Injection of medications used in opioid substitution treatment in Australia after the introduction of a mixed partial agonist–antagonist formulation

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ABSTRACT

Objectives: To examine the levels and predictors of injection of buprenorphine–naloxone (BNX) — a combination of a partial opioid agonist and an opioid antagonist for treating opioid dependence — which was specifically developed to limit injecting. Comparison was made with injecting of two other opioid substitution treatment medications, methadone and buprenorphine (BPN); severe harms have been documented after injection of the latter.

Design and participants: Injecting was studied in regular injecting drug users ("IDUs") and current opioid substitution treatment clients ("clients"). Regular IDUs are interviewed annually in each Australian capital city (about 900 per year) and data for 2003–2007 were used; 399 clients were interviewed in 2007. Data on injection of opioid substitution treatment medications between 2003 and 2007 were adjusted for availability of medications (from national sales data for methadone, BPN and BNX). Predictors of injecting were analysed by multiple regression analyses.

Setting: Capital cities of all Australian states and territories.

Main outcome measure: Injection of opioid substitution treatment medications among individuals both in and out of treatment.

Results: In the year after its introduction in Australia, BNX was injected less frequently and by fewer regular IDUs and clients compared with BPN, particularly when differences in the availability of medications were taken into account. Some individuals did nonetheless regularly inject BNX. Injection of methadone, BPN and BNX was more likely to occur among those injecting other pharmaceutical opioids.

Conclusions: A partial opioid agonist–antagonist combination appears to be less commonly and less frequently injected by clients in treatment and IDUs who are not. Further studies are needed to evaluate longer-term trends in use and harms.

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Opioid substitution treatment — administering a substitute opioid to help manage withdrawal or maintain a patient on a controlled dose — aims to reduce illicit opioid use and its attendant harms.[1-4] Non-adherence with directions for taking opioid substitution treatment medication includes injection when it is not prescribed as injectable, and diversion for injection by a person for whom it is not prescribed.[5,6] Both injection and diversion of pharmaceutical opioids (including those prescribed for pain management) cause significant public health problems in many countries.[7-10] However, few strategies to deter injection or reduce diversion have been empirically evaluated.

In Australia, methadone is the most widely used opioid substitution treatment, but since November 2000, higher-dose formulations of buprenorphine (BPN; Subutex, Reckitt Benckiser) have been registered for this purpose. Implementation of BPN is largely based on that used for methadone (Box 1), but with very restricted availability of takeaway (unsupervised) doses, because of the problems of injection and diversion. Injection of BPN sublingual tablets has been associated with limb ischaemia and tissue necrosis, abscesses, cellulitis, endocarditis, nerve damage, thrombosis, pulmonary granuloma, and candida endophthalmitis.[9,12-14]

Diversion and injection of opioid substitution treatment medications vary according to prescribing, client supervision and dispensing practices; cost of treatment; the availability of other drugs; and cultural factors.[10,15] There is suggestive evidence that supervised dosing, and both dilution of methadone takeaways and restricted access to syringes facilitating injection of large volumes, may reduce diversion and injection, respectively.[16] To deter injection, a new formulation of opioid substitution treatment has been developed — buprenorphine (a partial opioid agonist) combined with naloxone (an opioid antagonist) in a 4:1 ratio (BNX; Suboxone, Reckitt Benckiser).[17,18] When taken sublingually, BNX's actions are indistinguishable from BPN alone. However, when injected by a person dependent on a full agonist, such as heroin or methadone (but who is *not* in withdrawal), BNX can precipitate a more aversive withdrawal syndrome than injecting BPN alone.[17,19] There is also limited laboratory evidence that it can be injected by those already taking BPN without causing withdrawal features.[20]

BNX was released on the Pharmaceutical Benefits Scheme in April 2006. Policies regarding takeaway doses have varied, but most Australian states have allowed a more liberal takeaway policy for BNX. Despite this, few clients receive more than 1 week's takeaway supply at a time. There is limited documented experience of the impact of the introduction of BNX on diversion and injection.

We aimed to monitor the levels and predictors of injection of BNX, compared with injection of methadone and BPN, adjusting for availability.

METHODS

Injecting was studied in two populations: regular injecting drug users ("IDUs") not in opioid substitution treatment, and current opioid substitution treatment clients ("clients").

Regular IDUs

The Illicit Drug Reporting System (IDRS) is an established program of research that monitors trends in Australian illicit drug use and markets.[11,21] It includes interviews with regular IDUs (about 900 each year) who are

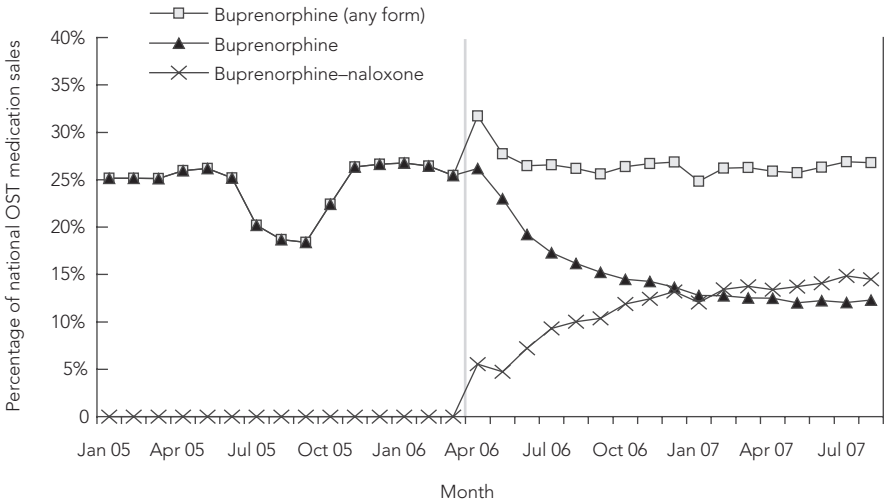
1 Opioid substitution treatment in Australia

Opioid substitution treatment has been available in Australia for 15 years; treatment coverage is relatively good, with over 30 000 people receiving treatment.[11] Methadone, buprenorphine, and buprenorphine–naloxone are the medications used.

Opioid substitution treatment is highly regulated through systems that include: accreditation for doctors and pharmacies to prescribe and dispense treatment; individual client registration; and a supervised dispensing model, based initially around specialist clinics, as well as primary care settings (including community pharmacies).

There are no restrictions on the length of time in treatment, and continued intermittent drug use while in treatment does not usually result in discharge. ◆

2 Estimated proportion of opioid substitution treatment (OST) medication sales accounted for by buprenorphine and buprenorphine–naloxone, January 2005 – August 2007



selected because of their involvement in central inner-city drug markets in Australian capital cities. We included data from the 2003–2007 IDRS interviews with IDUs.

Clients enrolled in treatment

In 2007, structured interviews were conducted with 399 clients receiving methadone, BPN or BNX in private and public clinics in the capital cities of New South Wales, Victoria and South Australia. Participants had been in their current treatment episode for a median of 60 weeks (range, 1–1039 weeks).

Sales data for BPN, BNX and methadone

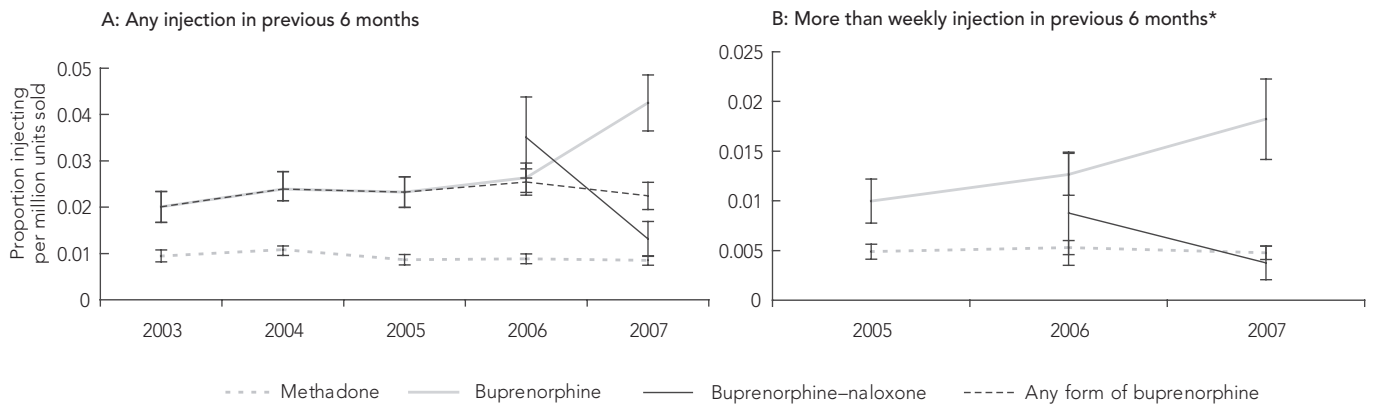
National monthly sales data for BPN and BNX were provided by Reckitt Benckiser, who also provided commercially available data on sales of methadone liquid formulations (Methadone syrup [GlaxoSmithKline] and Biodone [National Sales Solutions]). Sales data were expressed in "factored units" of average doses of methadone in Australia, assumed to be 70 mg, and average doses of buprenorphine (BPN or BNX), assumed to be 12 mg; these levels are derived from previous research on client doses in Australia.[22,23]

Statistical analysis

Time trends in injection of opioid substitution treatment medications were plotted, with consideration given to the amount being prescribed. The data are presented as the ratio of the proportion of regular IDUs reporting injection of each opioid in the previous 6 months to the number (per 100 million) of factored units sold in the same 6-month period. Thus, the levels of methadone, BPN and BNX injection documented among regular IDUs were "standardised" according to background availability (ie, amounts being prescribed).

Multiple logistic regression analyses were conducted using SPSS, version 17 (SPSS Inc, Chicago, Ill, USA) to ascertain the predictors of recent injection of opioid substitution treatment medication among IDUs and clients. The following variables were included: sex; age; prison history; jurisdiction of interview; heroin use; injection of methadone, BPN, BNX, and other pharmaceutical opioids (morphine, oxycodone); and, for clients only, number of months in treatment; any takeaway doses (in the previous month); and pharmacy dosing.

3 Ratio of injection of opioid substitution treatment (OST) medications by regular injecting drug users to volume of sales of OST medications, 2003–2007



Bars are 95% CIs. *Data on days of injection were only available for 2005 onwards, and could not be aggregated for buprenorphine forms. ◆

4 Methadone, buprenorphine and buprenorphine–naloxone injection among regular injecting drug users (IDUs) currently not being treated, and clients enrolled in opioid substitution treatment (OST) in 2007

	Regular IDUs ($n = 513$)*		Current OST clients ($n = 399$)†	
Proportion injecting:	Per cent (95% CI)	No.	Per cent (95% CI)	No.
Methadone‡				($n = 157$)
In the previous 6 months	17% (14%–20%)	89	24% (17%–31%)	37
Weekly or more frequently§	7% (5%–9%)	35	8% (4%–12%)	13
Buprenorphine				($n = 126$)
In the previous 6 months	23% (19%–27%)	116	30% (22%–38%)	38
Weekly or more frequently§	8% (6%–10%)	43	13% (7%–19%)	17
Buprenorphine–naloxone				($n = 116$)
In the previous 6 months	9% (7%–12%)	47	10% (5%–16%)	12
Weekly or more frequently§	3% (2%–5%)	12	7% (2%–12%)	8

All figures include injection of a client's own OST medication, both licitly and illicitly obtained.

* Data from Illicit Drug Reporting System interviews, 2007. † Data from interviews in 2007 with clients enrolled in OST (the proportions refer to those receiving that form of OST).

‡ The prevalence of injection of methadone includes Methadone syrup, Physeptone (GlaxoSmithKline) and Biodone (National Sales Solutions). § Proportions injecting on > 24/180 days. ◆

Ethics approval

Ethics approval was obtained from the University of New South Wales Human Research Ethics Committee (HREC) (Committee A), South Eastern Sydney and Illawarra Area Health Service HREC (Northern Network), Sydney South West Area Health Service HREC (Western Zone), the University of Adelaide HREC, and the Victorian Department of Human Services HREC.

RESULTS

The proportion of opioid substitution treatment medication sales in Australia accounted for by BPN and BNX is shown in Box 2. There was a steady increase in sales of BNX from April 2006; by August 2007, it accounted for more of the total Australian opioid substitution treatment medication sales than BPN. The total buprenorphine (BPN plus BNX) market share did not change: it consistently accounted for just over 25% of all doses (with methadone accounting for the remainder).

Injection of opioid substitution treatment medications

Box 3 presents data on injection of the three opioid substitution treatment medications by regular IDUs in Australian capital cities, adjusting for the volume of sales of each medication type (expressed as the ratio of the proportions injecting in the previous 6 months per 100 million units sold in the same period). Injection of methadone includes Methadone syrup, Biodone and Physeptone (GlaxoSmithKline). The data were derived from the total samples of IDUs in each year reporting injection of each type of opioid substitution treatment in the previous 6 months.

The graphs clearly show that BPN was injected at a higher rate than methadone, adjusted for available volume. In 2006, when BNX was first introduced, the adjusted rate of any injection of BNX was higher than that for BPN, although more than weekly injection was less common. This had dropped substantially by 2007, with BNX having a lower level of injection relative to availability, compared with both methadone and BPN. This difference was particularly marked when more than weekly injection was considered, with BNX clearly having the lowest adjusted levels in 2007. Interestingly, the ratio for more than weekly BPN injection increased in 2007; although sales decreased, the level of more than weekly injection among regular IDUs did not.

Box 4 shows the proportions of (i) regular IDUs not in any form of drug treatment, and (ii) clients currently in each form of opioid substitution treatment, who reported any and more than weekly injection of each opioid substitution treatment medication during the 6 months before interview. The former group represent a group injecting someone else's medication (ie, diversion); the latter represent a group presumed to be injecting their own medication (ie, non-adherence).

Among IDUs, there were no differences in levels of methadone or BPN injection. In contrast, BNX was less commonly injected in the previous 6 months (at any time, or more than weekly) compared with methadone and BPN (although the confidence intervals for proportions reporting more than weekly injection of methadone and BNX touched).

Among clients, significantly lower levels of any injection of own medication was reported by those taking BNX, compared with clients receiving methadone and BPN (there were no differences in the levels of injection reported by clients receiving methadone and BPN). However, levels of more than weekly injection were not significantly different among clients receiving BNX compared with those receiving methadone or BPN.

Predictors of recent injection of opioid substitution treatment

The results of multiple regression analysis of predictors of recent injection of opioid substitution treatment medications are shown in Box 5. In both clients and IDUs, the strongest predictors were the recent injection of other pharmaceutical opioids. Clients and IDUs who injected one type of medication were likely to inject a range of medications. Days of heroin use was not related to injection of opioid substitution treatment, and, for clients, nor was length of time in treatment. However, there were jurisdictional differences in the levels of injection of opioid substitution treatment medications. For example, IDUs from Western Australia and Queensland were 27.5 and 20.3 times, respectively, more likely to inject BNX than IDUs from NSW, reflecting lower levels of BNX prescribing in NSW.

DISCUSSION

We were able to assess changes in the levels of injection of opioid substitution treatment medications among at-risk IDUs in all Australian capital cities, adjusting for availability as indicated by sales data, and allowing for direct comparisons of three opioid substitution treatment medications. These data suggest that BNX is less likely to be regularly injected than either methadone or BPN, consistent with laboratory studies.[24]

Given that BNX has not only overtaken market sales of BPN, but is also generally available as takeaway medication (unlike BPN), the deterrent effect of the combination product may be even greater than the comparisons in our study suggest. This finding has important implications for public health, given the potential for severe consequences of BPN injection. We acknowledge that particular local factors (eg, treatment

access and the illicit drug market) will also exert a strong influence on non-adherence and injection. Nevertheless, our findings, together with those showing that weekly dispensed BNX treatment has comparable efficacy to and greater cost-effectiveness than daily supervised BPN,[25] suggest that BNX may be expanded as a safe and effective treatment, with perhaps less requirement for supervised dispensing.

5 Predictors of injection in the previous 6 months of opioid substitution treatment (OST) medication (odds ratios [95% CIs]) among regular injecting drug users (IDUs) currently not being treated, and clients enrolled in OST

Regular IDUs ($n = 513$)	Methadone injection	Buprenorphine injection	Buprenorphine–naloxone injection
Male	1.2 (0.6–2.2)	1.2 (0.7–2.2)	1.1 (0.5–2.7)
Age	1.0 (1.0–1.1)	1.0 (1.0–1.0)	0.9 (0.9–1.0)*
Prison history	0.9 (0.5–1.5)	1.2 (0.7–2.0)	1.5 (0.7–3.3)
Days of heroin use	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Injection of:			
Methadone	—	1.6 (0.8–3.1)	1.8 (0.7–4.7)
Buprenorphine	1.7 (0.9–3.3)	—	7.9 (3.6–17.2)†
Buprenorphine–naloxone	1.9 (0.8–4.5)	7.4 (3.5–15.9)†	—
Morphine	4.3 (2.3–7.9)†	1.2 (0.7–2.1)	1.1 (0.5–2.5)
Oxycodone	1.2 (0.7–2.2)	1.5 (0.9–2.6)	3.3 (1.5–7.2)†
New South Wales	1.00	1.00	1.00
Australian Capital Territory	0.8 (0.3–2.4)	4.7 (1.9–11.5)†	5.3 (0.5–59.2)
Victoria	0.3 (0.1–0.8)*	1.5 (0.7–3.3)	12.9 (1.5–113.7)*
Tasmania	2.2 (0.7–6.2)	0.4 (0.1–1.3)	—‡
South Australia	0.7 (0.3–2.0)	0.2 (0.1–0.9)*	—‡
Western Australia	0.4 (0.1–1.3)	0.7 (0.3–1.9)	27.5 (2.8–272.6)†
Northern Territory	0.2 (0.1–0.7)*	0.2 (0.0–0.6)†	4.7 (0.2–100.0)
Queensland	0.4 (0.1–1.0)*	0.9 (0.4–2.1)	20.3 (2.2–185.2)†
Clients enrolled in OST§	**Methadone injection**	**Buprenorphine injection**	**Buprenorphine–naloxone injection**
Male	1.2 (0.4–3.4)	0.3 (0.1–1.1)	0.4 (0.0–4.1)
Age	1.0 (0.9–1.1)	1.0 (1.0–1.0)	1.0 (0.9–1.1)
Prison history	0.9 (0.3–2.7)	0.6 (0.2–1.6)	7.7 (1.4–43.0)*
Days of heroin use	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Time in treatment	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Takeaway dose(s)	1.1 (1.0–1.2)	0.9 (0.8–1.1)	1.1 (1.0–1.2)
Dosed at pharmacy (v other)	2.7 (0.6–12.2)	6.8 (0.5–90.2)	9.0 (0.1–678.9)
Injection of:			
Methadone	—	3.3 (0.1–161.0)	0.5 (0.3–8.7)
Buprenorphine	6.7 (0.7–68.0)	—	0.7 (0.1–7.7)
Buprenorphine–naloxone	—¶	10.0 (1.6–62.9)*	—
Morphine	10.7 (3.0–38.8)†	2.0 (0.4–10.9)	15.0 (1.8–128.5)*
Oxycodone	2.3 (0.6–8.9)	2.3 (0.4–13.8)	0.4 (0.0–5.5)
Victoria	1.00	1.00	1.00
New South Wales	21.5 (3.1–148.8)†	3.1 (0.2–43.1)	—**
South Australia	8.2 (0.8–85.3)	51.5 (2.0–1318.9)*	3.2 (0.0–234.7)

* $P < 0.05$. † $P < 0.01$. ‡ These variables were dropped from the model as redundant (no IDUs in these states reported recent injection of buprenorphine–naloxone).
§ Only clients currently receiving each form of OST were included in the regression analyses (sample sizes: methadone, $n = 157$; buprenorphine, $n = 126$; buprenorphine–naloxone, $n = 116$).
¶ Among clients who had injected their methadone, none had recently injected buprenorphine–naloxone.
** No clients in NSW reported recent injection of buprenorphine–naloxone. ◆

Despite the lower levels of injection, we documented that BNX was injected by IDUs and clients. Thus, even with a formulation designed to deter injection, there continues to be some level of non-adherence and injection. Many factors independent of medication formulation are likely to influence the extent of diversion and injecting, including availability of heroin and policies allowing multiple takeaway doses, as well as client characteristics. Client selection to ensure takeaway doses are restricted to those who have largely ceased injecting and have social stability is the basis of the current Australasian Chapter of Addiction Medicine's Clinical Guidelines.[26] This recommendation is consistent with studies suggesting that the people most likely to inject BPN are more chaotic and socially marginalised.[27,28]

There was clear evidence in our study that IDUs and clients who were injecting other pharmaceutical opioids were also more likely to inject opioid substitution treatment medication, suggesting a preference for injection, even if the medications are not designed to be injected. The role of injectable opioids as a form of opioid substitution treatment has been hotly debated. There is now evidence showing the feasibility and effectiveness of injectable opioid treatment in reducing unsanctioned drug use and related crime, and in enhancing general health and psychosocial functioning.[29] The propensity for this group to inject existing pharmaceutical opioids (eg, methadone, BPN, morphine) suggests that these medications may be more feasible alternatives to establishing a heroin treatment program, with all its complex medicolegal hurdles. A randomised controlled trial comparing injectable methadone, injectable heroin and oral methadone is currently underway in the United Kingdom.[30]

A limitation of our study was that BNX's introduction was accompanied by an information campaign suggesting that injecting it would cause "bad effects", and emphasising the importance of patient selection; namely, that takeaway doses should only be provided to clients who were "stable". Doctors may have selected such patients for BNX, while those most at risk of injecting continued to receive BPN, and this might account in part for the higher levels of BPN injection. Further and ongoing studies are needed to investigate this and to examine possible changes across time in the levels and correlates of injection. The IDUs and clients recruited for our study were selected from capital cities and areas where levels of injection of opioid substitution treatment medications may be higher;

the levels of injection should not be taken to be representative of all clients in opioid substitution treatment in Australia.

In the 18 months after its introduction in Australia, BNX was injected by fewer IDUs and less frequently, compared with BPN, particularly given emerging differences in the availability of these different opioid substitution treatment medications. Some individuals did nonetheless regularly inject BNX. Postmarketing studies must continue for sufficient time to evaluate longer-term trends in use and harms, because it cannot be assumed that more IDUs will not develop practices to minimise the adverse consequences associated with injection of BNX. Although adaptations of drug formulations have an important role in minimising misuse of opioid medications and enhancing adherence with treatment, they must not replace good clinical care and ongoing patient assessment and monitoring. Furthermore, the trends reported here might change if BPN is no longer used as an opioid substitution treatment medication (as some people currently injecting BPN might begin BNX injection), or if other treatment conditions change. Research is underway to examine ongoing patterns of injecting of this medication.

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COMPETING INTERESTS

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