causality should be accurate. Self-report is not without limitations however, self-report in noncoercive circumstances by this population is generally accepted as a reliable and valid form of evidence (Darke, 1998; Morrison, Elliott, & Gruer, 1997).

In interpreting these data, it should also be remembered that not all presentations may have been related to methadone and buprenorphine substitution treatment. Methadone- and buprenorphine-related attendances may result from either use in licit use in substitution therapy or pain management or its illicit use. The database does not differentiate between different sources of methadone and buprenorphine; hence, these figures may overestimate the numbers of attendances related to licit substitution treatment. Illicit use, particularly in the case of buprenorphine (Jenkinson et al., 2005), and use for treatment of pain with methadone and buprenorphine may increase the numbers exposed to methadone and buprenorphine, which may potentially have a nonfatal ambulance attendance. Notwithstanding, the overwhelming majority of methadone and buprenorphine supplied in this jurisdiction is in the context of treatment of opioid dependence (United Nations National Drug control System, 2006).

This study has shown how a database of ambulance attendances can be used for monitoring adverse events related to methadone and buprenorphine treatment in a population. We have been able to show important features of cases and highlight the differences in the effects of the two medications. Given the concerns that exist with safety of treatments for opioid dependence and misuse of prescription medication, such information is vital. The monitoring system we have developed could easily be established in other jurisdictions to detect these drug-related harms and enable an appropriate public health response.

In conclusion, a relatively small number of buprenorphine- and methadone-related attendances were identified with methadone being associated with more severe presenting symptoms. Characteristics of some cases suggested that not all cases presented with symptoms typical of opioid overdose—a finding that warrants further investigation. Ongoing monitoring of methadone- and buprenorphine-related ambulance attendances may be used in the future to identify changes in attendances potentially associated with changes in policy or introduction of new treatments.

References


McGRAW-HILL, Medical Publishing Division.


