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# The diversion and injection of the pharmaceutical opioids used in opioid substitution treatment: Findings from the post-marketing surveillance of buprenorphine-naloxone, 2006-2008

**NDARC Technical Report No. 302**

# THE DIVERSION AND INJECTION OF THE PHARMACEUTICAL OPIOIDS USED IN OPIOID SUBSTITUTION TREATMENT:

## Findings from the Australian post-marketing surveillance studies of buprenorphine-naloxone, 2006-2008

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**Technical Report No. 302**

**ISBN: 978-0-7334-2792-3**

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# ACKNOWLEDGEMENTS

These studies would not have been possible without the generous participation of people who inject drugs and/or receive treatment for opioid dependence. Our thanks go to those individuals who gave their time and openly shared accounts of what is often highly stigmatised behaviour.

Special thanks also go to the key experts (KE) who shared their expertise. Many KE have participated in prior National Drug and Alcohol Research Centre (NDARC) research projects and were interviewed out-of-hours. They willingly gave their time without reimbursement.

Thank you to the jurisdictional coordinators and interviewers who work on the Illicit Drug Reporting System nationally. Thank you also to the treatment services, doctors and pharmacies in New South Wales (NSW), Victoria (VIC) and South Australia (SA) who assisted with recruitment of OST clients for the study.

A number of NDARC staff provided support and advice to this project, and thanks go to Emma Black, Natasha Sindicich, Elizabeth Maloney, Gabrielle Campbell, Matthew Dunn, Peter Gates, Fiona Shand, Amanda Roxburgh and David Krimmer. Special thanks go to Susannah O'Brien, who coordinated the study and oversaw the 2008 data collections.

Our thanks go to colleagues in SA and VIC who recruited and/or interviewed opioid substitution treatment clients and KE in their respective states. Thank you to Robyn Vial, Aylza Donaldson, Nancy White and Steven Savvas (DASSA) for conducting the SA arm of the study. Thank you to Paul Dietze (Burnet Institute/Turning Point), Sanja Pahoki (Turning Point), Suzi Nielson (Turning Point), Rebecca Jenkinson (Turning Point), Heidi Strickland (Turning Point), Danielle Horyniak (Burnet Institute) for conducting the VIC arm of the study. Special thanks go to Danielle Horyniak for her comments on an earlier draft of this report.

The research questions, methodology and analyses for these studies were informed by an expert panel of advisors made up of treatment providers, consumer group representatives, policy makers and researchers, who shared their time and expertise with the study in face-to-face meetings and via email. Thank you to the following Advisory Committee members for their contribution:

- Mr Chris Boag (Department of Human Services)
- Dr Nico Clark (Turning Point)
- Mr Paul Dessauer (WASUA)
- A/Prof Paul Dietze (Burnet Institute)
- Dr Adrian Dunlop (NSCCH)
- Dr Linda Gowing (DASSA)
- Ms Louise Grant (AIVL)
- Prof Wayne Hall (University of Queensland)
- Mr Sam Liebelt (AIVL)
- Ms Sarah Lord (VIVAIDS)
- Ms Kristie Mammen (Langton Centre)
- Dr Benny Monheit (South City Clinic)

- Mr Peter Muhleisen (Turning Point)
- Mr Irvine Newton (VIC pharmacist)
- Dr Allan Quigley (Next Steps)
- A/Prof Alison Ritter (NDARC)
- Ms Robyn Vial (DASSA)
- Ms Nicole Wiggins (AIVL)

Special thanks go to Nicole Wiggins, Nicky Bath and AIVL's Suboxone Peer Educators whose detailed feedback in 2006 informed the development of the OST client questionnaires.

Thank you to those agencies and individuals who provided the study with indicator data: Ingrid van Beek and Marianne Jauncey (MSIC); Robert Kemp and Susan Ballantyne (Queensland Health); Jenny Iversen and Lisa Maher (Australian NSP Survey, NCHECR); and Reckitt Benckiser/IMS for providing the OST medication marketshare data used in this report.

The study investigators were Prof Louisa Degenhardt (NDARC), Prof Richard Mattick (NDARC), Ms Briony Larance (NDARC), A/Prof James Bell (SESIAHS) , A/Prof Robert Ali (University of Adelaide), A/Prof Nick Lintzeris (SSWAHS) and Dr Adam Winstock (SESIAHS). These studies were funded by Reckitt Benckiser by way of an untied educational grant. Thank you to Telea Slavin and Chris Chapleo for the provision of background information and sales data. The studies' design, conduct and interpretation of findings are the work of the investigators; Reckitt Benckiser had no role in these. The funder also played no role in the conception or writing of this report.

# ABBREVIATIONS

| | |
|---|---|
| AIVL | Australian Injecting and Illicit Drug Users' League |
| BHRS | Brisbane Harm Reduction Service |
| BNX | Buprenorphine-naloxone |
| BUP | Buprenorphine |
| CI | Confidence Interval |
| DASSA | Drug and Alcohol Services South Australia |
| GP | General Practitioner |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| IDRS | Illicit Drug Reporting System |
| IDU | Injecting Drug User(s) |
| INCB | International Narcotics Control Board |
| IMS | IMS Health (market intelligence for pharmaceutical and health industries) |
| KE | Key Expert(s) |
| MET | Methadone |
| MSIC | Medically Supervised Injecting Centre |
| NAT | National |
| NCHECR | National Centre for HIV Education and Clinical Research |
| NDARC | National Drug and Alcohol Research Centre |
| NOPSAD | National Opioid Pharmacotherapy Statistics Annual Data |
| NSP | Needle Syringe Program |
| NSW | New South Wales |
| OST | OST |
| PBS | Pharmaceutical Benefits Scheme |
| QLD | Queensland |
| SA | South Australia |
| TGA | Therapeutic Goods Administration |
| UNSW | University of New South Wales |
| US | United States |
| VIC | Victoria |
| WHO | World Health Organisation |

# EXECUTIVE SUMMARY

## 1. Introduction

Opioid substitution treatment (OST) is effective in treating opioid dependence, and results in significant reductions in the negative health consequences and adverse effects on public order. In Australia, OST is highly regulated: it is available only with an individual patient authority, there is licensing of doctors, and a strong focus on supervised administration of medication. Adherence with OST is important for maximising a range of positive treatment outcomes, but is especially important in preventing injection, "leakage" of prescribed medication to the illicit market, overdose and mortality.

The introduction of an opioid agonist-antagonist formulation in Australia was a new approach that was hoped to result in lower levels of injection of the medication. By deterring injection, buprenorphine-naloxone (registered as Suboxone®) may reduce its attractiveness in illicit markets.

Post-marketing surveillance of the diversion and injection of Suboxone® was required as a condition of the product's registration in Australia. Reckitt Benckiser approached the National Drug and Alcohol Research Centre to conduct the study independently, by way of an untied educational grant.

### 1.1. Terminology

*Post-marketing surveillance studies* are usually observational in design and monitor the safety of new medications being used in real-life applications. Pre-marketing (clinical) studies usually involve detailed protocol constraints and small sample sizes, and although they may suggest which medications are likely (or not likely) to be misused, they are limited in their ability to detect and quantify actual misuse.

*Diversion* is used in this report to describe the unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended.

*Adherence* is used to describe the taking of medication in accordance with prescription directions and the meeting of all the specified conditions of treatment (e.g. consumption of the dose under supervision, attendance at designated dosing times, meeting requests for urinalysis, etc). *Non-adherence* is, therefore, any use of a medication by the individual to whom it was prescribed where the medication was not taken exactly as directed. This includes (but is not limited to) removing all or part of a supervised dose from the dosing site for personal use or diversion to illicit markets, splitting doses, stockpiling doses, taking more or less than the prescribed dose, and injection of prescribed medication(s).

### 1.2. Scope of this report

This report seeks to answer the following questions:

*(i) Is there injection of the agonist-antagonist formulation - buprenorphine naloxone - following its large-scale introduction into treatment programs for opioid dependence?*

*(ii) To what extent is buprenorphine-naloxone injected compared to existing OST formulations, and in particular compared to the mono-buprenorphine product, among those receiving treatment and among out-of-treatment injecting drug users (IDU)?*

*(iii) Is diverted buprenorphine-naloxone less attractive in illicit markets?*

*(iv) What influences the diversion and/or injection of buprenorphine-naloxone?*

## 2. Methodology

The post-marketing surveillance studies utilised multiple data sources, each with its own strengths and limitations. Wherever possible, comparisons were made between methadone, buprenorphine and buprenorphine-naloxone across three Australian jurisdictions (NSW, VIC and SA).

Data sources used in this report included:

- indicators of availability of OST medications;
- interviews with regular (out-of-treatment) IDU;
- interviews with OST clients;
- interviews with key experts (KE);
- postal survey of authorised OST prescribers; and
- population-level indicators of injection.

Each chapter of this report draws on the data sources most relevant to its aims.

Measures of the relative availability of the three OST medications in the wider community are important for interpreting the levels of diversion and injection. The more widely available a medication, the more opportunity there is for that medication to be diverted and/or injected. Adjusting for availability enabled better comparisons to be made between the three medications, and enabled a better assessment of the impact of drug formulation. This is the first study of diversion and injection of buprenorphine-naloxone to make these adjustments. In Australia, sales data were the only national indicator to routinely separate the two buprenorphine formulations.

Out-of-treatment IDU are the group that are most able to comment on the characteristics of the illicit market for OST medications and the extent to which diverted medication is injected. Approximately half the IDU who participated in the Illicit Drug Reporting System (IDRS) received methadone, buprenorphine or buprenorphine-naloxone in the six months prior to interview. As the IDRS intentionally recruits a 'sentinel' population of regular IDU (i.e. current, active participants in illicit drug markets who have been injecting regularly in the six months prior to interview), participants who report being in treatment cannot be taken as representative of treatment populations more generally.

Accordingly, a separate study group of OST clients were surveyed. These participants were interviewed in three jurisdictions (NSW, VIC and SA) and recruitment strategies were targeted to ensure the sample was more representative of treatment populations. Estimating how frequently non-adherent behaviours occur among OST clients is important for understanding the dynamics of diversion and injection.

Additional data from KE, authorised OST prescribers and population-level indicators served to validate the self-report of IDU and OST clients. KE and prescribers' views also provided important information on the wider context of service delivery and policy that may impact on the extent to which OST medications are misused.

Although this study sought to include a range of population-level indicators of availability, patterns of use and harms, most indicator data sets do not routinely separate buprenorphine from buprenorphine-naloxone. The current study identified a limited number of data sources, mainly from Needle Syringe

Programs (NSPs), that enabled comparisons between methadone, buprenorphine and buprenorphine-naloxone, and these have been included in this report. This is an area that could be improved in routine Australian data collections.

# 3. Findings

## 3.1. Overview of OST in Australia

*Uptake of buprenorphine-naloxone*

Methadone retains the largest OST market share nationally (approximately 70-75% of all OST medication sales). Buprenorphine (any form, including mono-buprenorphine and buprenorphine-naloxone) retains approximately 25-30% of the market share nationally, and this proportion has remained stable since July 2006. Buprenorphine-naloxone sales now outstrip those for mono-buprenorphine.

The three study jurisdictions, NSW, VIC and SA, have taken different approaches to incorporating buprenorphine-naloxone in their OST policies. These policy differences were associated with differences in the uptake of buprenorphine-naloxone.

Although not its primary aim, some KE reported that buprenorphine-naloxone has the potential to lead to more flexible treatment options in Australia. Increasing the number of unsupervised doses of OST medication was viewed as beneficial to clients, potentially enabling a more 'normal' life, work opportunities, improved treatment retention and greater treatment satisfaction. In SA, however, the introduction of buprenorphine-naloxone did not lead to an increase in the maximum number of unsupervised doses available to stable patients. The medication was perceived as not being used to its full potential in this regard.

*Supervised and unsupervised administration of OST medication*

In general, OST medication in Australia is administered under supervision. There is provision for unsupervised administration of doses, mainly for methadone and buprenorphine-naloxone, and extremely limited provision for unsupervised buprenorphine. The proportions of OST clients being administered their doses under supervision is not monitored in routine data collections at a national level.

The proportion of doses consumed under direct observation of a clinician/pharmacist (defined as high, medium, low and minimal levels of supervision in this report) is determined by an individualised risk assessment. In NSW and VIC, minimal supervision (defined in this report as receiving 20 or more unsupervised doses per month, sometimes even 28-day dispensing) is only available to clients who are stable on buprenorphine-naloxone.

## 3.2. Non-adherence among OST clients

Despite best efforts, some level of non-adherence with medication occurs. This is the case for many areas of medicine, not just OST. It is important to be specific regarding behaviours of concern, as different behaviours are associated with risks of differing severity.

There are many indicators of 'adherence' with medical treatment, and many ways of measuring these indicators.

This report examined the following indicators of (non)adherence:

- removal of all or part of a supervised dose;
- injection of OST medication;
- selling/giving away medication;
- accessing multiple doctors; and

- general indicators of adherence with treatment (such as attendance at appointments).

We examined the prevalence of these behaviours, as well as the volumes of medication not taken as directed, relative to the overall number of doses dispensed.

*Removal of supervised doses*

Buprenorphine was removed from the dosing site by a larger number of clients, at a greater rate, than either methadone or buprenorphine-naloxone. Buprenorphine-naloxone was removed by the smallest number of clients, but in larger quantities than methadone, possibly because it is easier to secret out of the dosing site than methadone syrup. A minority of OST clients reported removal of supervised doses for injection; even fewer reported removal to sell. The most common motivations for removing supervised doses included stockpiling or saving for later and to help a friend in withdrawal, particularly among buprenorphine-naloxone clients. The sharing of medication among peers or partners constitutes *diversion* to a third party.

*Diversion of doses*

Diversion in this study was defined as selling and/or giving away medication to a third party (to whom the medication was not intended). Overall, diversion occurs infrequently. More buprenorphine doses were diverted than buprenorphine-naloxone doses, despite the fact that more buprenorphine-naloxone doses are dispensed as take-home medication. More buprenorphine-naloxone doses were diverted than methadone doses. These findings suggest that there continues to be some demand for diverted buprenorphine-naloxone, despite the addition of naloxone, but that the demand is less than that for buprenorphine.

*Injection of doses*

Among OST clients, the reported levels of buprenorphine injection were higher than that for methadone and buprenorphine-naloxone (both in terms of prevalence and quantity of medication injected). The prevalence of injection was lowest among buprenorphine-naloxone clients, but these clients injected at a rate (per 1000 doses dispensed) that was equivalent to that for methadone.

Substantial proportions of OST clients who inject their medication do so for reasons other than 'liking of the drug effect'. Many OST clients reported experiencing difficulties in stopping injecting in drug treatment. For many, injectable forms of OST (under medical supervision) are an attractive treatment option.

*Prescriber reports of non-adherence*

Prescribers suspected higher levels of removal of supervised buprenorphine (than methadone or buprenorphine-naloxone), but were not sure about the extent of diversion (to a third party). Prescribers were somewhat more confident in assessing the risk of patients injecting medication than the risk of diversion to others (because injecting sites can be inspected for physical evidence of injection). Prescribers suspected higher levels of methadone injection (the main source of which was presumed to be unsupervised medication), a perception that was not supported by the reports of OST clients. In general, prescriber perceptions were that diversion and injection of buprenorphine-naloxone was minimal.

### 3.3. Injection of diverted OST medication

The injection of OST medications among out-of-treatment populations may give some indication of the relative attractiveness of the medication in environments where the medication is potentially less accessible and more costly to the individual (in terms of street price). The injection of OST medications among OST clients indicates the relative attractiveness of the medication among treatment populations, who have ready access to what they have been prescribed.

This is the first study to compare the injection of all three OST medications (including buprenorphine-naloxone), adjusting for availability, among OST clients and regular IDU. This chapter draws on data from interviews with out-of-treatment IDU. This data is compared to the reports of OST clients, KE and population-level indicators.

The injection of buprenorphine-naloxone was reported by IDU, both in and out-of-treatment, and KE. Population-level data (from Needle Syringe Programs, or NSPs) also indicates low levels of buprenorphine-naloxone injection, although there are limitations and caveats that apply to the collection of this data.

The levels and frequency of buprenorphine-naloxone injection were lower than that for mono-buprenorphine among out-of-treatment IDU. This difference was even more marked when the levels were adjusted for background levels of availability.

NSP data clearly demonstrated that there are higher levels of injection of pharmaceutical opioids (morphine and oxycodone in particular) than the opioids used in OST. This may indicate the success of regulatory controls in the prescribing of OST medications.

*Predictors of injection among IDU in and out-of-treatment*

Current injection of an OST medication, among IDU in and out-of-treatment, was associated with prior injection of a range of pharmaceutical opioids. This may prove to be a useful clinical indicator in identifying OST clients at increased risk of injecting their prescribed OST medication.

### 3.4. Characteristics of the market for diverted OST medication

The rationale for the inclusion of naloxone in buprenorphine-naloxone was that it would deter injection, therefore diversion, of the medication. This assumes that the desirability and street value of pharmaceutical opioids are dependent on the ease with which a medication can be injected without adverse effects. This is the first time the market for illicit buprenorphine-naloxone has been examined in detail.

The indicators of diversion considered in this report include;

- demand for OST medications;
- motivations for use;
- source of diverted medication; and
- street price of buprenorphine-naloxone.

Data sources included interviews with regular (out-of-treatment IDU), OST clients, KE and prescribers.

There is some demand for diverted OST medications among both IDU and OST clients in Australia, mainly for methadone and buprenorphine, and to a lesser extent, buprenorphine-naloxone. Generally, however, the demand for diverted OST medications is less than that observed for other pharmaceutical opioids such as morphine or oxycodone. Not all diverted medication is injected. The most common motivation for using

diverted OST medication among out-of-treatment IDU was self-treatment (of withdrawal symptoms).

This study highlights the importance of personal networks in sourcing/sharing diverted OST medications. Among those OST clients involved in diversion, OST medications are more commonly given away (no exchange of money) than sold, particularly for buprenorphine-naloxone.

Buprenorphine-naloxone has a street price that was equivalent to that for mono-buprenorphine in 2008. Consumers in the illicit drug market did not make a distinction between the two formulations. There is a market for diverted buprenorphine-naloxone, despite its agonist-antagonist formulation. This indicates that the extent to which OST medications are diverted and/or injected is influenced by a range of variables, not just the ease with which the medication can be injected without adverse consequences.

# 4. Discussion

Preventing diversion and injection of the pharmaceutical opioids used in OST reduces harms to the individual (such as dependence, injection-related injuries and diseases and overdose) and protects the integrity of the OST program. Reports of buprenorphine or methadone injection can undermine public support for OST. This in turn may limit future investment and development, and hinder efforts to make OST more attractive and accessible.

There is limited post-marketing data examining the impact of agonist-antagonist formulations upon injecting practices. This is the first detailed study comparing the levels of methadone, buprenorphine and buprenophine-naloxone injection among two populations: IDU in- and out-of-treatment. Unlike previous post-marketing studies of buprenorphine-naloxone, this study drew on additional data from KE and prescribers, and examined population-level indicators of OST medication injection. The three OST medications were monitored over a three-year period following the widespread uptake of buprenorphine-naloxone. This is also the first time the levels of methadone, buprenorphine and buprenorphine-naloxone injection have been examined among IDU, adjusting for background availability of each medication.

## 4.1. Summary of key findings

*(i) Is there injection of the agonist-antagonist formulation - buprenorphine-naloxone - following its large-scale introduction into treatment programs for opioid dependence?*

A minority of IDU, both in and out-of-treatment, reported recent injection of buprenorphine-naloxone despite its agonist-antagonist formulation. Buprenorphine-naloxone injection was also documented in KE and prescriber reports, and population-level indicators (such as NSP data).

*(ii) To what extent is buprenorphine-naloxone injected compared to existing OST medication formulations, and in particular compared to the mono-buprenorphine product, among those receiving treatment and among out-of-treatment IDU?*

Among OST clients, fewer buprenorphine-naloxone clients reported injecting their medication than methadone or buprenorphine clients. The number of buprenorphine-naloxone doses injected (adjusted for the total number of doses dispensed) was less than that for mono-buprenorphine, but equivalent to that for methadone. A similar pattern was observed among out-of-treatment IDU; fewer IDU reported recent injection of diverted

buprenorphine-naloxone, compared to methadone and buprenorphine. Adjusting for background availability, the levels of buprenorphine-naloxone injection were less than those for mono-buprenorphine (despite rapid expansion of buprenorphine-naloxone prescribing in Australia), but were similar to those for methadone syrup. These patterns of OST medication injection among IDU and OST clients were consistent with the reports of KE, OST prescribers and NSP data.

Although there were large jurisdictional differences in uptake, national buprenorphine-naloxone sales outstrip those for mono-buprenorphine. The vast majority of unsupervised buprenorphine doses are the agonist-antagonist formulation. Given that buprenorphine-naloxone is, therefore, the more accessible medication in terms of injection, the finding that it is injected less than the mono-buprenorphine product is an important one.

*(iii) Is diverted buprenorphine-naloxone less attractive in illicit markets?*

Despite its agonist-antagonist formulation, diverted buprenorphine-naloxone has some value in illicit markets. Previous studies have found that the street price of buprenorphine-naloxone was half that for equivalent doses of mono-buprenorphine. The present study found that the street price of buprenorphine-naloxone increased from 2007 to 2008; in 2008 it was equivalent to that for mono-buprenorphine. With an additional year of experience, out-of-treatment IDU did not distinguish between the two formulations in terms of price. This demonstrates the importance of longer-term monitoring of new medications. This finding also indicates that the ease with which a medication can be injected without adverse consequences is not the only factor to influence its value in illicit markets.

Despite similarities in street price, our findings indicated that buprenorphine-naloxone is less attractive than both methadone and buprenorphine in illicit markets. The proportion of IDU injecting diverted OST medications is substantially smaller than those injecting other opioids (morphine and/or oxycodone). This finding implies that the infrastructure, supervision and careful monitoring of patients have been successful in preventing widespread diversion and injection of the opioids used in OST.

*(iv) What influences the diversion and/or injection of buprenorphine-naloxone?*

The most common motivation for using diverted buprenorphine-naloxone (among out-of-treatment IDU) was self-treatment of dependence, particularly withdrawal symptoms. This is consistent with the finding that substantial proportions of out-of-treatment buprenorphine-naloxone injectors reported *never* experiencing precipitated withdrawal following injection of buprenorphine-naloxone.

The addition of naloxone to sublingual buprenorphine tablets reduces the extent to which the medication is injected by limiting the circumstances in which it can be injected. The inclusion of naloxone does not act as a deterrent in all situations, however. Clinical studies of buprenorphine-naloxone have demonstrated that the agonist-antagonist formulation was equivalent to mono-buprenorphine if taken sublingually, but could precipitate an uncomfortable withdrawal syndrome if injected by someone who is full-agonist dependent. Buprenorphine-naloxone may not have an aversive effect, however, if injected by a person who is (a) an irregular opioid

user; (b) a regular user of full-agonists who is experiencing severe withdrawal symptoms; or (c) a regular buprenorphine user only.

Localised patterns of drug use, or "drug cultures", can develop among small groups of personal networks. This study identified high levels of buprenorphine injection in some suburbs of Melbourne. These "hot spots" of buprenorphine injection may reflect differences in the practice of supervised dosing and may indicate the need for local, targeted responses. Alternatively, the higher levels of buprenorphine injection in Victoria might, more generally, reflect a lower threshold, more accessible model of treatment. By rapidly expanding OST provision through increased buprenorphine prescribing in primary care settings, the Victorian model may be attracting a more marginalised group of clients who would not have been in treatment otherwise.

The extent to which buprenorphine-naloxone is diverted and/or injected is not simply a function of its drug formulation. Naloxone only acts as a deterrent in a specific set of circumstances: when the person is a regular, dependent user of full-agonist opioids. Not all use of diverted medication was by injection and some IDU consumed the diverted drug as it was intended to be taken (sublingually).

Environmental variables that may influence diversion and injection of OST medications include: heroin availability and fluctations in price and/or purity; the availability of other (more desirable) pharmaceutical opioids; and the levels of background availability of OST medications.

Treatment variables also play a role, such as: insufficient OST places; accessibility/cost of treatment; dose adequacy; dissatisfaction with treatment medication's effects; theft or "standovers"; and differences in the extent to which supervised doses are directly observed.

The individual variables that influence diversion and injection include: ambivalence about treatment; a strong preference for (or difficulty stopping) injecting; willingness to help a friend in withdrawal; and concerns about being "registered". The price an individual is willing to pay for diverted buprenophine-naloxone will also depend on his or her motivations (e.g. seeking intoxication versus self-treating dependence) and whether or not he or she is in withdrawal and, therefore, experiencing a level of discomfort. The policy implications for these various motivations differ.

### 4.2. Implications for OST in Australia

Over the past 30 years of methadone experience, prescribers have developed an understanding that an individual patient's behaviour can never be predicted with certainty. Some level of non-adherence can be expected, as occurs in all areas of medicine. Experience also suggests that some diversion and injection of medications will occur among OST clients, and are to some extent (in the case of injection) tolerated. This study's findings suggest that supervised administration of doses does not prevent all non-adherent behaviours. Some buprenorphine and buprenorphine-naloxone clients removed supervised doses from the dosing site, and buprenorphine clients reported the highest levels of injection despite this group reporting higher levels of supervision.

Among the OST clients in this study, larger proportions received unsupervised methadone than unsupervised buprenorphine or buprenorphine-naloxone. Many clinicians appear willing to accept a level of risk associated with

methadone, despite the potential for overdose. Buprenorphine-naloxone is a safer medication in terms of overdose, and its potential for diversion and injection appears to be, at worst, the same as that for methadone (and may be less in some circumstances). There may be a case for relaxing the current level of regulation for buprenorphine-naloxone to allow for further expansion of low-threshold treatments in primary care settings. The issue is complex, however. Sublingual buprenorphine-naloxone is safer in overdose than methadone syrup, but the risks increase with concurrent use of depressants such as alcohol and benzodiazepines, or injection of the tablets (especially when secreted in the mouth).

The attractiveness of OST for some dependent opioid users may be compromised as a result of overly restrictive requirements. Methadone requires daily, and buprenorphine often requires daily or second-daily, attendance at a dispensing clinic or pharmacy. This limits a client's movements and his or her ability to work, especially if extended travel is involved. It is important that a range of treatment options be available and patients be informed about these options. Supervised administration of medication is costly and inconvenient to clients and pharmacists. Increased provision of unsupervised buprenorphine-naloxone doses for stable patients may prove an attractive addition to the OST program.

Given that the injection of buprenorphine-naloxone may not precipitate withdrawal among buprenorphine-maintained individuals, the present study's findings of lower levels of injection among the buprenorphine-naloxone clients need to be interpreted with caution. The lower levels of injecting may be an artefact of jurisdictional treatment policies. As buprenorphine-naloxone is the preferred medication for unsupervised dosing, it is reasonable to expect a larger proportion of clinically stable clients among the group receiving this medication.

Alternatively, anxiety about the effects of naloxone among opioid-dependent individuals may be driving the lower levels of buprenorphine-naloxone injection. If the effects of naloxone are overstated, OST clients may lose trust in the information given to them, and be less likely to share open accounts of their drug use, particularly harmful patterns use of use such as injection of their dose. Some KE (and their clients) reported the perception that buprenorphine-naloxone has been used as a punitive measure in some jurisdictions. These perceptions may impact on the ability of buprenorphine-naloxone to attract and retain people in treatment.

Responses that diminish harm related to non-adherence with OST, including diversion, are necessary, but punitive restriction upon patients and prescribers is unlikely to be effective. Responses need to be guided by the dual maxims of minimising harm and maximising therapeutic benefits. "Optimally-designed" drug diversion control programs have three goals: (i) to limit access to only those with a legitimate need for the drug; (ii) to track and identify cases where control over this access is compromised; and (iii) to minimise the effect of these controls on legitimate medical practice.

Evidence strongly suggests that higher OST doses are more effective in retaining patients in treatment, and reducing misuse, diversion and other opioid use. There is continued debate about the need for varied OST medications to assist different patients (e.g. heroin, morphine) who may not be adequately held by standard OST medications such as methadone and buprenorphine. There is also debate about the need for injectable forms of OST for those clients unwilling or unable to cease injecting. This group

is at risk of disengaging with treatment services through removal and injection of their dose secretly, which in turn can erode trust between clinicians and clients. Finally, diversion to assist other users obviously indicates a need for more treatment places of sufficient attractiveness to retain more users in treatment.

### 4.3. Implications for future research

Injecting behaviour, in itself, is rarely the focus of treatment, despite OST clients citing difficulty stopping injecting as the main motivation for non-adherence with OST. Route of administration has been acknowledged in tobacco cessation with the development of nicotine inhalers. Development of interventions for addressing injecting behaviour (psychosocial treatments and injectable forms of OST) and evaluations of their effectiveness are needed.

Further studies are also needed to evaluate clinical practices, such as whether the dilution of unsupervised methadone doses reduces injection, whether crushing buprenorphine tablets decreases the likelihood of clients removing supervised doses from the dosing site, and whether there is better treatment adherence among clients receiving higher doses of OST medications.

The evidence base for determining the severity of non-adherent behaviours, and differentiating between 'low', 'medium' and 'high risk' patients needs further research. The development and evaluation of new interventions to maximise adherence in OST are also needed.

The emergence of illicit markets for other opioid analgesics (such as morphine and oxycodone) in Australia also warrants further research. This research needs to consider the interface between treatment of opioid dependence and pain management.

### 4.4. Study limitations

Each data source used in this report has its strengths and limitations. The methodology was based on a number of cross-sectional surveys (not cohort studies) and convenience (not random) sampling, which limits the extent to which inferences can be drawn about the wider opioid-dependent population and changes in patterns of drug use among individuals over time. The comparison of multiple data sources (the surveys of IDU, OST clients, KE and prescribers, and population-level indicators of injection) is intended to minimise the potential biases and serves to validate the self-report of OST clients and IDU.

### 4.5. Conclusions

Agonist-antagonist formulations, such as buprenorphine-naloxone, may diminish abuse liability by injection, but will not deter all injection. The inclusion of naloxone appears to have reduced the extent to the medication is injected, given its availability, but has not led to a lower street price in Australia. This implies that the market for diverted medications is complex. There continues to be a place for other measures to reduce diversion and injection; agonist-antagonist formulations cannot replace risk assessment, careful patient selection for unsupervised dosing, and ongoing patient monitoring. These remain essential strategies for ensuring the safety and integrity of OST.

Post-marketing surveillance of new medications needs to be conducted over a sufficient time period to detect changes that occur with increased uptake of the medication and the development of experience. Ongoing surveillance of the injection of OST medications, and other

pharmaceutical opioids, is needed in Australia.

Finally, the findings of this study might change if key variables were to change; e.g. less regulated, widespread prescribing of buprenorphine-naloxone, the introduction of new drug formulations, or removal of the mono-buprenorphine product from the market.

# 1. THE POST-MARKETING SURVEILLANCE STUDIES OF BUPRENORPHINE-NALOXONE: INTRODUCTION AND BACKGROUND

## 1.1. Summary


- *Post-marketing surveillance studies* are usually observational in design and monitor the safety of new medications being used in real-life applications. Pre-marketing studies usually involve detailed protocol constraints and small sample sizes, and although they may suggest which medications are likely (or not likely) to be misused, they are limited in their ability to detect and quantify actual misuse.

- *Diversion* is used in this report to describe the unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended.

- *Adherence* is used to describe the taking of medication in accordance with prescription directions and the meeting of all the specified conditions of treatment (e.g. consumption of the dose under supervision, attendance at designated dosing times, meeting requests for urinalysis, etc). *Non-adherence* is, therefore, any use of a medication by the individual to whom it was prescribed where the medication was not taken exactly as directed. This includes (but is not limited to) removing all or part of a supervised dose from the dosing site for personal use or diversion to illicit markets; splitting doses; stockpiling doses; taking more or less than the prescribed dose; and injection of prescribed medication(s).

- Adherence to opioid substitution treatment (OST) is important for maximising a range of positive treatment outcomes, but is especially important in preventing injection, overdose, mortality and leakage of prescribed medication to the illicit market. To minimise the risks, the provision of OST is highly regulated (e.g. available only with an individual patient authority, licensing of doctors, and a strong focus on supervised administration of medication).

- The introduction of an agonist-antagonist formulation in Australia is a new approach to the problem to the problems of diversion and injection. Buprenorphine-naloxone is intended to deter injection of the medication, therefore reducing its attractiveness in illicit markets.

- Post-marketing surveillance of Suboxone® diversion was required as a condition of the product's registration in Australia.


(continued over page)

Summary (continued)

- The main aim of the post-marketing surveillance studies was to monitor the diversion and injection of the three OST medications in Australia for three years following the introduction of buprenorphine-naloxone (Suboxone®). This report seeks to answer the following questions:

    1. Is there injection of the agonist-antagonist formulation – bupreorphine naloxone – following its large-scale introduction into treatment programs for opioid dependence?
    2. To what extent is buprenorphine-naloxone injected compared to existing OST formulations, and in particular compared to the mono-buprenorphine product, among those receiving treatment and among out-of-treatment injecting drug users (IDU)?
    3. Is diverted buprenorphine-naloxone less attractive in illicit markets?
    4. What influences the diversion and/or injection of buprenorphine-naloxone?

## 1.2. Introduction

Pharmaceutical opioids prescribed for the treatment of opioid dependence (opioid substitution treatment, or OST) are effective in reducing drug use, criminal activity, HIV transmission and mortality[1-6]. There are also risks. Elevated mortality, particularly during induction onto methadone treatment, and "leakage" of prescribed medication to the black market are of particular concern[7-18]. To minimise the risks, the provision of pharmaceutical opioids is highly regulated. In Australia, OST is available only with an individual patient authority, from a doctor licensed to prescribe OST. There is also a strong focus on supervised administration of medication. Despite these strategies, some level of non-adherence and diversion occurs[19-39].

Pharmaceutical opioids, in general, differ in the extent to which they are likely to be misused, due to different potencies and *dependence liabilities*[1]. Different opioids also vary in the ease with which they can be injected (e.g. whether they are in injectable, tablet or patch form), and degree to which adverse effects occur following injection[40-42]. The diversion and injection of pharmaceutical opioids also depends on environmental variables. Availability plays an obvious role; the more available a medication is, the more opportunity there is for diversion and misuse[43]. The availability of pharmaceutical opioids is affected by the extent to which clinicians can and do prescribe different opioid medications, and how easy they are to obtain from a doctor. In addition, misuse and diversion will also depend upon the availability of other illicit drugs, particularly heroin and opium[44].

[1] The WHO defines dependence liability as "the extent to which a substance, as a consequence of its pharmacological effects on physiological or psychological functions, gives rise to dependence on that substance. It is determined by the intrinsic pharmacological properties that can be measured in animal and human drug testing procedures".

In the context of OST, diversion and injection of medication probably varies according to differences in prescribing, client supervision, dispensing practices, cost of treatment, the availability of other drugs and varied cultural factors (e.g.[26 28 45 46]). Supervised dosing, and both dilution of methadone takeaways and restricted access to syringes facilitating injection of large volumes, may reduce diversion and injection, respectively[21 30 36 45-48]. Despite the consequences for client and public health, few strategies to deter injection or reduce diversion have been empirically evaluated[44].

## 1.3. Definitions of diversion, adherence and non-adherence

Very often, the term *diversion* is unclear, yet definitional clarity is important for consistency in research, informing appropriate responses, and to consider appropriate policy responses for different behaviours. For researchers, clinicians, policy-makers and consumers to understand and communicate about the issues involved, there needs to be clear definitions of the problems. Different behaviours carry risks of differing severity, and responses (based on the dual maxims of minimizing harm and maximizing therapeutic benefits) need to be targeted accordingly.

Our definition of the terms *diversion*, *adherence* and *non-adherence* are summarised below. A more detailed discussion of terminology has been submitted as a paper for publication (See Appendix 1).

*Diversion* is used in this report to describe the unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended[49 50]. It does not refer to use of medications by a patient outside the doctor's recommended treatment regime.

In the context of opioid treatment, *adherence* is used to describe the taking of medication in accordance with prescription directions and the meeting of all the specified conditions of treatment (e.g. consumption of the dose under supervision, attendance at designated dosing times, meeting requests for urinalysis, etc). *Non-adherence* is, therefore, any use of a medication by the individual to whom it was prescribed where the medication was not taken exactly as directed. This includes (but is not limited to):

- removal of all or part of a supervised dose from the dosing site for personal use or diversion to illicit markets;
- splitting doses;
- stockpiling doses;
- taking more or less than the prescribed dose; and
- injection of prescribed medication(s).

Diversion and non-adherence with OST are associated with a range of harms, such as injection-related injuries and diseases, use among opioid-naïve individuals, dependence and overdose[9 11 19-39 51-63].

## 1.4. Background to the post-marketing surveillance studies

This report summarises the preliminary findings from post-marketing surveillance studies carried out by the National Drug and Alcohol Research Centre (NDARC) (from 2006 to 2008) following the listing of buprenorphine-naloxone on the Pharmaceutical Benefits Scheme (PBS) in April 2006. The studies compare the extent of diversion and injection of the three opioid medications registered in Australia for the treatment of opioid dependence: methadone syrup (registered as Methadone Syrup® and Biodone®), buprenorphine (registered as Subutex®) and buprenorphine-naloxone (Suboxone®).

Buprenorphine-naloxone is a new formulation of OST medication that was specifically developed to deter injection: buprenorphine (a partial opioid agonist) combined with naloxone (an opioid antagonist) in a 4:1 ratio [64-66]. Pre-marketing, experimental studies have shown that when taken *sublingually*, the combination drug's actions are indistinguishable from buprenorphine alone[65-67]. When *injected*, however, buprenorphine-naloxone can exert different effects depending on individual characteristics and patterns of drug use[65 66 68-74]. When injected by an individual dependent on a full agonist such as heroin or methadone (*not* in withdrawal), the combination product can precipitate a more aversive withdrawal syndrome than injecting buprenorphine alone[65 71 72 74]. When injected by individuals dependent on buprenorphine, or non-neuroadapted individuals, buprenorphine-naloxone may be reinforcing (although pleasurable opioid effects may be initially attenuated)[69 74]. There is only limited post-marketing data available, however, on the degree to which the inclusion of naloxone deters injection of the medication, and reduces its attractiveness in illicit markets in real-life settings.

*Post-marketing surveillance studies* are usually observational in design and monitor the safety of new medications in real-life applications. Clinical studies (conducted prior to marketing) usually involve detailed protocol constraints and small sample sizes, and although they may suggest which medications are likely (or not likely) to be misused, they are limited in their ability to detect and quantify actual misuse[75-81].

To the authors' knowledge, four studies of the diversion and injection of buprenorphine-naloxone have been conducted in non-experimental, real-life settings. In 1991 in New Zealand (NZ), the mono-buprenorphine product was withdrawn from the OST market and replaced with buprenorphine-naloxone, due to an escalating illicit market for diverted buprenorphine. Robinson et al (1993) conducted two surveys of OST clients: one just prior to the introduction of buprenorphine-naloxone (1990), and one following its introduction (1991/1992). They reported that in the period immediately following its introduction, buprenorphine-naloxone had a lower street price than buprenorphine, and was less attractive to some, but not all, groups of injecting drug users (IDU). There were some IDU who injected the medication, possibly in lower doses to avoid the aversive effects of naloxone[22]. The limitation of their study was that there was a timelag in the removal of buprenorphine, and some leakage of buprenorphine to the illicit market via importation. In addition, the self-report data was collected on entry to treatment, and new OST clients may have been reluctant to openly share accounts of illicit behaviour (their use of urine detection to validate self-report was limited by the short half-life of naloxone). This study examined misuse among a single population (new OST clients).

In the United States (US), Schuster and colleagues (Wayne State University) conducted post-marketing studies of buprenorphine (Subutex®) and buprenorphine-naloxone (Suboxone®) and the methodology of the present study (outlined in detail in Chapter 2) has been informed by their work [82]. Their studies of diversion mainly drew on data obtained from OST clients (using a tool they called the 'Product Familiarity Interview') and from ethnographers working with IDU, as well as a range of indicator data sources indicating harms (such as the DAWN system). Their conclusions were that Suboxone® had a low abuse and diversion potential, and the medication that was leaked was used mainly for what they termed *therapeutic* reasons (e.g. self-treatment of withdrawal symptoms). The major limitations of their data, however, were: no adjustments were made for background availability of the opioid medications studied; their interviews did not include out-of-treatment IDU (this group are most able to comment in detail on the illicit market for OST medications); and they did not collect data on the frequency of injection of OST medication [83].

In Finland, Alho and colleagues interviewed needle and syringe program (NSP) clients regarding their experiences with Suboxone®. They too concluded that buprenorphine-naloxone had a low abuse liability, and a lower street value than mono-buprenorphine[82]. The major limitation of this study was that the survey was conducted at a single point in time, with a single population, soon after the introduction of the newer formulation. The study, therefore, was potentially subject to expectancy biases, such as anxiety about the inclusion of naloxone and the prospect of precipitated withdrawal and/or the "novelty" of a new medication, both of which may change over time given more experience with the medication.

The most recently published post-marketing study of buprenorphine-naloxone injection was a study conducted in Malaysia by Bruce and colleagues (2009). The authors found that among the buprenorphine-naloxone injectors they interviewed, the majority had previously injected buprenorphine and approximately half increased the quantities injected following the switch to the new formulation. Their findings offer some support for the laboratory studies which suggest that buprenorphine-naloxone injection among buprenorphine-dependent individuals may still be reinforcing, despite the initial effects being attenuated by naloxone (e.g.[70]). Only a small sample (n=41) of current buprenorphine-naloxone injectors were interviewed, there was no comparison with other groups of IDU, and they did not examine other population-level indicators. As a result, they were unable to ascertain whether the newer combination formulation has had an impact on patterns of drug use at a population level.

Buprenorphine-naloxone (Suboxone®) was registered in Australia in 2005, and has been available on the Pharmaceutical Benefits Scheme since April 2006. A condition of the product's registration was that independent post-marketing surveillance of Suboxone® be carried out, with specific reference to a consideration of the extent of diversion and injection of the medication. The Company approached the NDARC to conduct this study independently, by way of an untied educational grant.

## 1.5. Aims of this report

The main aim of the post-marketing surveillance studies was to monitor the diversion and injection of the three OST medications in Australia for three years following the introduction of buprenorphine-naloxone (Suboxone®).

This report seeks to answer the following questions:

1. Is there injection of the agonist-antagonist formulation - buprenorphine-naloxone – following its large-scale introduction into treatment programs for opioid dependence?
2. To what extent is buprenorphine-naloxone injected compared to existing OST medication formulations, and in particular compared to the mono-buprenorphine product, among those receiving treatment and among out-of-treatment IDU?
3. Is diverted buprenorphine-naloxone less attractive in illicit markets?
4. What influences the diversion and/or injection of buprenorphine-naloxone?

With these questions in mind, the report is structured as follows:

- Chapter 2 gives an overview of the methods used and rationale for the data sources included in the post-marketing studies;
- Chapter 3 outlines the jurisdictional policy contexts and background availability of the three OST medications in the period immediately preceding and following the introduction of buprenorphine-naloxone;
- Chapter 4 examines the prevalence of key indicators of adherence with treatment as directed among clients receiving OST (specifically, the removal of supervised doses, diversion of doses and injection of their prescribed medication);
- Chapter 5 examines the prevalence, correlates and predictors of injection of OST medications among regular IDU(representing a group assumed to have accessed diverted medication);
- Chapter 6 describes the characteristics of the market for diverted OST medications, with particular focus on buprenorphine-naloxone; and
- Chapter 7 discusses the overall findings in light of the above research questions.

The outputs (conference presentations and papers) arising from the post-marketing surveillance studies to date are listed in Appendix 1. It is intended that further (more specific) investigations arising from the wider studies will be reported in the peer-reviewed literature.

## 1.6. Conclusions

Adherence to OST medication is associated with positive treatment outcomes. Non-adherence leads to morbidity/mortality among those in treatment and diversion of prescribed medications to illicit markets. To minimise the risks, the provision of OST is highly regulated (e.g. available only with an individual patient authority, licensing of doctors, and a strong focus on supervised administration of medication). The introduction of an agonist-antagonist formulation in Australian OST was a new approach to the problem. The inclusion of naloxone in buprenorphine-naloxone is intended to deter injection of the medication, therefore reducing its attractiveness in illicit markets.

The effects of injecting buprenorphine-naloxone vary according to individual characteristics and patterns of drug use, and the inclusion of naloxone may not act as a deterrent in all situations. The results of previous studies of buprenorphine-naloxone misuse are mixed and are limited by a number of methodological constraints, some of which are resolved by the study designs employed in this report. In general, however, the results from Schuster et al (2006) and Alho et al (2008) suggested that buprenorphine-naloxone has a lower 'abuse liability' and may have a lower street value, than mono-buprenorphine. The NZ experience indicates that in some circumstances, buprenorphine-naloxone may be misused, but still has beneficial applications.

This study collected data over a three-year period and from a wide range of sources. This is the first detailed examination of diversion and non-adherence comparing all three OST medications in Australia. It is the first study to make estimates of how frequently these behaviours occur, and the quantity of medication that is diverted, relative to the amount of OST prescribed. The specific indicators of diversion and non-adherence have been clearly defined. Among OST clients, the main indicators of adherence that were examined included the removal of supervised doses, injection of doses and selling/giving away medication. The indicators of the illicit market for diverted OST medications that were considered in this report include demand, source, street price and levels of injection.

Very often, the term *diversion* is unclear, yet definitional clarity is important for consistency in research, informing appropriate responses, and to consider appropriate policy responses for different behaviours. For researchers, clinicians, policy-makers and consumers to understand and communicate about the issues involved, there needs to be clear definitions of the problems. Different behaviours carry risks of differing severity, and responses (based on the dual maxims of minimising harm and maximising therapeutic benefits) need to be targeted accordingly.

# 2. METHODS

## 2.1 Summary

- The post-marketing surveillance studies utilised multiple data sources, each with its own strengths and limitations. Wherever possible, comparisons were made between methadone, buprenorphine and buprenorphine-naloxone across three Australian jurisdictions (NSW, VIC and SA).

- Data sources included: indicators of availability of OST medications; interviews with regular IDU; interviews with OST clients; interviews with KE; postal survey of authorised prescribers; and other indicator data sets.

- Measures of the relative availability of the three OST medications in the wider community are important for interpreting the levels of diversion and injection. The more widely available a medication, the more opportunity there is for that medication to be diverted and/or injected. Adjusting for availability enables better comparisons to be made between the three medications, and enables a better assessment of the impact of drug formulation. This is the first study of diversion and injection of buprenorphine-naloxone to make these adjustments. In Australia, sales data were the only national indicator to routinely separate the two buprenorphine formulations.

- Out-of-treatment IDU are the group that are most able to comment on the characteristics of the illicit market for OST medications and the extent to which diverted medication is injected. Approximately half the Illicit Drug Reporting System (IDRS) samples are in some form of OST (methadone, buprenorphine or buprenorphine-naloxone) in the six months prior to interview. As the IDRS intentionally recruits a 'sentinel' population of regular IDU (i.e. current, active participants in illicit drug markets who have been injecting regularly in the six months prior to interview), participants who report being in treatment cannot be taken as representative of treatment populations more generally. Accordingly, this report interviewed a separate study group of OST clients.

- OST clients were interviewed from three jurisdictions (NSW, VIC and SA). Recruitment strategies were targeted to ensure the sample was more representative of treatment populations (than those IDRS participants who reported being in treatment). Previous studies have identified that the blackmarket for OST medications in Australia can be characterised as large numbers of individuals sharing small quantities of medication between peers in a haphazard fashion. Quantifying the non-adherent behaviours among OST clients is important for understanding the dynamics of diversion and injection.

- Given the limitations with self-report and urine detection of buprenorphine-naloxone (due the short half life of naloxone), the study sought to validate the self-report of IDU and OST clients with data from KE and authorised prescribers. KE and prescriber views also provide important information on the wider context of service delivery and policy that may impact on the extent to which OST medications are misused.

(Continued over page)

Summary (continued)

- Although this study sought to include a range of population-level indicators of OST medication availability, patterns of use and harms, most indicator data sets do not routinely separate buprenorphine from buprenorphine-naloxone. The current study identified a limited number of data sources, mainly from NSPs, that enabled comparisons between methadone, buprenorphine and buprenorphine-naloxone, and these have been included in this report. This is an area that could be improved in routine Australian data collections.

## 2.2. Overview of the methodology

The post-marketing surveillance studies of buprenorphine-naloxone are observational studies that utilise data from cross-sectional surveys of opioid dependent persons in and out-of-treatment over the period 2003-2008. The cross-sectional surveys provide data on the self-reported prevalence and frequency of injecting various pharmaceutical opioids, including methadone syrup, the originally marketed form of buprenorphine, buprenorphine-naloxone and other pharmaceutical opioids. These surveys have been triangulated with data from a number of different sources (detailed below).

Each data source has its own strengths and weaknesses, and the methods are intended to complement and supplement each other. Wherever possible, comparisons have been made between methadone, buprenorphine and buprenorphine-naloxone. Given important differences across Australia in treatment options, illicit drug markets and policy contexts, the studies also compare diversion and injection of OST medications in three Australian jurisdictions (SA, VIC and NSW) with different prescribing policies, treatment settings and geographic patterns of drug use.

The data sources used in the post-marketing surveillance studies include:

- indicators of availability of OST medications (sales/prescription data);
- interviews with regular IDU;
- interviews with OST clients;
- interviews with KE;
- postal survey of authorised OST prescribers; and
- other indicator data.

Each data source is outlined in detail below.

## 2.3. Data sources

### 2.3.1. Indicators of exposure to OST medications

The present study sought to obtain data indicating the relative extent of exposure to methadone, buprenorphine and buprenorphine-naloxone in the community. Unfortunately, some jurisdictions do not reliably separate buprenorphine from buprenorphine-naloxone in prescription data and routine data monitoring numbers of patients. The most reliable indicator of exposure (separating methadone, buprenorphine and buprenorphine-naloxone) available to the present study was sales data.

National sales data for buprenorphine and buprenorphine-naloxone were provided by IMS/Reckitt Benckiser, who also provided commercially available data on sales of Methadone syrup® and Biodone®. Sales data were expressed in 'factored units' of average daily doses of methadone in Australia assumed to be 70 mg, and average doses of buprenorphine assumed to be 12mg; these levels are derived from previous research on client doses in Australia[84 85]. It was estimated that market share apportioned across the three OST medications could be accurately derived from sales data provided by IMS/Reckitt Benckiser. While sales data gives a reasonable indication of the number of client doses of the three medications, it does not give an indication of the number of patients.

### 2.3.2. Regular out-of-treatment IDU

The Illicit Drug Reporting System (IDRS) has been monitoring Australian drug trends nationally since 2001. Although the study draws on a number of different data sources, the key component is the annual interviews with a sentinel sample of approximately 900 regular IDU [86]. IDU are recruited in each capital city around the country. To be eligible for participation, IDU are aged 17 years and older; have injected at least monthly in the six months prior to interview; are resident for at least twelve months in the city in which they are interviewed; and report no significant periods of incarceration, rehabilitation or other time away [87]. Having been recruited on this basis, the IDRS sample of IDU are able to comment in detail on inner-city drug markets, where emerging trends are most likely to be observed. They also represent a group who are able to comment on the availability of diverted OST medications.

The core IDRS interview monitors patterns of drug use and includes questions on price, purity and availability of the main drug types. In 2006-2008 (specifically for the post-marketing studies) additional questions were included in the interview regarding methadone, buprenorphine and buprenorphine-naloxone use, injection, availability and street price.

Approximately half the IDRS samples are in some form of OST (methadone, buprenorphine or buprenorphine-naloxone) in the six months prior to interview. As the IDRS intentionally recruits a 'sentinel' population of regular IDU (i.e. current, active participants in illicit drug markets who have been injecting regularly in the six months prior to interview), participants who report being in treatment cannot be taken as representative of treatment populations more generally (our separate study of OST clients is documented

below). To give the best indication of the illicit market, and use of OST medications among regular IDU not in treatment, the in-treatment group were excluded from the majority of analyses. Wherever possible, we directly compared the diversion and injection of methadone, buprenorphine and buprenorphine-naloxone among out-of-treatment IDU. Table 1 below lists the proportions of IDU who have been included in the analysis for this report. Approximately 450 out-of-treatment IDU were interviewed for the IDRS from 2006 to 2008.

**Table 1: IDU included in this analysis**

| | 2006 N=914^ | 2007 N=909^ | 2008 N=909 |
|---|---|---|---|
| Number of IDU who reported currently receiving some form of OST (methadone, Subutex, Suboxone) in last six months* | 465 | 448 | 456 |
| Number of IDU NOT in any form of OST in past six months | 448 | 453 | 444 |

** this group has been excluded from analyses in this report. In future, all references to out-of-treatment IDU include only those IDU who have not been in any form of OST in the six months prior to interview, unless otherwise stated.*
*^ 1 case missing data in 2006, 8 cases missing data in 2007, 9 cases missing data in 2008*

Tables outlining the patterns of illicit drug use and alternate routes of buprenorphine/buprenophine-naloxone administration are presented in Appendix 2. Greater detail on previous years of the IDRS data collection may be found at http://ndarc.med.unsw.edu.au/NDARCWeb.nsf/page/IDRSa.

There are limitations of self-report data, although self-report from illicit drug users has been shown to be sufficiently reliable to monitor patterns of drug use[88]. The other major limitation is that the IDU interviewed in the IDRS cannot be taken to represent all IDU nationally. For example, IDU living in remote and rural regions may report different patterns of drug use. The advantage of the interview data from out-of-treatment IDU is the detail provided on the street price, patterns of use and frequency of injection, which are essential in characterising the illicit market for OST medications. By using the existing IDRS framework, the data has been collected in a consistent manner in the period preceding and following the introduction of buprenorphine-naloxone, allowing trends to be examined across time.

### 2.3.3. OST clients

Previous studies have suggested that the illicit market for diverted medications is characterised by a large number of individuals sharing medications in a haphazard fashion[89], although few studies have examined the specific behaviours among treatment populations (i.e. injecting, saving, sharing, selling or giving away of medications to individuals to whom it was not prescribed)[29 34 35 48 90 91]. The present study interviewed independent samples of methadone, buprenorphine and buprenorphine-naloxone clients on two occasions during the post-marketing period for buprenorphine-naloxone (mid-year in 2007 and again in 2008) regarding diversion and injection of the medications prescribed to them for the treatment of opioid dependence.

Participants were recruited from OST services in the three study jurisdictions: SA, VIC and NSW. Recruitment strategies were targeted in each jurisdiction to ensure representation from a range of treatment settings that reflected the mix of public clinics, private clinics, general practice, and pharmacy dispensers in that jurisdiction. To be interviewed for the study, participants had to be aged 18 years and older; and had to have been in their current treatment episode for at least one month.

OST clients were asked similar questions to those asked in the IDRS, as well as questions regarding adherence with treatment, the removal of supervised doses from the dosing site, selling or giving away medications to others, and injection of their medication.

The study did not recruit its target sample size of 50 methadone, 50 buprenorphine and 50 buprenorphine-naloxone clients in SA, VIC and NSW (i.e. total of 450 pharmacotherapy clients each year). This was due to jurisdictional differences in the market penetration of the different OST medications (see Chapter 3 for more detail). In VIC, where there was rapid uptake of buprenorphine-naloxone, it was difficult to recruit clients still receiving the mono-buprenorphine product. In NSW, where fewer OST clients were prescribed buprenorphine-naloxone, particularly during 2007, it was very difficult to recruit buprenorphine-naloxone clients. The pharmacotherapy client sample sizes for 2007 and 2008 are summarised below in Table 2.

**Table 2: Number of participants (N) interviewed by OST type and jurisdiction, 2007-2008**

| | 2007 | | | | 2008 | | | |
|---|---|---|---|---|---|---|---|---|
| | **SA** | **VIC** | **NSW** | **TOTAL** | **SA** | **VIC** | **NSW** | **TOTAL** |
| Methadone | 50 | 50 | 57 | **157** | 51 | 49 | 53 | **153** |
| Buprenorphine | 29 | 36 | 61 | **126** | 37 | 51 | 61 | **149*** |
| Buprenorphine-naloxone | 41 | 64 | 11 | **116** | 55 | 63 | 20 | **138** |
| **TOTAL** | **120** | **150** | **129** | **399** | **143** | **163** | **134** | **440** |

** In 2008, there were 13 clients who received mono-buprenorphine product for supervised doses and buprenorphine-naloxone for takeaway doses.*

The interviews with OST clients are subject to the limitations of self-report. Illicit drug use, and in particular injecting drug use, is a highly stigmatised activity. The 'illicit' nature of this behaviour is heightened further in the context of treatment (or specifically, non-adherence with treatment). The study took measures to minimise perceived pressure among OST clients to respond in a socially-desirable manner. All interviews were conducted by researchers who were independent of the treatment services from which the OST clients were recruited. Although recruitment fliers were displayed at treatment services and pharmacies, interested participants contacted the researchers directly (by phone). In this initial phone call, it was explained to participants that the research involved questions about occasions when they did not necessarily follow 'treatment as directed'. All interviews were conducted at neutral locations (most commonly, the research organisations' offices, cafes or public locations). The interviews were treated as confidential and no feedback was given to those OST services and pharmacies who advertised the study regarding whether or not individuals had participated in the research.

The interviews with OST clients gave important data on the attractiveness of the OST medications in terms of diversion and injection. The interviews also gave estimates of how frequently non-adherence occurs relative to the overall level of OST provision.

### 2.3.4. KE

A total of 73 KE were interviewed in 2007 and again in 2008. KE in this study are professionals, who, through the nature of their work, have regular contact with opioid-dependent persons and/or possess knowledge of issues relating to diversion and injection of OST medications.

To be eligible as KE, participants had at least weekly contact with opioid-dependent persons, and/or contact with a minimum of 10 different opioid-dependent persons, or regular IDU, in the six months preceding the interview. All but seven KE satisfied these criteria, the former being: a public drug service manager; five Government department heads/ policy officers; and a researcher. Although these KE had no direct contact with opioid-dependent people in the last six months, all were interviewed for this project because they were considered to have in-depth knowledge of OST delivery, diversion and/or buprenorphine-naloxone.

The study interviewed a broad range of KE, including drug treatment workers (nurse unit managers, community health centre/drug service managers, counsellors and MSIC staff), health education officers (NSP workers and outreach workers), GP prescribers, dispensing pharmacists, researchers, policy officers and user group representatives. Similar to the OST client samples, KE were drawn from a range of geographical areas across Sydney, Melbourne and Adelaide.

In 2007, 39 KE were interviewed (18 males, 21 females). In 2008, 24 of the original KE from 2007 were re-contacted, representing a follow-up rate of 62%. The primary reason original KE were not re-interviewed was because they had since left the drug and alcohol field and/or no longer satisfied inclusion criteria. Eight new KE were interviewed in 2008.

The KE interview schedule was a semi-structured instrument, which covered similar topic areas to the OST client interview. The interview included sections on: background

demographics; diversion of OST to illicit markets; injection of OST; advantages/limitations of buprenorphine-naloxone; and general comments. The confidential phone interviews took approximately 45 to 60 minutes to conduct (range 30-105 minutes), depending on the knowledge and confidence of the participant. Detailed notes were taken during the interview and transcribed in full afterwards. The content of open-ended responses were analysed by theme.

When the interviews were conducted in 2007, most KE (with the exception of perhaps some VIC KE and prescriber KE) felt that they had not had sufficient experience with buprenorphine-naloxone to evaluate its impact with confidence. A substantial minority of KE still felt this was the case when interviewed 12 months later. As many KE were selected on the basis of their frequent contact with regular IDU, and not their specific knowledge of buprenorphine-naloxone, they were not necessarily knowledgeable of the detailed pharmacokinetics of the medication. KE reports may have been subject to expectancy biases, specifically relating to the deterrent effects of naloxone.

The advantage of the KE interviews is that their comments place the reports of out-of-treatment IDU and OST clients in the wider social context of jurisdictional policy and the challenges of providing treatment services.

### 2.3.5. Authorised prescribers

A national postal survey of authorised opioid substitution prescribers (N=300) was conducted in 2007. The survey assessed their experiences of diversion of methadone, buprenorphine and buprenorphine-naloxone. Information was collected on: demographics and treatment setting; reports of non-adherence, diversion, injection and 'doctor shopping' for multiple prescriptions; and harms associated with diversion and injection. A series of statements were devised to elicit prescribers' level of self-confidence in assessing and responding to diversion/injection, views on takeaway policies and usefulness of guidelines assessing client stability.

Health departments of each jurisdiction provided lists of all active OST prescribers (total N=1,278) and each prescriber was sent by mail a survey, information sheet and consent to participate form during May to August 2007. In VIC the mail-out was performed by WFDS Pty Ltd on behalf of the Department of Human Services. In all other jurisdictions, the mail-outs were managed by NDARC researchers. Reminder letters were sent at weeks four and eight after the initial mail-out, and prescribers who returned their surveys went in a draw to receive book vouchers.

Although the overall response rate for this survey was low (23%, see Table 3 for more detail), the total number of clients served by participating prescribers was 12,045 for methadone (approximately 44% of methadone clients Australia-wide at June 2007[92]), 2,715 for buprenorphine (approximately 39% of buprenorphine clients nationally) and 3,838 for buprenorphine-naloxone (approximately 97% of buprenorphine-naloxone clients nationally, although the data for the number of buprenorphine-naloxone patients nationally may be less reliable)[92]. Many prescribers with large numbers of clients were among those who returned the survey.

**Table 3: Prescriber response rate by jurisdiction**

| State | No. of prescribers sent surveys | No. of completed surveys returned | % of total surveys returned |
|---|---|---|---|
| **NSW** | 540 (42%) | 132 | 44 |
| **VIC** | 467 (37%) | 73 | 24 |
| **SA** | 65 (5%) | 26 | 9 |
| **QLD** | 106 (8%) | 32 | 11 |
| **NT** | 9 (<1%) | 3 | <1 |
| **TAS** | 35 (3%) | 13 | 4 |
| **WA** | 56 (4%) | 22 | 7 |
| **TOTAL** | **1,278 (100%)** | **301*** | **100 (%)** |

** 10 surveys missing prescribing data were excluded from analysis, leaving n=291*

Table 4 (below) summarises some of the key characteristics of participating prescribers. The majority of authorised prescribers were male (74%), working from a general practice (53%), in a metropolitan region (67%), with clients who were dosed from a community pharmacy (75%).

**Table 4: Participating prescriber characteristics (N=291)**

| Characteristic | % respondents |
|---|---|
| Sex[1] | |
| Male | 74 |
| Female | 26 |
| Location of prescriber[2] | |
| Rural | 33 |
| Metropolitan | 67 |
| Main prescribing setting | |
| A general practice | 53 |
| A public clinic | 28 |
| A private clinic | 9 |
| A correctional setting | 3 |
| 'Other' settings | 7 |
| Main dosing setting | |
| Pharmacy | 75 |
| Public clinic/hospital | 16 |
| Private clinic | 4 |
| Correctional setting | 3 |
| Doctors surgery | 2 |
| Detoxification unit | <1 |
| Primary prescriber of | |
| Methadone (n=274) | 94 |
| Buprenorphine (n=211) | 73 |
| Buprenorphine-naloxone (n=171) | 59 |
| Prescribing to at least one client receiving | |
| Methadone takeaways | 97 |
| Buprenorphine takeaways | 50 |
| Buprenorphine-naloxone takeaways | 90 |
| Number of clients per prescriber | Median (range) |
| Methadone | 24 (1 - 420) |
| Buprenorphine | 6 (1 - 210) |
| Buprenorphine-naloxone | 7 (1 - 550) |

[1] *4 cases missing data*
[2] *12 cases missing data*

There are limitations of the prescriber survey findings. The results are based on prescriber perceptions of diversion and injection rather than actual frequency. It is difficult to control for clinician expectation regarding the deterrent effects of naloxone. These prescribers were surveyed very early on in their experience of working with buprenorphine-naloxone (mid-2007), and if they were surveyed again now, they may report differently.

This survey is the first in Australia to document prescribers' views on the issues relating to diversion and injection of OST medications and their evaluation of the relative risks and harms. Although the response rate was 23%, those prescribers who participated in the survey were providing OST to a large proportion of Australian OST clients, particularly buprenorphine-naloxone clients. This group were best able to compare the drug formulations. They also provided useful comments on jurisdictional policies.

### 2.3.6. Other (population-level) indicators

The study identified secondary data sources, such as NSP collections, that indicate the extent of diversion and injection of OST medications. *Last drug injected* data is reported from the following collections:

- Medically Supervised Injecting Centre (MSIC) (Sydney, NSW);
- Australian NSP survey (NCHECR, UNSW);
- Biala NSP (Brisbane, QLD);
- Brisbane Harm Reduction Service (BHRS, QLD).

Although this study sought to include a range of data sources giving an indication of availability, patterns of use and harms, most indicator data sets do not routinely separate buprenorphine from buprenorphine-naloxone. These studies identified some data sources, mainly from NSPs, that enabled comparisons between methadone, buprenorphine and buprenorphine-naloxone. This is an area which could be improved in routine Australian data collections.

The data collected by the MSIC and the Australian NSP survey were subject to these limitations; the occasions of buprenorphine-naloxone injection are not routinely separated from those for mono-buprenorphine (i.e. the global category is recorded as 'buprenorphine' and buprenorphine-naloxone is only recorded in free-text fields when specifically mentioned). The Brisbane NSP collections (Biala NSP and BHRS), however, do routinely make these separations.

Indicator data sets are not subject to the same biases as cross-sectional surveys. The NSP data provides population-level indicators of OST medication injection, relative to the injection of heroin and other pharmaceutical opioids (such as morphine, oxycodone, etc). This data will inform our understanding how much opioid injection involves OST medications compared to other pharmaceutical opioids.

## 2.4. Conclusions

The post-marketing surveillance studies utilised a range of data sources, each with its own strengths and limitations. Wherever possible, comparisons were made between methadone, buprenorphine and buprenorphine-naloxone.

To answer the question of whether there is injection of buprenorphine-naloxone following its large scale introduction to OST in Australia, the study used national sales data to give an indication of the level of uptake by jurisdiction, and examines reports of injection among out-of-treatment IDU and OST clients via cross-sectional surveys and NSP data collections.

To assess the extent of buprenorphine-naloxone injection, quantitative comparisons were made with methadone and buprenorphine injection (among two key populations: regular IDU and OST clients), adjusting for background level of OST provision. Qualitative data from KE interviews and the postal survey of prescribers also provides an indication of the scale of the problem and related harms.

The key data source used to assess whether diverted buprenorphine-naloxone is attractive in illicit markets were the cross-sectional interviews with out-of-treatment IDU. These interviews provided data on demand, source and street price as well as levels of injection. The data from OST clients, KE and authorised prescribers served to validate the IDU reports.

All of the above data sources were used to consider what influences the diversion and/or injection of buprenorphine-naloxone at an individual, and population, level.

# 3. OVERVIEW OF OST IN AUSTRALIA

## 3.1 Summary

- Methadone retains the largest OST marketshare nationally (approximately 70-75% of all OST medication sales). Buprenorphine (any form, including mono-buprenorphine and buprenorphine-naloxone) retains approximately 25-30% of the marketshare nationally, and this proportion has remained stable since July 2006. Buprenorphine-naloxone sales now outstrip those for mono-buprenorphine.

- In general, OST medication in Australia is administered under supervision. There is provision for unsupervised administration of doses, mainly for methadone and buprenorphine-naloxone, and extremely limited provision for unsupervised buprenorphine. The proportion of OST clients being administered their doses under supervision is not monitored in routine data collections at a national level.

- The main benefits of supervised administration of doses include the close supervision and monitoring of patients, maximising adherence with treatment, reducing the risk of consumption other than as prescribed, minimising the risk of diversion to the illicit market, and reducing the risk of injection. There are disadvantages. Supervised administration of doses can be costly in terms of clinician/pharmacist/client time, and the constraints imposed by services administering supervised doses (such as restricted opening hours and dosing times, and queuing with other service clients) can be in themselves barriers to participating in treatment and social reintegration.

- The level of supervision (described as high, medium, low and minimal in this report) is determined by an individualised risk assessment. Minimal supervision (defined in this report as receiving 20 or more unsupervised doses per month, sometimes even 28-day dispensing) is only available to clients who are stable on buprenorphine-naloxone.

- NSW, VIC and SA have taken different approaches to incorporating buprenorphine-naloxone in their OST policies. These policy differences were associated with differences in the uptake of buprenorphine-naloxone: VIC sales data showed high levels of market penetration; SA data showed average market penetration; and NSW data showed low market penetration.

- The background availability of OST medications is important when considering the extent of diversion and injection. If a medication is widely available in the general community, there are more opportunities for diversion and/or injection (than a medication that is less available).

## 3.2 Introduction

This chapter gives an overview of OST in Australia just prior to and following the introduction of buprenorphine-naloxone. It outlines the national policies for supervised and unsupervised administration of doses. Supervising the administration of the dose is the main strategy for managing the risks associated with OST (in particular, the risk of diversion, injection, use among opioid-naïve individuals, and overdose). This chapter also summarises the approaches of the three study jurisdictions (NSW, VIC and SA) in incorporating buprenorphine-naloxone into their existing OST policies.

## 3.3. Methods and data sources

To give an indication of the availability of the three OST medications in the general community, this chapter examines data from the National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) collection and pharmacotherapy sales data provided by Reckitt Benckiser (via IMS Health). This chapter also draws on the interviews with KE for their evaluation of the implementation of buprenorphine-naloxone in each jurisdiction (NSW, VIC and SA).

## 3.4. The supervised and unsupervised administration of OST medications in Australia

### 3.4.1. Supervised administration of doses

OST clinics (private or public) and approved pharmacies can dispense methadone, buprenorphine and buprenorphine-naloxone according to the prescribing doctor's specified dosing plan. When commencing treatment, clients usually attend the clinic or pharmacy to take their doses under supervision. In most jurisdictions, OST doses are generally administered under supervision on a daily basis. Supervised administration involves a pharmacist or clinician directly observing the client consuming the dose. In the case of buprenorphine or buprenorphine-naloxone, the tablet(s) are held under the tongue, where they take between eight and 15 minutes to dissolve (depending on the dose and individual variability)[65 93]. Some pharmacists/clinics crush or break the tablets to speed up absorption time. In the case of methadone, the syrup is swallowed.

Although the supervised administration of doses is resource-demanding (in terms of client and pharmacist/clinician time, etc), the benefits include:

- close supervision and monitoring of patients;
- maximising adherence with treatment and minimising the risk of consumption other than as prescribed;
- minimising the risk of diversion to the black market; and
- minimising the risk of injection[94 95].

Supervised dosing, however, does not eliminate all diversion and injection of medication among OST clients and some leakage occurs. For example, one study has suggested that where buprenorphine is dispensed through community pharmacies (as opposed to specialist drug treatment clinics), pharmacists suspect a high level of diversion[36]. There are also other disadvantages. For some individuals, the constraints imposed by services administering supervised doses (such as restricted opening hours and dosing times, and queuing with other service clients) can be in themselves barriers to participating in treatment and social reintegration [48 96 97].

### 3.4.2. Unsupervised administration of doses ('takeaways')

Some OST clients may be eligible for some unsupervised doses of their medication (i.e. they are dispensed their medication to take without being directly observed by a pharmacist/clinician). Policies for unsupervised doses of methadone are determined for each jurisdiction in line with the National Policy on Methadone Treatment[98-100]. The policy for unsupervised dosing of buprenorphine and buprenorphine/naloxone is determined by each Australian jurisdiction[92]. Prescribers need to check with the relevant authority in their jurisdiction as to which formulation of buprenorphine is used for unsupervised dosing[101].

In order to prescribe unsupervised (or 'takeaway') doses of OST medication in Australia, practitioners need to undertake individualised risk assessments with each patient, conduct appropriate patient education, monitor the patient's progress, and reassess suitability over time[92 94]. The decision-making process needs to be clearly documented on the patient's medical file. In assessing a patient's suitability for unsupervised dosing, the national buprenorphine guidelines highlight three broad domains for consideration:

- **Continued dependent use or misuse of drugs**: Continued dependent use or misuse of drugs (opioids, benzodiazepines, alcohol, psychostimulants) is a contra-indication to providing regular unsupervised/takeaway doses.
- **Risk assessment**: Some situations are definite contra-indications to prescribing unsupervised doses, and others are relative contraindications.
- **Access issues:** Access to OST may be limited by geographic factors or work commitments. For some buprenorphine clients, reducing the frequency of supervised administration to alternate days or three times a week may minimise the burden of travel. For methadone clients, and some buprenorphine clients, this is not an acceptable alternative. In these cases, there are grounds for prescribing unsupervised doses as long as there are no contra-indications[94].

The jurisdictional health department policies outlining eligibility and number of unsupervised doses (or 'takeaways') vary around the country, although all policies are guided by the above principles. The level of supervision is matched to the clinician's assessment of client stability, ranging from minimal to low supervision (for stable clients), to medium to high levels of supervision (for less stable clients requiring a higher level of monitoring and support). This report has defined high, medium, low and minimal supervision based on the number of unsupervised doses permitted in the NSW, VIC and SA methadone and buprenorphine policies (Table 5 below). This approach has not taken into account differences in jurisdictional policies regarding the required period of time in treatment and key indicators of stability.

**Table 5: Summary of the supervision levels for administering OST medications as used in this report**

| Level of supervision | Number of unsupervised ('takeaway') doses permitted |
|---|---|
| HIGH | 0-1 takeaway dose in past month |
| MEDIUM | 2-8 takeaway doses in past month |
| LOW | 9-20 takeaway doses in past month |
| MINIMAL* | 20+ takeaway doses in past month |

*Note: This summary is based on the numbers of takeaway doses permitted in NSW, VIC and SA policies only. There are jurisdictional differences in the number of takeaway doses permitted, the dilution of methadone takeaways, the required period of time in treatment and the key indicators of stability.*
** Buprenorphine-naloxone only*

In general, methadone and buprenorphine-naloxone can be prescribed as unsupervised doses. The provision of unsupervised buprenorphine is highly restricted and only permitted for those buprenorphine clients who are pregnant, breastfeeding, or have an identified naloxone allergy, and in States where there is a reliance on pharmacies that only operate six days per week.

The extent to which unsupervised doses may be associated with extensive misuse or diversion probably varies across pharmaceutical opioid preparations and geographic location. Different geographic regions of Australia have different patterns of availability of illicit drugs and different patterns of drug use.

Dispensed doses that can be administered without the constraints of supervision are greatly valued by OST clients. They enable clients to work, study, travel and lead more normal lives[48 102]. This in turn has obvious benefits to those clients who have achieved a degree of stability in terms of drug use and lifestyle. If buprenorphine-naloxone is safer, both in terms of overdose and in terms of its propensity for diversion and injection, then this may lead to more flexible treatment options for stable clients.

Despite the development of policies that reduce the risks associated with OST, some level of non-adherence with policy requirements and prescription directions occurs, as does diversion and injection.

## 3.5. The introduction of buprenorphine-naloxone in South Australia, Victoria and New South Wales

Across Australia, jurisdictional health departments have taken different approaches to the introduction of the buprenorphine-naloxone formulation. Some have adopted buprenorphine-naloxone in preference to mono-buprenorphine for all buprenorphine clients (e.g. Western Australia and Queensland) for both supervised and unsupervised administration. In NSW, where a larger number of clients are dosed from specialist clinics than in other jurisdictions, the introduction of buprenorphine-naloxone has been seen as an opportunity to provide unsupervised dosing of buprenorphine to stable clients (with a view to future dosing being moved from public clinics to community pharmacies)[102], thus freeing up treatment places for waitlisted patients. In general, most jurisdictions have allowed takeaway doses of buprenorphine-naloxone, but have very restricted takeaway doses of buprenorphine (if any). The policy approaches of the three study states (NSW, VIC and SA) are outlined in more detail in Appendix 3.

OST in NSW has been dominated by methadone and there has always been a comparatively flexible methadone policy (methadone takeaways are not diluted in NSW). The NSW approach to buprenorphine-naloxone has been even more flexible with regard to the number of takeaways (NSW permits up to 28 days dispensed medication for long-term, stable clients), but has a higher threshold for buprenorphine-naloxone treatment than any other jurisdiction. Patients are stabilised on the mono-buprenorphine product for a minimum of three months before transferring to buprenorphine-naloxone for takeaway medication (where requested and when assessed as suitable). Prescribers in NSW are required to undergo an additional Advanced Prescribers Training Module to be able to prescribe buprenorphine-naloxone. This training focuses on the assessment of client stability and suitability for unsupervised administration of buprenorphine-naloxone[103]. Unlike SA and VIC, the NSW policy does not actively encourage the use of buprenorphine-naloxone in supervised settings for clients who are persistently removing supervised doses to inject and/or divert to the illicit market.

Prior to 2006, VIC had a highly restrictive policy regarding both methadone and buprenorphine takeaways. The old policy permitted a maximum of one unsupervised dose per week for stable clients, or three unsupervised doses in exceptional circumstances for one week per month. Anything outside of this allowance had to be arranged via permits obtained through Drugs and Poisons Unit, Department of Human Services. The VIC policy also mandates the dilution of unsupervised methadone and the crushing of supervised buprenorphine doses. Previous studies have suggested that among those IDU who inject medications, the dilution of methadone takeaways may have displaced the problem of OST injection to buprenorphine (which is easier to secret out of the dosing site) [48]. In VIC, the introduction of buprenorphine-naloxone coincided with a major review of takeaway policies for all OST medications. The new policy provides a structured (checklist) assessment of client stability, which in turn specifies the appropriate level of supervision for dosing (low, medium or high). Patients who are on high levels of supervision are not eligible for takeaways – all doses are supervised. The low level of supervision permits a maximum of five unsupervised doses of dispensed medication per week. Even at the 'low' level of supervision in VIC, patients must attend for supervised administration two days per week. There is some provision for 'minimal' supervision of buprenorphine-naloxone administration, but this must be arranged through the Drugs and Poisons Unit[104].

Prior to the introduction of buprenorphine-naloxone, SA had a more liberal buprenorphine takeaway policy than VIC or NSW as a result of a reliance on some pharmacies that are open six-days per week for dispensing. All new patients are dosed at seven-day pharmacies where possible (although one unsupervised dose per week is permitted where this is not possible). After two months of treatment, stable clients are permitted six takeaways doses per month; after nine months, 12 takeaway doses per month are permitted; and after 18 months, up to 18 takeaway doses per month are permitted. Their revised policy allows for both buprenorphine and buprenorphine-naloxone takeaways. Mono-buprenorphine takeaways are permitted for those clients who were already receiving buprenorphine takeaways at the time buprenorphine-naloxone was introduced. Otherwise, buprenorphine-naloxone is encouraged for all new buprenorphine patients, when initiating takeaways or where the patient is suspected of diversion[105-107].

## 3.6. Uptake of buprenorphine-naloxone

### 3.6.1. Number of clients in opioid-substitution treatment in Australia

The National Opioid Pharmacotherapy Statistics Annual Data (NOPSAD) collection has collected data on OST clients in Australia since 2005. The data are based on an annual 'snapshot' day, usually a specified day mid-year. Caveats apply to the data however, largely arising from jurisdictional differences in monitoring and reporting[92].

In 2007, there were approximately 38,500 clients in OST nationally. The largest proportions of clients were in NSW and VIC, which together accounted for approximately 70% of the treatment population nationally. Although, nationally, the number of clients in OST has increased by approximately 50% since 1998, the numbers have remained stable since 2004 [92]. Introducing buprenorphine-naloxone in Australia has not led to an increase in the total number of people receiving treatment for opioid dependence.

The 2007 NOPSAD report indicates that approximately 10% of clients in OST were receiving buprenorphine-naloxone on the 'snapshot' day (5.5% in 2006)[92]. There were, however, recording issues in NSW and QLD: these States (which together accounted for 54% of all OST clients nationally) could not provide the NOPSAD collection with data separating buprenorphine clients from buprenorphine-naloxone clients. Of the remaining jurisdictions able to identify clients receiving buprenorphine-naloxone (which collectively accounted for 46% of all OST clients nationally), the largest number of clients were in VIC and WA: 22-26% of OST clients in these States received the buprenorphine-naloxone formulation [92].

### 3.6.2. Sales data

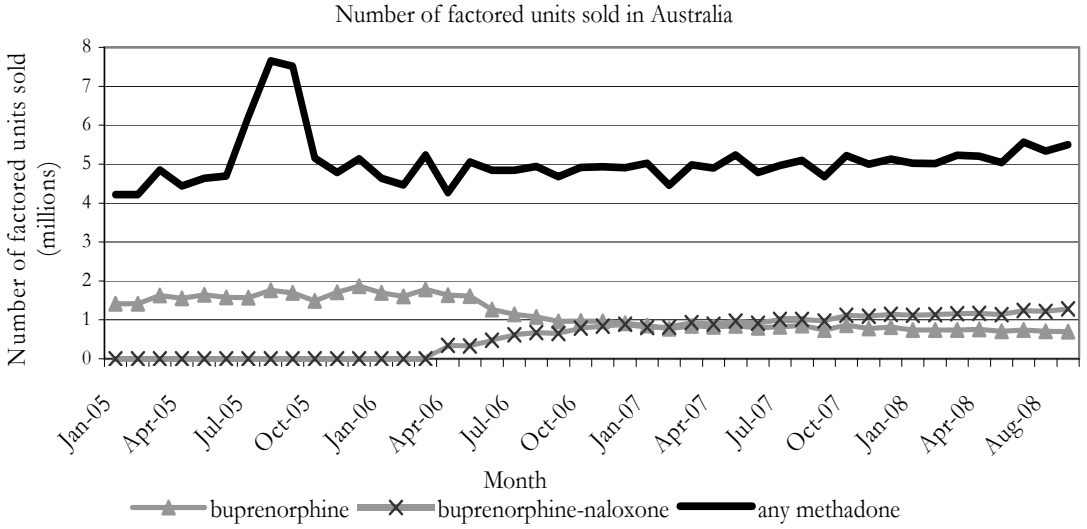
For the present studies, the best available indicator of buprenorphine-naloxone uptake nationally was sales data provided by IMS/Reckitt Benckiser. Sales data allows for direct comparisons of methadone, buprenorphine and buprenorphine-naloxone.

The following graphs represent the changes that have occurred in the OST medication market since the introduction of buprenorphine-naloxone onto the PBS. These graphs are based on the following assumptions:

- a daily dose ('factored unit') in Australia was estimated to be on average 70mg for methadone and 12mg for buprenorphine [84 85];
- *market share* apportioned across the three OST could be accurately derived from sales data provided by IMS/Reckitt Benckiser.

Figure 1 (below) shows the number of estimated 'factored units' sold in Australia by month, of methadone, buprenorphine and buprenorphine-naloxone. As indicated below, methadone retains the largest share of the OST market.

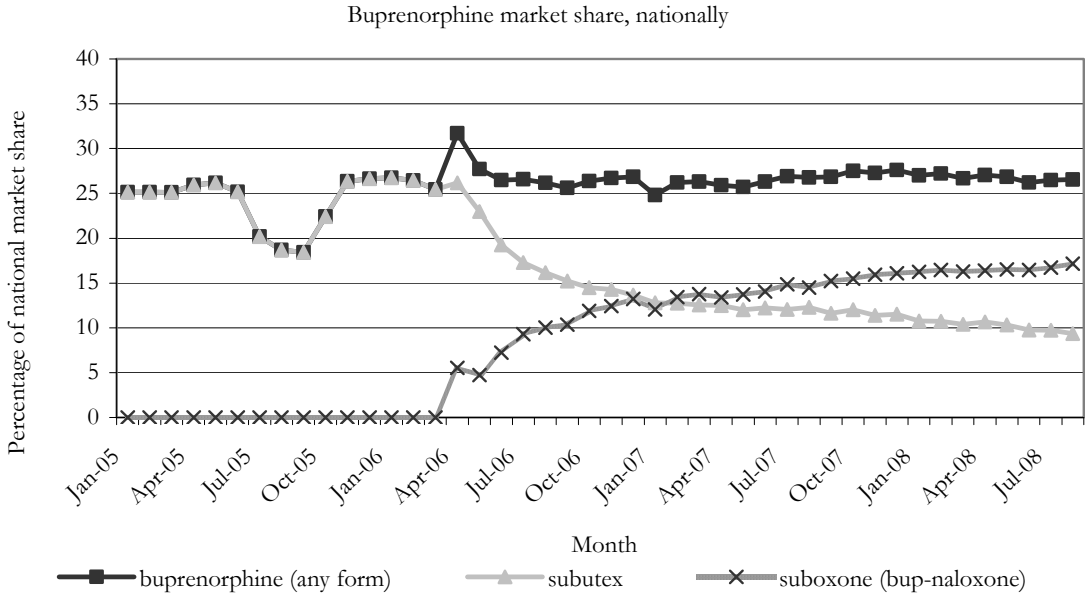
**Figure 1: Estimated factored units sold of methadone, buprenorphine and buprenorphine-naloxone by month, Australia, 2005-2008**




***Notes:*** *Sales data provided by IMS/Reckitt Benckiser. Methadone includes both Methadone syrup and Biodone®. One unit is an estimated daily dose of 70 mg methadone and 12mg of buprenorphine/buprenorphine-naloxone, based upon previous studies of routine Australian prescribing [84 85].*

There was no apparent relative increase in *overall market share* of any form of buprenorphine as an OST (Figure 2), but buprenorphine-naloxone now accounts for a greater market share of total buprenorphine sales than buprenorphine (Subutex).

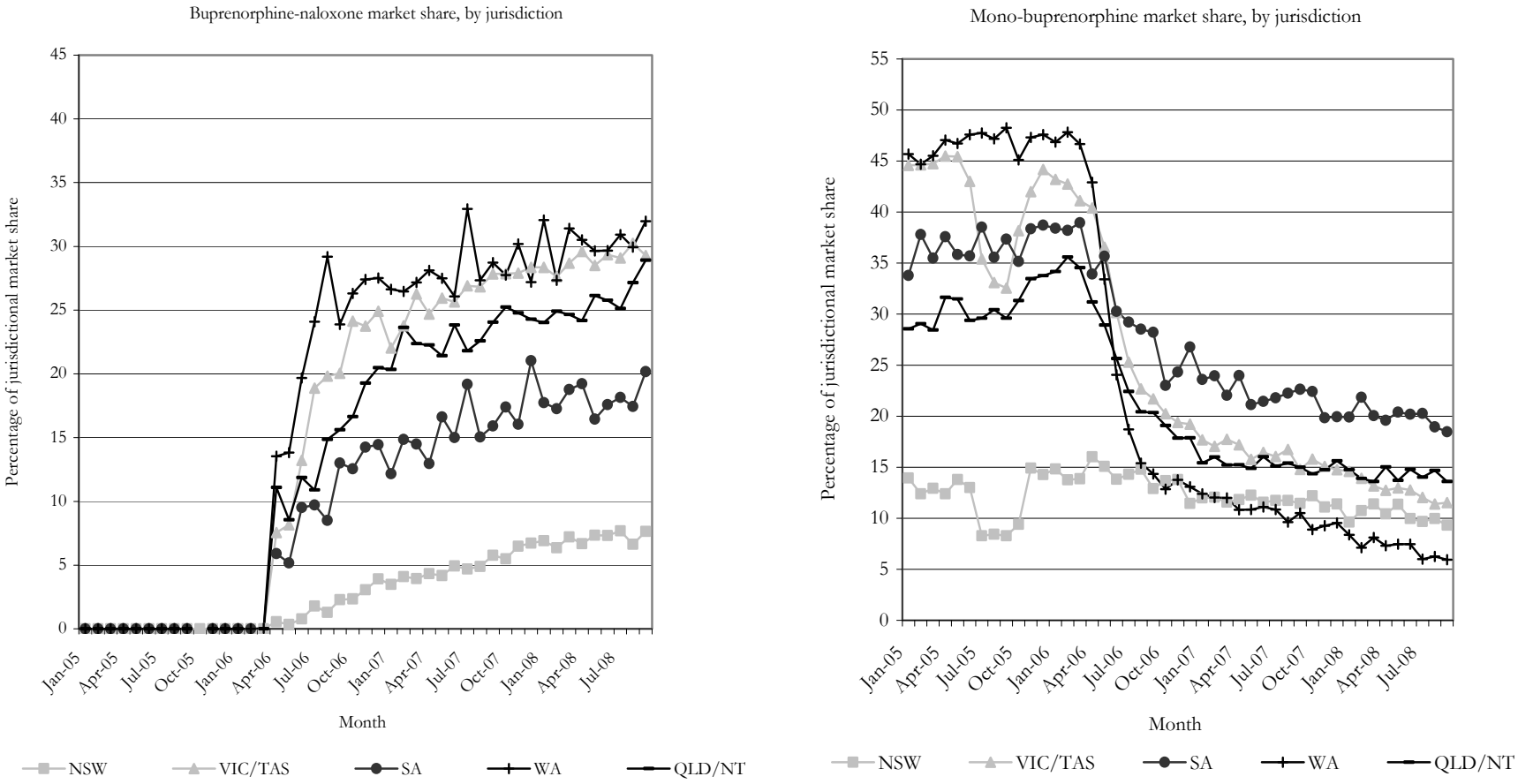
**Figure 2: Estimated market share accounted for by buprenorphine by month, Australia, 2005-2008**




***Notes:*** *Sales data provided by Reckitt Benckiser. Methadone includes both Methadone syrup® and Biodone®. One unit is an estimated daily dose of 70 mg methadone and 12mg of buprenorphine/buprenorphine-naloxone, based upon previous studies of routine Australian prescribing [84 85].*

There have been extremely large jurisdictional differences in the extent to which buprenorphine-naloxone has been introduced as an OST form, based on sales data (Figure 3), and this is apparent among the jurisdictions of interest to the present study. NSW has seen the most limited market penetration, VIC has very high penetration, and SA is intermediate between the two. The uptake of buprenorphine-naloxone in each jurisdiction is important as the more widely available a medication is, the more opportunity there may be for diversion (compared to a less available medication).

**Figure 3: Estimated market share accounted for by buprenorphine and buprenorphine-naloxone by month, by jurisdiction, 2005-2008**



## 3.7. KE reports on the implementation of buprenorphine-naloxone

The KE interviewed in 2007 and 2008 were asked to evaluate the implementation of buprenorphine-naloxone in their jurisdictions (NSW, VIC and SA). A more detailed summary of their comments is provided in Appendix 4. The following summarises the perceived benefits and limitations of buprenorphine-naloxone.

On the whole, KE reports indicate that buprenorphine-naloxone was viewed positively and had the potential to reduce buprenorphine injection, either because it is less attractive to inject or due to the uptake of the newer formulation leading to less availability of the mono-buprenorphine product. It was difficult for KE to separate the advantages associated with increasing the number of unsupervised doses permitted from the advantages of the buprenorphine-naloxone formulation per se. KE were hopeful that buprenorphine-naloxone would lead to more flexible, integrated treatment options, greater treatment satisfaction and improved retention.

Some KE perceptions indicated that buprenorphine-naloxone was not being used to its full potential in OST. In NSW, there was debate regarding whether the threshold was too high for buprenorphine-naloxone treatment, and whether the medication had wider applications. In VIC, OST clients' reluctance or refusal to accept the medication was perceived as a limitation. In SA, the introduction of buprenorphine-naloxone did not lead to an increase in the maximum number of unsupervised doses prescribers were able to prescribe to stable patients.

KE in all three jurisdictions reported that the acceptability of buprenorphine-naloxone among OST clients was potentially being compromised by the perception of "punitive actions" of treatment providers, specifically forced transfer to buprenorphine-naloxone, refusal to dispense mono-buprenorphine, and the transfer of clients who persistently remove doses/divert their medication to buprenorphine-naloxone.

Overall, KE shared a realistic view of the impact of an agonist-antagonist formulation in preventing diversion and injection of medications; namely, that the newer formulation may not prevent the problem entirely, but may be of some assistance.

## 3.8. Conclusions

Methadone is the predominant OST medication in Australia, retaining the largest OST market share nationally (approximately 70-75% of all OST medication sales). Buprenorphine-naloxone sales now outstrip those for mono-buprenorphine (and together the formulations make up the other 25-30% of the OST marketshare).

Although not a core reason for its introduction to OST in Australia, buprenorphine-naloxone presented the opportunity to develop more flexible treatment options in Australia. Increasing the number of unsupervised doses of OST medication could also free up capacity for new treatment places, and make OST more attractive to new treatment clients. The addition of buprenorphine-naloxone to the range of medications, however,

has not led to an increase in the number of opioid dependent people in treatment in Australia to date.

OST medication in Australia is generally administered under supervision. The exact proportions are difficult to ascertain, however, as supervised vs unsupervised administration of dosing is not monitored in routine data collections nationally. The aims of supervision are the monitoring of patients; to maximise adherence with treatment and minimise the risk of consumption other than as prescribed, to minimise the risk of diversion to the illicit market, and reduce the risk of injection. There is provision for unsupervised administration of doses, mainly for methadone and buprenorphine-naloxone, and extremely limited provision for unsupervised buprenorphine. Currently in Australia, the level of supervision (described as high, medium, low and minimal in this report) is determined by an individualised risk assessment. In the jurisdictions of interest to the present study, minimal supervision (defined as receiving 20 or more unsupervised doses per month, sometimes even 28-day dispensing) is only available to clients in VIC and NSW who are stable on buprenorphine-naloxone.

NSW, VIC and SA took different approaches to incorporating buprenorphine-naloxone in their OST policies. These policy variances led to differences in the uptake of buprenorphine-naloxone, with VIC sales data showing high levels of market penetration, SA showing average market penetration (in the Australian context), and NSW showing low market penetration. The views of KE in these jurisdictions were varied. Overall, there was a sense that buprenorphine-naloxone was not being used to its full potential, although generally KE expressed some confidence that buprenorphine-naloxone is beneficial in terms of reduced injection and more flexible treatment (through increased number of unsupervised doses) for a small group of stable clients.

The present report does not evaluate the implementation of buprenorphine-naloxone in Australia. A separate study monitoring policy compliance and treatment issues has been conducted by Mammen and colleagues (2009)[108].

The focus of this report was to compare the adherence with, and injection of, methadone, buprenorphine and buprenorphine-naloxone, and to describe the characteristics of the illicit market for buprenorphine-naloxone in detail. The background availability of OST medications is important when considering the extent of diversion and injection. If a medication is widely available in the general community, there are potentially more opportunities for diversion and/or injection (than for a medication that is less available). There are marked differences in the availability of the three OST medications, nationally and by jurisdiction. In order to control for the volumes of medication being dispensed (and therefore evaluate the effect of drug formulation), levels of diversion and injection have been adjusted for background availability (sales and/or volume medication dispensed) where possible.

# 4. NON-ADHERENCE AMONG OST CLIENTS

## 4.1 Summary


- Despite best efforts, some level of non-adherence with medication occurs. This is the case for many areas of medicine, not just OST. It is important to be specific regarding behaviours of concern, as different behaviours are associated with risks of differing severity.

- There are many indicators of 'adherence' with medical treatment, and many ways of measuring these indicators. This chapter examines the following: removal of all or part of a supervised dose, injection of OST medication, selling/giving away medication, accessing multiple doctors, and general indicators of adherence with treatment (such as attendance at appointments). We reported the prevalence of these behaviours, as well as the volumes of medication not taken as directed relative to the overall number of doses dispensed.

- Buprenorphine was removed from the dosing site by a larger number of clients, at a higher rate (per 1,000 doses dispensed), than methadone or buprenorphine-naloxone. Buprenorphine-naloxone was removed by the smallest number of clients, at a higher rate (per 1,000 doses dispensed) than methadone, possibly because it is easier to secret out of the dosing site than methadone syrup (particularly where the syrup has been diluted). A minority of OST clients reported removal of supervised doses for injection; even fewer reported removal to sell. The most common motivations included stockpiling/saving for later (later use of own medication is probably less risky than diversion to another person) and to help a friend in withdrawal (particularly among buprenorphine-naloxone clients).

- Overall, diversion occurs infrequently. More buprenorphine doses (per 1,000 doses dispensed) were diverted than buprenorphine-naloxone doses, and more buprenorphine-naloxone doses were diverted than methadone doses. This suggests that there continues to be some demand for diverted buprenorphine-naloxone, despite the addition of naloxone, but that the demand is less than that for buprenorphine.

- Prescribers suspected higher levels of removal of supervised buprenorphine (than methadone or buprenorphine-naloxone), but were not sure about the extent of diversion (to a third party). Prescribers were somewhat more confident in assessing the risk of patients injecting medication than the risk of diversion to others (as injecting sites can be inspected for physical evidence of injection). Prescribers suspected higher levels of methadone injection (the main source of which was presumed to be unsupervised medication), a perception that was not supported by the reports of OST clients. In general, prescriber perceptions were that diversion and injection of buprenorphine-naloxone was minimal.


(Continued over page)

Summary (continued)

- Among OST clients, the reported levels of buprenorphine injection were higher than that for methadone and buprenorphine-naloxone (both in terms of prevalence and quantity of medication injected). The prevalence of injection was lowest among buprenorphine-naloxone clients, but these clients injected in quantities that were roughly equivalent to that for methadone.

- Substantial proportions of OST clients who inject their medication do so for reasons other than 'liking of the drug effect'. Many OST clients reported experiencing difficulties in stopping injecting in drug treatment, and for these clients, injectable forms of OST (under medical supervision) may be an attractive treatment option.

## 4.2 Introduction

As outlined in Chapter 1, this report make the distinction between behaviours associated with *non-adherence* (i.e. the removal of a supervised dose from the dosing site for personal use or diversion to another person, splitting doses, stockpiling doses, taking more or less than the prescribed dose, and the injection of one's own medication) and behaviours associated with *diversion* (i.e. the unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended). Although diversion represents one form of non-adherence, adherence has many facets: it includes taking the medication in accordance with prescription directions and meeting specified conditions of treatment (e.g. supervised consumption, attendance at designated dosing times, and taking medication in the specified dose, by the specified route of administration and at specified times). Use of the terms *adherence* and *non-adherence* brings the terminology used in OST in line with other areas of medicine: human immunodeficiency virus (HIV)[109], cardiac health[110], diabetes[110], and mental health[111]. Adherence to prescribed medication regimes is poor for many medical conditions (not just opioid dependence) and often carries significant adverse outcomes for patients.

The behaviours, intentions/motivations and the harms associated with non-adherence vary widely. For example, the motivations for injection may be very different to those associated with splitting a methadone dose over 24-hour period. Other behaviours, such as stockpiling doses, may be consumer attempts to circumvent treatment requirements that are counterproductive to leading a normal life (e.g. working or having a weekend away). Our use of the term *non-adherence* does not downplay the risks associated with a consumer disregarding prescription directions or conditions of treatment. The different behaviours that may be described as non-adherence, however, are associated with risks of differing severity. Behaviours associated with low levels of risk (e.g. splitting a takeaway dose in order to prevent breakthrough symptoms) may necessitate little or no response, compared to high-risk activities (e.g. injecting medications) that pose serious risks to individuals and the community.

There is evidence that, despite strategies to maximise adherence with treatment (such as the supervision of medication), some level of non-adherence still occurs in OST[90]. Wherever possible, this analysis examined specific indicators of adherence among methadone, buprenorphine and buprenorphine-naloxone clients.

## 4.3 Methods and data sources

The following analyses draw primarily on data obtained from the cross-sectional interviews conducted with OST clients in 2007 and 2008. Specifically, this chapter describes the characteristics of the current treatment episode, and examines the prevalence and frequency of the following indicators of adherence:

- removal of supervised doses from the dosing site;
- injection of doses;
- selling/giving away doses ('diversion');
- general indicators such as attendance at appointments and number of doses missed; and
- number of doctors involved in care.

Most studies have focused on the prevalence of non-adherent behaviours among OST clients. This chapter quantifies the problem in terms of the volumes of medication not being taken as directed. We report estimates of *how often* non-adherent behaviours occur for the three OST types, adjusting for the total number of daily doses dispensed to the client group as a whole (expressed as the number of doses not taken as directed per 1,000 daily doses dispensed).

These estimates make the following key assumptions:

- the frequency of behaviours in the *past six months* can be reasonably extrapolated from the frequency of *past month* behaviours reported by clients in treatment (specifically number of takeaway doses, etc); and
- the number of *days used (medication) in the past six months* is the best available proxy to the number of *daily doses dispensed* (number of *days used* has been used in preference to number of *days in treatment* to account for second and third-daily dosing schedules).

The reports of adherence among OST clients are then compared and contrasted with the perceptions of OST prescribers (from the postal survey conducted in 2007). The prescribers were surveyed on their estimation of the numbers of their patients suspected of removing doses, injecting doses and selling doses, as well as their confidence in identifying and responding to diversion and injection.

## 4.4. The 2008 sample of buprenorphine clients in Victoria

A change in organisations overseeing the VIC arm of the study from 2007 to 2008 made retaining the same sampling strategies challenging. In 2007, the recruitment of OST clients was overseen by Turning Point, who recruited mainly from the city and northern suburbs of Melbourne. In 2008, recruitment was conducted by researchers at Burnet Institute, who interviewed participants from additional suburbs (in particular, Footscray and Frankston; see Appendix 5). IDU from these areas are currently known to Burnet Institute researchers from their field-based research projects, such as the Networks studies (see the Burnet Institute website for more information[2]). Previous studies have identified differing patterns of buprenorphine use and injection across different suburbs of Melbourne[20 39], leading to concerns about the representativeness of the 2008 buprenorphine sample.

Frankston, in particular, has been noted for its higher levels of buprenorphine injection[39]. Preliminary analyses also identified high levels of injection among Footscray buprenorphine clients. Including these cases in the wider analyses may over-represent the levels of buprenorphine injection in Victoria more generally. Accordingly, the data obtained from Frankston and Footscray buprenorphine clients (n=16) was removed from the main analyses and discussed separately below. This way, the 2007 and 2008 samples are best matched in terms of geographic spread across Melbourne, enabling comparisons across years. All notes for figures and tables will specify where data from these suburbs has been retained in the main analyses.

*Non-adherence among buprenorphine clients in Frankston and Footscray (n=16), Melbourne*

The buprenorphine clients from Frankston and Footscray (n=16) were grouped together and compared to: (i) the rest of the buprenorphine sample (n=133); and (ii) the other VIC buprenorphine clients (n=35). There were no differences between the groups in mean age or gender. Larger proportions of Frankston/Footscray clients reported a prison history compared to both the larger buprenorphine sample (75% vs 47%, Fishers Exact Test, p=0.037), and the other VIC buprenorphine clients (75% vs 40%, Fishers Exact Test, p=0.034).

There were no differences between the groups in length of time in treatment or number of takeaway doses in the past month. Significantly larger proportions of buprenorphine clients from Frankston/Footscray (compared to the larger buprenorphine sample, but not the VIC buprenorphine sample) were dispensed their dose from a pharmacy (100% vs 57%, Fishers Exact Test, p=0.001).

Frankston/Footscray buprenorphine clients reported higher levels of non-adherence. They were significantly more likely to have removed a supervised dose than the larger buprenorphine sample (75% vs 35%, Fishers Exact Test, p=0.00), but not the other VIC buprenorphine clients (75% vs 47%). Frankston/Footscray buprenorphine clients were significantly more likely to have injected in the past six months compared to the larger buprenorphine sample (75% vs 28%, Fishers Exact Test, p=0.00) and the other VIC buprenorphine clients (75% vs 31%, Fishers Exact Test, p= 0.006). They were also more likely to have reported weekly or more frequent injection compared to both the larger

[2] http://www.burnet.edu.au/home/cph/recent/idu_social_networks

buprenorphine sample (69% vs 11%, Fishers Exact Test, p=0.00) and the other VIC buprenorphine clients (70% vs 14%, Fishers Exact Test, p=000).

Previous studies have suggested that higher rates of buprenorphine injection in Frankston may be due to the higher price of heroin compared to inner city Melbourne[39], but there were no differences between the Frankston/Footscray group and the other VIC buprenorphine clients in the median days of heroin use in the past six months. Other studies have found that community-based pharmacists (as opposed to those working in public clinics) in VIC suspect a high level of buprenorphine diversion[36]. The geographic differences in treatment adherence in Melbourne might reflect differences in localised patterns of drug use and/or the extent to which supervised doses of OST medication are directly observed.

## 4.5. Characteristics of current treatment episode

In 2007 and 2008, OST clients reported having been in their current treatment episode a median of 15-17 months prior to interview (Table 6 below). The mean daily doses of methadone, buprenorphine and buprenorphine-naloxone were similar to the average doses found in other Australian studies [84] [85] (i.e. 70mg methadone and 12 mgs buprenorphine/buprenorphine-naloxone).

Comparisons between the 2007/2008 (total) sample characteristics and the 2007 report from the NOPSAD collection[92] indicate that, in general, similar proportions of both were being dosed at public clinics, private clinics and pharmacies. Similar proportions were also being prescribed in public vs private settings, although public clinic prescribers may have been over-represented in the 2008 sample (42% compared to 28% in the 2007 NOPSAD report).

**Table 6: Characteristics of current treatment episode, by jurisdiction, 2007-2008**

| | 2007 | | | | 2008 | | | |
|---|---|---|---|---|---|---|---|---|
| | **NSW** n=120 | **VIC** n=150 | **SA** n=129 | **TOTAL** N=399 | **NSW** n=143 | **VIC[1]** n=163 | **SA** n=134 | **TOTAL** N=440 |
| Median no. of weeks in current treatment (range) | 72 (2-1038) | 52 (1-623) | 72 (4-984) | 60 (1-1039) | 58 (4-1144) | 71 (1-1092) | 62 (4-1,000) | 68 (1-1144) |
| Mean daily dose (mgs) (SD) | | | | | | | | |
| Methadone | 77 (43.6) | 56 (39.4) | 62 (35.2) | 67 (40.5) | 81 (44.2) | 71 (31.3) | 72 (35.2) | 76 (38.4) |
| Buprenorphine | 12 (8.4) | 12 (8.2) | 9 (6.7) | 12 (8.0) | 11 (6.8) | 11 (8.5) | 11 (7.2) | 11 (7.5) |
| Bup-naloxone | 14 (10.3) | 10 (6.9) | 12 (6.0) | 11 (7.1) | 10 (6.9) | 9 (5.3) | 14 (8.5) | 11 (7.4) |
| Prescriber type (%) | | | | | | | | |
| Dr in public clinic | 43 | 7 | 43 | 30 | 52 | 18 | 59 | 42 |
| Dr in private clinic | 31 | 16 | 0 | 16 | 34 | 29 | 4 | 22 |
| General Practitioner | 26 | 76 | 56 | 54 | 14 | 53 | 37 | 36 |
| Dosing site (%) | | | | | | | | |
| Public clinic/hospital | 47 | 1 | 9 | 18 | 47 | 0 | 0 | 14 |
| Private clinic | 28 | 11 | 0 | 13 | 35 | 0 | 0 | 11 |
| Doctors surgery | 1 | 0 | 0 | 0 | 2 | 0 | 0 | 1 |
| Pharmacy | 25 | 88 | 91 | 69 | 16 | 99 | 100 | 74 |
| Median cost of treatment to client per week (range)[2] | $40 ($7-70) | $30 ($10-50) | $25 ($1-36) | $30 ($1-70) | $50 ($16-80) | $30 ($10-60) | $25 ($12-30) | $30 ($10-80) |

*1 Includes all VIC buprenorphine clients interviewed in 2008 (n=51)*

*2 Among those clients who paid for treatment (n=322 in 2007, n=370 in 2008)*

## 4.6. Supervised and unsupervised administration of doses among OST clients

Just under half the 2007 and 2008 samples (44% and 41% respectively) reported receiving *all* doses under supervision in the past month. In 2008, the proportions of clients receiving all their past month doses under supervision was higher among NSW clients (60%) compared to VIC and SA clients (31% and 32% respectively).

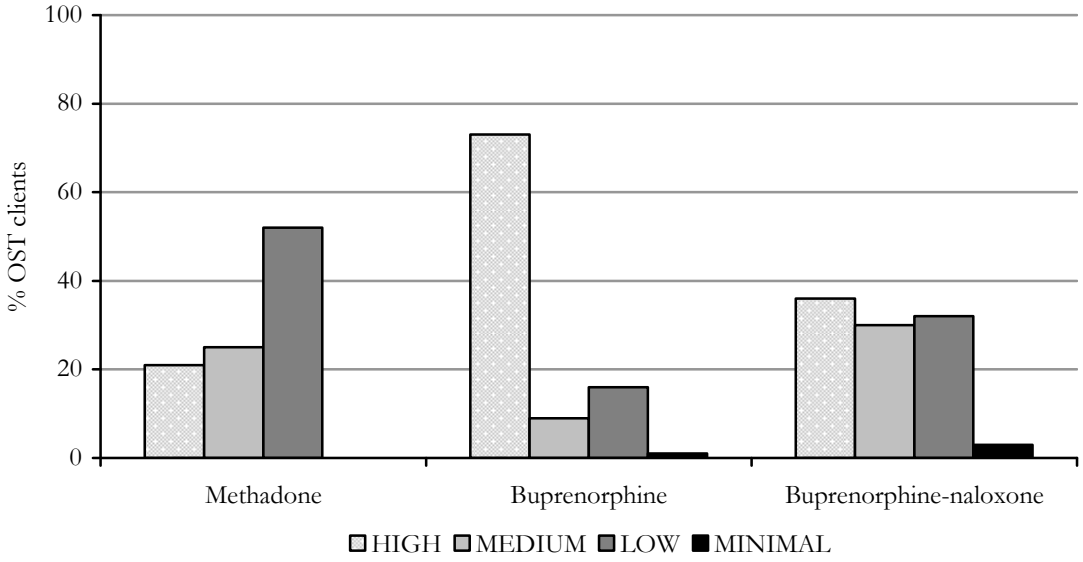
In 2008, there were 13 clients who received the mono-buprenorphine product for supervised doses and buprenorphine-naloxone for takeaway doses (contrary to national pharmacotherapy policy[98], which state all doses, supervised and unsupervised, should be buprenorphine-naloxone if the client is receiving any takeaways).

As seen in Figure 4, the 2008 OST client groups differed in the number of doses consumed under supervision in the past month. On average, despite a lower overdose potential, larger proportions of buprenorphine clients (73%) received their past month doses under HIGH levels of supervision (i.e. 0-1 unsupervised dose in the past month), followed by buprenorphine-naloxone, than methadone. The SA buprenorphine clients were an exception; substantial proportions (58%) received their doses under LOW levels of supervision. This is consistent with SA buprenorphine policy where there is reliance on community pharmacies that operate five to six days per week. The higher levels of supervision of buprenorphine doses (compared with methadone doses) in NSW and VIC are consistent with these States' policies and most likely relates to the ease with which the tablets can be diverted and/or injected.

On average, more methadone clients (52%) were being administered their past month doses under LOW levels of supervision (i.e. nine to 20 unsupervised doses in the past month) than clients in the two other forms of treatment, despite methadone carrying the greatest risk in terms of overdose. Only 20% of methadone clients received their past month doses under HIGH levels of supervision. These patterns of supervision for methadone doses were consistent across the three study jurisdictions.

Despite the lower overdose potential, the inclusion of naloxone to deter injection and policy provisions in NSW and VIC, very few clients received their past months' doses under MINIMAL supervision conditions. The exception was a small group of buprenorphine-naloxone clients in NSW (20% received their past month doses under MINIMAL supervision conditions). Thirty-two percent of all buprenorphine-naloxone clients received their dose under LOW levels of supervision, 30% under MEDIUM supervision and 36% under HIGH levels of supervision.

**Figure 4: Level of supervision of past month doses by OST type, 2008 (% OST clients)**




*N*otes:

- *The levels of supervision are defined as:*
  - *HIGH: 0-1 takeaway dose in past month*
  - *MEDIUM: 2-8 takeaway doses in past month*
  - *LOW: 9-20 takeaway doses in past month*
  - *MINIMAL: 20+ takeaway doses in past month*
- *Among OST clients in that form of treatment*
- *The above levels of supervision are summaries for the purpose of this report, based on the NSW, VIC and SA takeaway policies. There are some differences in jurisdictional policies (e.g. required period of time in treatment, key indicators of stability and the number of takeaways permitted) that have not been explicitly stated here. See Appendix 3 for more detail on NSW, VIC and SA buprenorphine policies.*
- *The above analyses includes all VIC buprenorphine clients interviewed in 2008 (n=51)*

## 4.7. Indicators of adherence and non-adherence

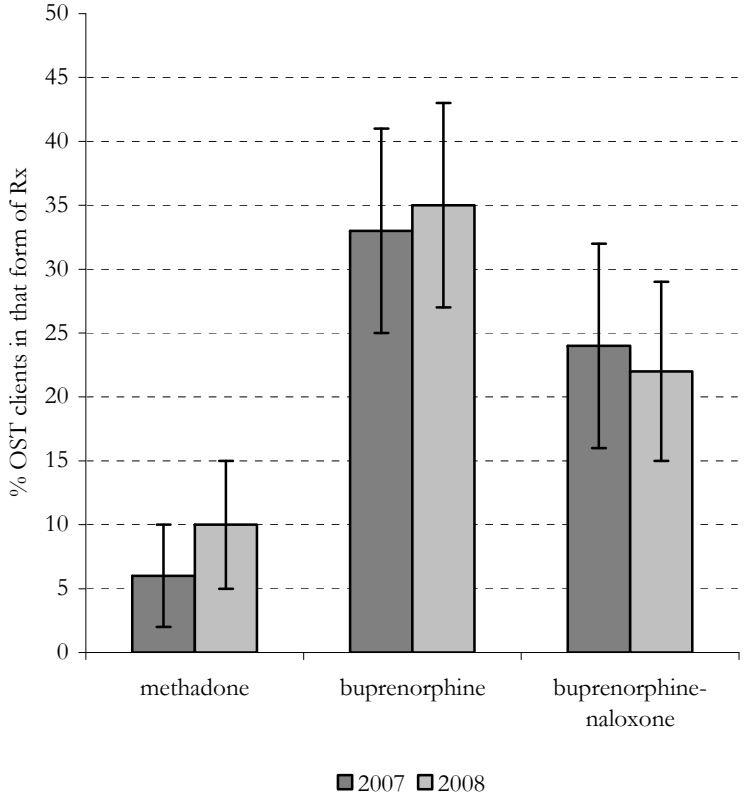
### 4.7.1. Removal of supervised doses

Figure 5.a. (below) shows that the removal of at least one supervised dose from the dosing site in the past six months was prevalent among buprenorphine (35% in 2008) and buprenorphine-naloxone clients (22% in 2008), and significantly less prevalent among methadone clients (10% in 2008). This finding is consistent with other Australian studies, which suggested that methadone syrup is more difficult to secret out of dosing site than sublingual buprenorphine/ buprenorphine-naloxone tablets[90]. In 2008, 75% of removed methadone doses in VIC had been diluted (despite VIC policy mandating dilution for unsupervised dosing only) and 38% in SA. No one reported dilution of methadone in NSW. In 2008, compared with 2007, there was a tendency towards smaller proportions of buprenorphine-naloxone clients having removed a dose than buprenorphine clients (although this difference was not statistically significant in 2008).

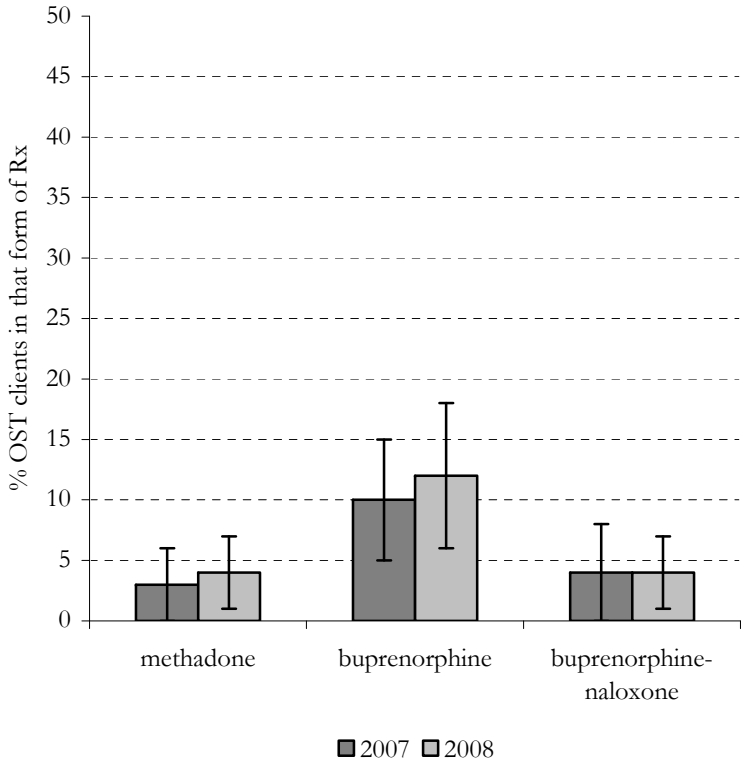
Very often, the assumption is that when a supervised dose is removed from the dosing site, it is either for injection or diversion to the illicit market. Figure 5.b. (below) shows that this is not the case: only a minority of clients reported removal of a supervised dose with the intention of injecting it. In 2007 and 2008, the proportion of buprenorphine-naloxone clients who reported removing a supervised dose to inject was equivalent to that for methadone clients (less than 5%). The vast majority of doses removed by OST clients had been in their mouths (73% for methadone, 90% for buprenorphine and 90% for buprenorphine-naloxone), leading to the potential for serious infection where the medication is later injected [51 53 54 112 113].

**Figure 5: Proportion (%) of OST clients[1] who reported recent removal of all or part of a supervised dose[2] from the dosing site, 2007-2008**

**5.a. Removal for any purpose**




**5.b. Removal for injection**




***Notes:***

*95% confidence intervals.*

*The above analyses adjusted for outliers among the buprenorphine clients interviewed in Victoria in 2008 (n=35).*

*[1] Among clients in that form of treatment. In 2007: methadone =157; buprenorphine =126; buprenorphine-naloxone = 116. In 2008: methadone = 153; buprenorphine = 133; buprenorphine-naloxone =138.*

*[2] At least once in the past six months.*

The most common motivations for removing a supervised dose (see Table 7 below) were to stockpile/save the dose for later, to inject the dose and to help a friend in withdrawal. Removing supervised doses to sell was reported by a very small proportion of the sample (one methadone client and five buprenorphine clients).

**Table 7: Most commonly reported motivations for removing all or part of a supervised dose from the dosing site, 2008 (n)**

| | Methadone (n=15) | Buprenorphine (n=57) | Buprenorphine-naloxone (n=31) |
|---|---|---|---|
| Stockpile/save for later | 3 (20%) | 35 (61%) | 17 (54%) |
| To inject | 6 (40%) | 27 (47%) | 6 (19%) |
| To help a friend in withdrawal | 4 (27%) | 1 (2%) | 8 (27%) |
| Self-treatment of dependence | 1 (7%) | 8 (14%) | 1 (3%) |
| Recently used other opiates | 0 | 11 (19%) | 0 |
| Didn't need to dose | 0 | 0 | 4 (13%) |
| To sell | 1 (7%) | 5 (9%) | 0 |

***Notes:***

- *Among those OST clients who reported removing all or part of a supervised dosing from the dosing site in the past six months.*
- *Multiple responses allowed – percentages do not sum to 100%.*
- *Other motivations included: intoxication; to split the dose; to keep for a holiday; and to save for the days when can't afford the dispensing fees.*
- *The above analyses include all VIC buprenorphine clients interviewed in 2008 (n=51).*

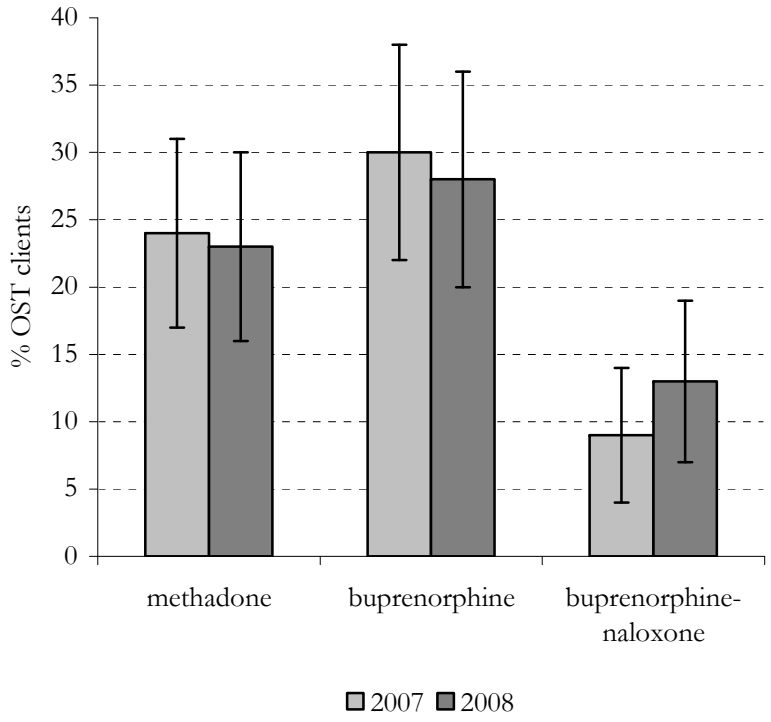
## 4.7.2. Injection of doses

Approximately one in four (22% to 28%) methadone and buprenorphine clients reported injecting their medication at least once in the past six months in 2007 and 2008 (Figure 6). In 2007, significantly fewer buprenorphine-naloxone clients reported recent injection of their medication (this difference remained significant in 2008 for buprenorphine-naloxone vs buprenorphine clients, but not buprenorphine-naloxone vs methadone clients).

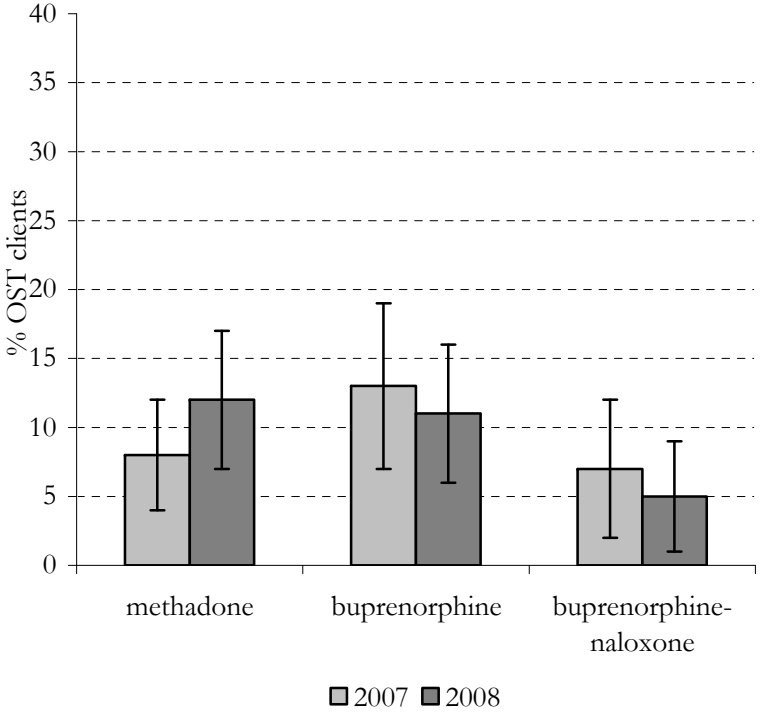
Overall, the proportions of OST clients reporting weekly or more frequent injection were substantially lower than the proportions reporting any injection in the past six months. There were no significant differences between client groups in the levels of regular injection.

**Figure 6: Proportion (%) of OST clients reporting recent[1] injection of their prescribed OST medication, by OST-type, 2007-2008**

**6.a. Any injection past six months[2]**




**6.b. Weekly+ injection[3] past six months[2]**




***Notes:***

*95% confidence intervals.*

*The above analyses adjusted for outliers among the buprenorphine clients interviewed in Victoria in 2008 (n=35).*

*[1] In the past six months.*

*[2] By clients in that form of treatment. In 2007: methadone =157; buprenorphine =126; buprenorphine-naloxone = 116. In 2008: methadone = 153; buprenorphine = 133; buprenorphine-naloxone =138.*

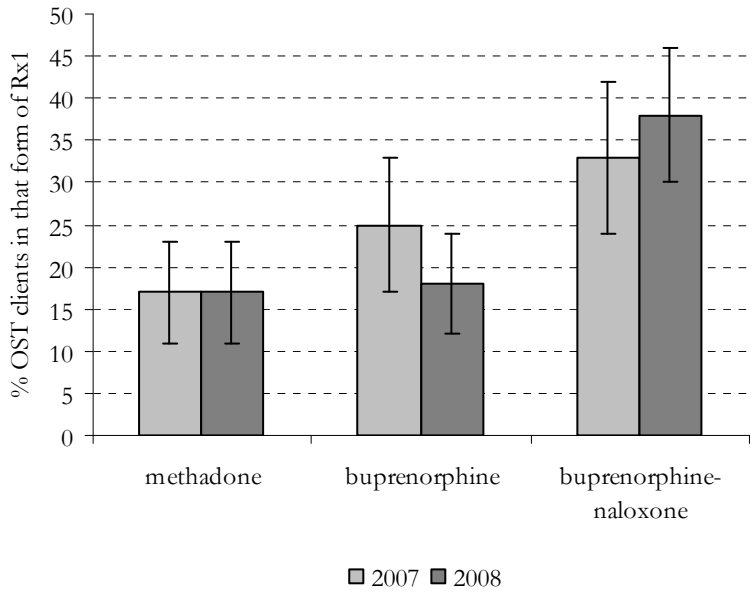
*[3] Injected on >26 out of the last 180 days*

*Liking of the drug effect obtained from injecting*

Those OST clients who reported injecting their OST medication in the past six months were asked to rate their liking of the drug effect obtained from injecting on a scale of 0-10 (where 0 was 'no liking' and 10 was 'liked it very much'). In 2008 (Figure 7), significantly more buprenorphine-naloxone clients reported 'no liking' of the drug effect obtained from injecting their medication than methadone and buprenorphine clients.

There were no differences by OST-type in the proportions reporting they were 'not at all likely' to inject again, suggesting that factors other than simply liking (or not liking) the drug effect also influenced whether or not a client may decide to inject their medication again in the future.

**Figure 7: Proportion (%) of OST clients who reported 'no liking' of the drug effect obtained from injecting their OST medication, by OST-type, 2007-2008**




***Notes:***
*Among clients in that form of treatment who reported injecting their medication in the six months prior to interview (in 2008: n=85 methadone clients; n=95 buprenorphine clients; and n=24 buprenorphine-naloxone clients).*
*95% confidence interval.*

*Motivations for injecting*

OST clients who reported recent injection of their OST medication were asked why they injected the medication, rather than take it as directed (orally or sublingually). In 2008, the most common motivations reported across all three OST-types were having a preference for injection, finding it difficult to stop injecting, and for a faster onset of effect (see Table 8 below). Some methadone clients (38%) specifically mentioned injecting their dose for intoxication/opioid effect. Some buprenorphine-naloxone clients (20%) mentioned finding it easier to abstain from injecting other drugs if they injected their doses.

The following comments are from buprenorphine-naloxone clients who had injected their medication:

> *"You can lose a lot of the effect when you take the tablet orally, because a lot gets stuck between your teeth and you end up swallowing some…"* (VIC)
>
> *"Orally also makes me feel normal, but it take a lot longer to kick in…"* (SA)
>
> *"There is no difference. I just inject to help me from not using other drugs. I find the routine of injection is a big part of my problem…"* (VIC)

**Table 8: Most commonly reported motivations for injecting prescribed OST medications, 2008, (n)**

| | **Methadone** (n=40) | **Buprenorphine** (n=49) | **Buprenorphine-naloxone** (n=15) |
|---|---|---|---|
| Preferred to inject | 27 (68%) | 33 (67%) | 9 (60%) |
| Difficulty stopping injection | 11 (28%) | 17 (35%) | 5 (33%) |
| Faster onset of effect | 19 (47%) | 11 (22%) | 1 (7%) |
| Intoxication/opioid effect | 15 (38%) | 5 (10%) | 1 (7%) |
| Easier to abstain from injecting other drugs | 0 | 7 (14%) | 3 (20%) |
| More efficient route of administration | 0 | 7 (14%) | 0 |
| Heroin substitute | 3 (8%) | 5 (10%) | 2 (13%) |
| Cheaper than other opiates | 3 (8%) | 5 (10%) | 2 (13%) |

***Notes:***

- *Among those OST clients who commented.*
- *Multiple responses allowed – percentages do not sum to 100%.*
- *The above analyses include all VIC buprenorphine clients interviewed in 2008.*

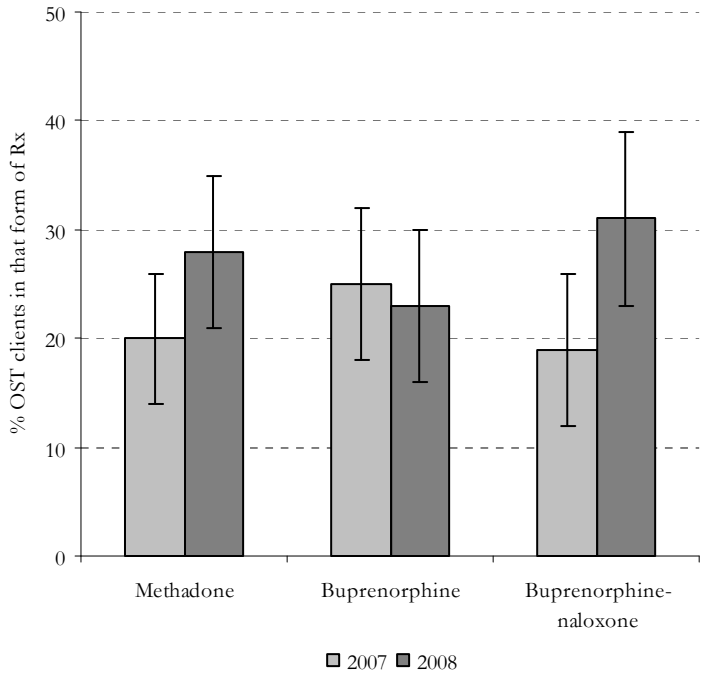
*Attractiveness of injectable forms of OST*

2008 OST clients were asked their views on the attractiveness of injectable forms of OST. Thirty-five percent of clients perceived injectable OST to be an attractive form of treatment. When asked if they would continue to view it as an attractive treatment option even if (i) there were no takeaways, and (ii) all injection had to be done under medical supervision (at a service like the MSIC), 30% of clients still reported it to be an attractive treatment option.

## 4.7.3. Diversion of doses

Diversion in this section refers to the selling and/or giving away of a dose of prescribed OST medication. Between 19% and 25% of OST clients diverted at least one dose of their OST medication in the past six months (see Figure 8 below). The proportions of OST clients reporting diversion remained stable from 2007 to 2008. There were no differences by OST-type, indicating that diversion among buprenorphine-naloxone clients occurs as frequently as diversion among methadone and/or buprenorphine clients. Diversion among OST clients is discussed in more detail in Chapter 6.

**Figure 8: Proportion (%) of OST clients reporting recent[1] diversion of their prescribed OST medication, by OST-type, 2007-2008**




***Notes:***

*95% confidence intervals.*

*The above analyses adjusted for outliers among the buprenorphine clients interviewed in Victoria in 2008 (n=35).*

*[1] In the past six months.*

*[2] By clients in that form of treatment. In 2007: methadone =157; buprenorphine =126; buprenorphine-naloxone = 116. In 2008: methadone = 153; buprenorphine = 133; buprenorphine-naloxone =138.*

## 4.8. Frequency of non-adherent behaviours relative to overall OST provision

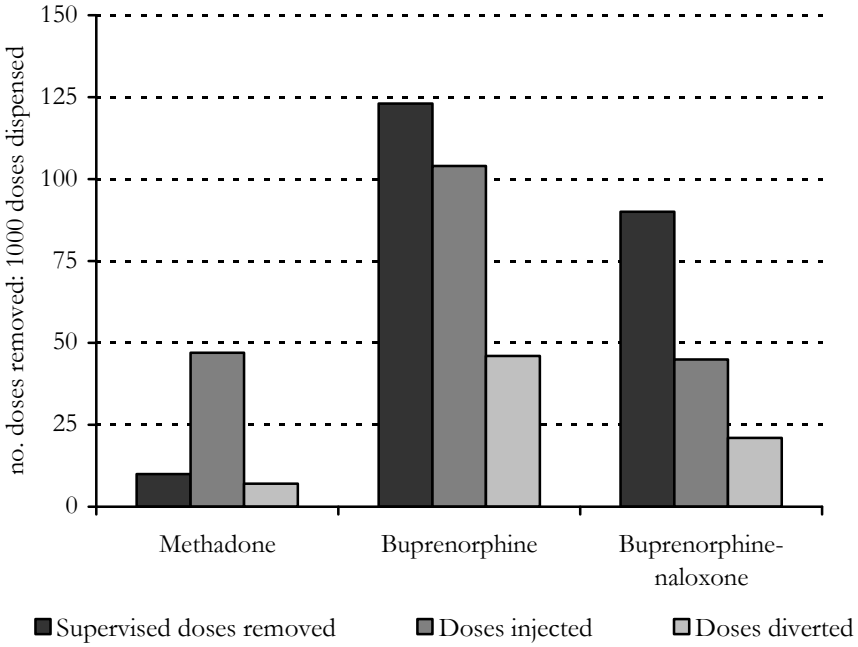
Prevalence data described in the sections above gives an indication of how many individuals reported non-adherent behaviours in the past six months, but do not indicate how often these behaviours occurred relative to the total number of doses of OST medication dispensed. Figure 9 (below) shows estimates of how frequently three non-adherent behaviours (removal of supervised doses, injection of doses, and diversion of doses) occur (aggregated by OST-type), adjusting for the total number of doses dispensed to the group as a whole. Jurisdictional breakdowns are provided in Appendix 6.

Figure 9 shows that, per 1,000 daily supervised doses dispensed, the removal of supervised doses occurred relatively infrequently compared to other types of non-adherence. Supervised buprenorphine doses were removed most frequently (123 doses removed per 1,000 supervised doses dispensed), followed by buprenorphine-naloxone doses (90 doses removed per 1,000 supervised doses dispensed), then methadone doses. The removal of supervised methadone doses happened very infrequently in the past six months (approximately 10 doses removed per 1,000 supervised doses dispensed). This is consistent with methadone syrup being more difficult than a sublingual tablet to secret out of the dosing site. There were jurisdictional differences in how often supervised doses were removed from the dosing site (Appendix 6), with buprenorphine clients in VIC reporting the most frequent removal of supervised doses (271 doses removed per 1,000 supervised doses dispensed), with the removal of Frankson/Footscray data.

Overall, the injection of doses (adjusted for the total number of doses dispensed) occurred more frequently among buprenorphine clients than methadone and buprenorphine-naloxone clients. The number of buprenorphine-naloxone doses injected (per 1,000 doses dispensed) was equivalent to that for methadone doses. There were some jurisdictional differences (Appendix 6). VIC buprenorphine clients reported the highest levels of injecting (adjusted for the total number of doses dispensed) compared to buprenorphine clients in the other two states.

In general, diversion (selling and/or giving away prescribed medication) occurred infrequently among OST clients. A larger number of buprenorphine doses were sold or given away than methadone or buprenorphine-naloxone doses, although this occurred in fewer than 50 out of every 1,000 doses dispensed among the group as a whole (Figure 9). VIC buprenorphine clients diverted medication more frequently than NSW and SA buprenorphine clients (Appendix 6).

**Figure 9: Frequency of non-adherent behaviours (removing supervised doses, injecting doses and diverting doses) per 1,000 doses dispensed[1], by OST-type, 2008**




***Notes:***

[1] *Based on total number of daily doses dispensed in the past 180 days to participants in that form of treatment (methadone n=153, buprenorphine n=133, buprenorphine-naloxone n=138). 'Days of use' (of prescribed OST) was used as best available proxy in preference to 'days in treatment' to adjust for second- and third-daily dosing regimes.*

*'Supervised doses removed' includes the total number of supervised doses removed from the dosing site in the past six months, adjusted per 1,000 supervised doses dispensed only (i.e. corrected for number of takeaways received).*

*'Doses injected' includes the total number of supervised and unsupervised doses injected in the past six months, adjusted per 1,000 doses dispensed.*

*'Doses diverted' includes the total number of supervised and unsupervised doses that were sold or given away in the past six months, adjusted per 1,000 doses dispensed.*

*The above analyses adjusted for outliers among the buprenorphine clients interviewed in Victoria in 2008 (n=35).*

*Data not collected in 2007.*

## 4.9. Adherence with other aspects of treatment

Among all three OST-groups, attendance at appointments and adherence with past week doses was generally high (see Table 9 below). On average, all three OST-groups saw their prescriber recently (median of two weeks) and spent an average of 15 minutes with their prescriber.

There were some differences between OST-types on other indicators of adherence. Methadone clients were less likely to have missed dosing appointments in the past month, and more likely to have taken the past week's supervised doses exactly as directed (than either buprenorphine or buprenorphine-naloxone clients). In general, there were no differences between buprenorphine and buprenorphine-naloxone clients on these measures, with the exception that buprenorphine-naloxone clients were more likely to take the past week's supervised doses as directed.

**Table 9: Other indicators of adherence with treatment among OST clients, by OST-type, 2008**

| | Methadone (n=153) | Buprenorphine (n=133) | Bup-naloxone (n=137) |
|---|---|---|---|
| | | *Median (range)* | |
| No. weeks since last saw prescriber | 2 (1-12) | 2 (0-8) | 3 (1-10) |
| Length of last appointment (mins) | 15 (1-75) | 15 (5-60) | 15 (2-60) |
| | | *% OST clients* | |
| Provided a urine drug screen(s) in past month | 43 | 44 | 32 |
| Missed attending dosing site in past month | 15 | 40 | 29 |
| Missed prescriber appointment in past month | 9 | 6 | 13 |
| Missed a dose in past month | 37 | 47 | 42 |
| Took a takeaway dose in advance in past month | 22 | 6 | 11 |
| Took all past week's supervised doses exactly as directed | 76 | 11 | 20 |

***Notes:***

- *Among clients in that form of treatment who responded.*
- *The above analyses adjusted for outliers among the buprenorphine clients interviewed in VIC in 2008 (n=35).*

## 4.10. Utilisation of additional healthcare services

The majority of OST clients interviewed for this study had not seen doctors other than their OST providers in the past month (65%), 27% of participants saw one other doctor, and 8% of participants saw two or more additional doctors. There were no differences between client groups in the number of doctors seen.

The reasons reported by participants for seeing other doctors were: to obtain benzodiazepines (n=37); mental health concerns (n=29); respiratory infection (cold/flu) (n=14); infection requiring antibiotics (n=11); pain (n=11); to obtain antidepressants (n=10); orthopaedic/limb injuries (n=10); women's health/contraception (n=9); liver/hepatitis C virus (HCV) treatment (n=9); cardiac/circulatory concerns (n=6); respiratory disease (n=5); to obtain prescription opioids (n=4); dental concerns (n=3); epilepsy (n=3); and severe allergies (n=2). These categories are not mutually exclusive, and many participants reported multiple health concerns.

Twenty-four percent of participants (n=100) reported experiencing a serious illness, injury or medical condition in the past month. Eight percent (n=34) had been admitted to hospital in the past month (including psychiatric care, surgery and detoxification).

## 4.11. Prescriber reports of non-adherence and doctor-shopping among their OST patients

The following summary outlines some of the key findings from the national postal survey of authorised OST prescribers conducted in 2007. On the whole, prescriber perceptions were that the majority of patients adhere with the conditions of OST. The different pharmaceutical opioids, however, were perceived as having different risk profiles in terms of diversion, injection, and resultant harms (see Table 10).

Prescribers were asked how many of their patients removed all or part of a supervised dose from the dosing site in the past month. Approximately half of all prescribers of each OST could not answer this item, responding that they 'didn't know'. Among those prescribers who did respond, more buprenorphine patients were suspected of removing supervised doses from the dosing site than methadone or buprenorphine-naloxone patients (Table 10), a finding that was consistent with OST client self-report. Some prescribers provided suggestions to reduce this issue, for instance: ongoing training and support of dosing staff/pharmacists; greater liaison between prescribers and dosing staff; seven day a week dosing sites/pharmacies; dedicated dosing spaces in clinics and pharmacies; and more stringent/uniform standards of supervision across dosing sites.

Approximately 60% of the prescribers of each OST reported they 'didn't know' how many of their patients injected their doses in the past month. Among those prescribers who commented, more methadone patients were suspected of injecting their doses than buprenorphine or buprenorphine-naloxone patients. OST client self-reports (discussed earlier in this chapter) showed slightly different patterns of use: there were no significant differences in the proportions reporting past six months injection of methadone and buprenorphine, but the injection of buprenorphine occurred more frequently among those who did inject their medication. The prescribers in this study believed some injection of buprenorphine-naloxone occurred, although at lower levels than the other two forms of OST.

Overall, prescribers identified few patients selling, giving away or trading their medication (i.e. "diverting") and reported no differences between the three medications.

Among those prescribers who reported patients as removing doses, diverting, and/or injecting, the majority were identified through patient self-report (51%), reports from the dosing pharmacist (49%) and reports from other staff (34%) (e.g. nurses, drug workers, clinic staff, colleagues, etc). Twenty-one percent also specified 'other' means of identifying these patients, which mostly involved reports from other patients, and clinical/physical examinations. Three prescribers mentioned receiving reports from hospital regarding their patients being admitted with injection-related problems.

**Table 10: Prescriber reports of non-adherence in the past month***

| | 0 patient | 1 patient | 2+ patients |
|---|---|---|---|
| *Removed all or part of supervised dose (%)* | | | |
| Methadone (n=130) | 72 | 19 | 9 |
| Buprenorphine (n=104) | 62 | 20 | 18 |
| Buprenorphine-naloxone (n=75) | 81 | 9 | 9 |
| *Injected their dose (%)* | | | |
| Methadone (n=104) | 61 | 24 | 15 |
| Buprenorphine (n=73) | 73 | 16 | 11 |
| Buprenorphine-naloxone (n=55) | 73 | 22 | 5 |
| *Gave away, sold or traded a takeaway dose (%)* | | | |
| Methadone (n=69) | 73 | 12 | 16 |
| Buprenorphine (n=59) | 78 | 9 | 14 |
| Buprenorphine-naloxone (n=39) | 80 | 15 | 5 |

** Among those prescribers who commented.*

Table 11 shows the proportion of prescribers who identified their patients were 'doctor shopping' to obtain multiple prescriptions. Around half or more of the prescribers surveyed (51-61%) reported that none of their patients 'doctor shopped' for methadone, buprenorphine, buprenorphine-naloxone or physeptone. 'Doctor shopping' for the medications morphine, oxycodone and benzodiazepines, however, was reported as being more common. 'Doctor shopping' for benzodiazepines was most prevalent, reported by 41% of the prescribers surveyed, who identified a total of 724 of their patients as having engaged in this behaviour in the past month.

Among those prescribers who reported patients as 'doctor shopping' (n=161), the majority were identified through patient self-report (56%), reports from the dosing pharmacist (32%) and 'other' sources (35%) (e.g. doctor shopping hotline or through communication with the Drugs of Dependence Unit). Twenty-two percent (22%) of prescribers stated they identified 'doctor shopping' through the Medicare Australia's Prescription Shopping Program (previously the Health Insurance Commission).

**Table 11: Prescriber reports of 'doctor shopping' among patients in the past month***

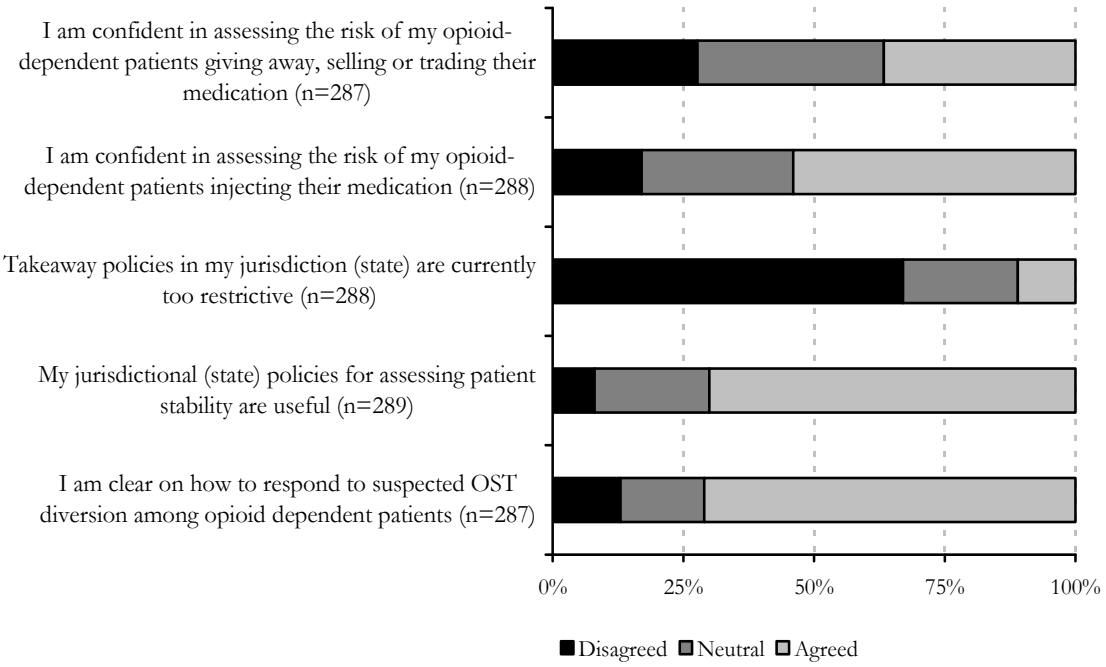
| | None % | Don't know % | 1+ patient % | Total patients 'doctor shopping' (median; range) |
|---|---|---|---|---|
| *'Doctor shopping' for:* | | | | |
| Methadone | 61 | 21 | 7 | 36 (1; 1-5) |
| Buprenorphine | 57 | 22 | 2 | 10 (1.5; 1-3) |
| Buprenorphine-naloxone | 54 | 22 | 1 | 4 (1; 1-2) |
| Physeptone | 51 | 23 | 2 | 9 (1; 1-3) |
| Morphine | 42 | 24 | 15 | 150 (2; 1-20) |
| Oxycodone | 39 | 24 | 18 | 163 (2; 1-15) |
| Benzodiazepines | 24 | 23 | 41 | 724 (3; 1-90) |

** Among total prescribers sample, n=291.*

Prescribers were somewhat more confident in assessing the risk of their patients injecting their medications than they were in assessing the giving away, selling or trading of patients' medication (Figure 10). Injection is easier to detect, as prescribers can inspect sites for physical evidence of injection. Detecting diversion is more difficult. Twenty-eight percent of prescribers reported finding it challenging to assess the risk of their patients *diverting* their medication.

Most of the prescribers (67%) *disagreed* that takeaway policies in their jurisdiction were too restrictive. The majority of prescribers (72%) found their jurisdictional guidelines for assessing patient stability to be useful and were, on the whole, clear about how to respond to suspected cases of diversion (although one in 10 indicated they were not).

**Figure 10: Prescriber confidence in identifying and responding to non-adherence and diversion**




***Notes:***

- *Proportions reported among those prescribers who commented.*
- *Strongly disagreed/disagreed and strongly agreed/agreed were combined in the above analyses.*

## 4.12. Conclusions

This is the first time estimates have been made of how often non-adherent behaviours occur relative to the level of OST provision. Although prevalence of past six month behaviours (such as removing doses, injecting doses and diverting doses) is useful in understanding the proportion of clients who may be at risk of harm, prevalence does not give an indication of how often these behaviours occur relative to the total number of doses dispensed. The latter measure gives an indication of volumes of medication not taken as directed.

Supervised administration of doses is the main strategy for minimising the risks associated with OST. The majority of OST clients take their medication under supervision as directed, although the extent to which this occurs varies by medication type. Removal of supervised doses is considered to be high-risk behaviour, mainly due to the assumption that doses are removed to either inject or divert to the illicit market. In reality, the motivations for removing dose vary, as do the associated risks. A minority of OST clients reported removal of supervised doses for injection; even fewer reported removal to sell. The most common motivations included stockpiling/saving for later (later use of own medication is probably less risky than diversion to another person) and to help a friend in withdrawal (particularly among buprenorphine-naloxone clients).

Buprenorphine appears to be removed from the dosing site by a larger number of clients, in larger quantities (adjusting per 1,000 supervised doses dispensed), than methadone or buprenorphine-naloxone. Buprenorphine-naloxone was removed by the smallest number of clients, but in larger quantities than methadone, possibly because it is easier to secret out of the dosing site than methadone syrup (particularly where the syrup has been diluted). The vast majority of all supervised doses removed by OST clients had been in their mouth, leading to potential for infection where later injected.

Overall, the number of doses diverted to a third party is relatively small. Adjusting per 1,000 doses dispensed, more buprenorphine doses were diverted than buprenorphine-naloxone doses, and more buprenorphine-naloxone doses were diverted than methadone doses. This suggests that there continues to be some demand for diverted buprenorphine-naloxone, despite the addition of naloxone, but that the demand is less than that for buprenorphine. Prescribers suggested a number of strategies to reduce diversion from OST programs, for instance: ongoing training and support of dosing staff/ pharmacists; greater liaison between prescribers and dosing staff; seven day a week dosing sites/ pharmacies; dedicated dosing spaces in clinics and pharmacies; and more stringent/ uniform standards of supervision across dosing sites.

Injection of (supervised and/or unsupervised) doses among OST clients is a concern, and is of particular interest to the present study. Buprenorphine was injected by a larger number of clients, in larger quantities (adjusting per 1,000 daily doses dispensed), than methadone and buprenorphine-naloxone. The prevalence of injection was lowest among buprenorphine-naloxone clients, but buprenorphine-naloxone was injected in quantities (adjusting per 1,000 daily doses dispensed) that were roughly equivalent to that for methadone. A limitation of the present study was that it could not quantify the proportion of injected doses that were dispensed to OST clients for unsupervised administration.

Substantial proportions of OST clients who inject their medication do so for reasons other than 'liking of the drug effect'. Many OST clients reported experiencing difficulties in stopping injecting in drug treatment. Almost one third of OST clients reported injectable forms of OST (under medical supervision) to be an attractive treatment option.

The National Pharmacotherapy Policy for People Dependent on Opioids (2007) states that patients should not receive unnecessary medication. Since the naloxone in buprenorphine-naloxone has no therapeutic benefit in itself, it is appropriate for supervised doses of medication to be the mono-buprenorphine product, and unsupervised doses to be buprenorphine-naloxone. Where a patient receives both supervised and takeaway doses, they would need multiple prescriptions, and there is potential for confusion. The policy therefore states that it is appropriate for them to receive only one formulation (the combination product) [98]. The present study highlights that, in practice, this policy is not being adhered to (13 OST clients reported receiving buprenorphine for supervised doses and buprenorphine-naloxone for unsupervised doses).

# 5. INJECTION OF DIVERTED OST MEDICATION

## 5.1. Summary

- The injection of OST medications among OST clients indicates the relative attractiveness of the medication among treatment populations who have ready access to what they have been prescribed. The injection of OST medications among out-of-treatment populations indicates the relative attractiveness of the medication in environments where the medication is potentially less accessible and more costly to the individual (in terms of street price).

- This is the first study to compare the injection of all three OST medications (including buprenorphine-naloxone), adjusting for availability, among OST clients and regular IDU. This chapter draws on data from interviews with out-of-treatment IDU. This data is compared to the reports of OST clients, KE and population-level indicators.

- A minority of IDU, both in and out-of-treatment, reported recent injection of buprenorphine-naloxone, despite its agonist-antagonist formulation. Adjusting for background availability, the levels of buprenorphine-naloxone injection were lower than those for mono-buprenorphine (despite rapid expansion of buprenorphine-naloxone prescribing in Australia), but were similar to those for methadone syrup. These patterns of OST medication injection among IDU and OST clients were consistent with the reports of KE, OST prescribers and NSP data.

- Although there are some jurisdictional differences in uptake, national buprenorphine-naloxone sales outstrip those for mono-buprenorphine. The vast majority of unsupervised buprenorphine doses are the agonist-antagonist formulation. Given that buprenorphine-naloxone is, therefore, the more accessible medication in terms of availability for injection, the finding that it is injected less than the mono-buprenorphine product is an important one.

- Current injection of an OST medication, among IDU in and out-of-treatment, was associated with prior injection of a range of pharmaceutical opioids. This may prove to be a useful clinical indicator in identifying OST clients at increased risk of injecting their prescribed OST medication.

- NSP data clearly demonstrate that there are higher levels of injection of pharmaceutical opioids (morphine and oxycodone in particular) than the opioids used in OST. This may indicate the success of regulatory controls in the prescribing of OST medications.

## 5.2. Introduction

Chapter 4 discussed the injection of OST medications among OST clients as an indicator of non-adherence with treatment. Injection among this group indicates the relative attractiveness of the medication among treatment populations, who have ready access to what they have been prescribed. Given the harms associated with injection (outlined below in section 5.3.), and the widespread prescribing of the agonist-antagonist formulation of buprenorphine-naloxone, this chapter has been dedicated to examining the levels of injection of OST medications in a different population: regular IDU. The injection of OST medications among out-of-treatment populations indicates the relative attractiveness of the medication in environments where the medication is potentially less accessible and more costly to the individual (in terms of street price).

Most frequently, studies have examined the injection of one OST medication (most commonly methadone or buprenorphine) in a single population (either among IDU or treatment populations). This is the first study to compare the injection of all three OST medications, including buprenorphine-naloxone, adjusting for availability, among OST clients and regular IDU.

The main focus of this chapter is to present the levels and predictors of methadone, buprenorphine and buprenorphine-naloxone among regular IDU who were not in OST in the six months prior to interview. The levels and predictors of injection among IDU are then compared with those of OST clients. The self-report of these groups is validated with data from interviews with KE and authorised prescribers, and population-level indicators.

## 5.3. Review of the harms associated with injection of OST medications

### 5.3.1. HIV and viral hepatitis

Although few studies have examined the association between Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV) and the injection of pharmaceutical opioids, it is reasonable to assume that in countries where most injecting drug use is occurring with pharmaceutical opioids, and where HIV/HCV transmission is occurring, that unsafe injection of these drugs is driving the epidemic [4 44]. Compared to active heroin users, the risks of HCV transmission among pharmaceutical opioid injectors might be lower if the the medication is injected less frequently (as might reasonably be expected for buprenorphine which has a longer duration of action). Evidence on the extent of HIV/HCV injection risk among this group, however, is limited[44].

### 5.3.2. Injecting risk behaviours

Injection of methadone syrup has been associated with higher levels of injection-risk behaviour[21 62]. Among an Australian sample of heroin users, methadone injectors reported poorer general health, more injection-related problems and were also more likely to report having passed on used injecting equipment[21]. Other studies have examined the injection-related HIV risk behaviours associated with injection of OST, such as methadone and buprenorphine[21 30 47 62 114], with mixed findings.

In France, however, buprenorphine injectors have been found to display *fewer* injection-related HIV risk behaviours than other groups of illicit drug users. One study surveyed IDU and found that 34% were polydrug users who occasionally injected buprenorphine in addition to heroin and/or cocaine, while 24% had only injected buprenorphine in the previous six months. IDU in this latter group were significantly younger, injected more frequently, and were more frequently on buprenorphine substitution therapy, but they were less likely to be HIV-infected and to report HIV-related risky injecting behaviours[114]. Injection-risk behaviours appeared more likely among those who were primarily using *diverted* buprenorphine (as opposed to injection of one's own medication); these users were also more likely to be unemployed and to be polydrug users[114 115].

### 5.3.3. Injection of drugs formulated for oral/sublingual administration

The solutions that are prepared from oral methadone syrup and sublingual buprenorphine tablets for injection pose risks[116 117]. The viscous consistency of oral liquids such as methadone make it unsuitable for injection and increase the likelihood of vein damage[27]. In one study of methadone clinic attendees who injected methadone, it was found that 58% had difficulty accessing veins and 30% had experienced vein problems as a result of injecting methadone[29]. Adding non-sterile water to methadone syrup or sublingual buprenorphine tablets carries the additional risk of infection/contamination. The crushing and dissolution of tablets (such as morphine, oxycodone, etc.) intended for oral administration also carries further risks. For example, the additives and particulate matter in tablets developed for oral ingestion can cause vein damage. Further, tablets are not produced in sterile environments and contain insoluble particulates, which add to the risks of injection-related problems[44].

The most common injury associated with injection of oral or sublingual drug formulations is vascular and soft tissue damage, which can lead to a range of secondary complications[53 54]. The injection of oral and sublingual formulations of pharmaceutical opioids (such as methadone, buprenorphine and oxycodone) has been associated with thrombosis[54 118], limb ischaemia (in some cases leading to amputation)[54 57 118], nerve damage[57], tissue necrosis[53], rhabdomyolysis[118], pulmonary granuloma[119], and ocular candidiasis[120].

When buprenorphine is injected by an opioid-dependent individual, it can precipitate an uncomfortable withdrawal syndrome. This may last several hours or, if used in large quantities, may last as long as three to four days[118 121], and may be even more exacerbated if buprenorphine-naloxone is injected[65 74 82].

### 5.3.4. Infective complications

Injection of a non-sterile preparation of a pharmaceutical (that is itself not produced in a sterile environment) carries the risk of contamination with bacteria, fungi and other microbes that can cause infection and disease. Contamination may occur through contact with skin flora, re-use/sharing of injecting equipment, contact with non-sterile surfaces, removal of a supervised dose from the mouth (for injecting at a later time), and repeated puncturing of veins (leaving injecting sites vulnerable to infection).

The injection of methadone has been associated with abscesses and infections at injecting sites[21]. The injection of buprenorphine has been associated with abscesses, cellulitis, endocarditis, myositis/pyomyositis, and multiple reports of candida endophthalmitis[51 54 57 113 120 122]. Candida endophthalamitis has been associated with the injection of buprenorphine prepared with lemon juice containing fungus (*C albicans*) or contaminated with fungi from an oral infection (in the case of removal of a supervised dose)[44].

### 5.3.5. Polydrug use

Opioids, alcohol and benzodiazepines all have sedative effects, and the interactions between these drugs increase the risk of toxicity and adverse events. The combination of opioids with other sedative drugs places users at increased risks of polydrug dependence, overdose and perhaps more severe withdrawal. There is good evidence of high rates of comorbid benzodiazepine and opioid use in particular[47 89 123-130]. Among a cohort of methadone patients in Israel, those with comorbid benzodiazepine use problems were more likely to have experienced significant social and drug use problems during follow-up[131]. A recent United Kingdom (UK) study also found that dependence upon benzodiazepines worsened the withdrawal syndrome for opioids[132].

The clinical picture for IDU with comorbid opioid and other drug dependence also tends to be much more complex. There is evidence that those with comorbid benzodiazepine use problems are more disadvantaged, engage in higher levels of risk behaviours (both injecting and other), and that they are likely to have comorbid mental health problems[47 89 123-130].

### 5.3.6. Non-fatal overdose

Among heroin users, non-fatal overdose is a significant risk, particularly for those injecting the drug[133]. The risks associated with the injection of pharmaceutical opioids is less well studied, but there are good reasons to expect that the magnitude of risk might be less than for heroin because of the slower onset of effects, and/or the partial agonist effects[134 135].

There are risks nonetheless. The injection of methadone carries risks due to its unique pharmacological characteristics: it builds slowly to peak blood levels and has a long half-life, leading to an accumulation in the body that can result in toxicity and increased likelihood of mortality[28 47 116]. Buprenorphine carries virtually no risk of non-fatal opioid overdose (resulting from respiratory and CNS depression) if the drug is taken on its own without any other CNS depressants. The risks are greater when polydrug use occurs: a number of studies have found that the toxicity of methadone and buprenorphine are increased when used in conjunction with other opiates, benzodiazepines and/or alcohol[52 127 134-138].

A recent study found that among persons who had used both buprenorphine and methadone, symptoms of opioid toxicity were more likely for methadone and non-fatal overdose on methadone was 10 times more likely[127]. Injection of the medication was more strongly related to buprenorphine toxicity, whereas methadone toxicity was likely to have accompanied co-administration of heroin. The consumption of benzodiazepines was common in both cases[127].

### 5.3.7. Mortality

Compared to heroin, the risk of death – both for overdose and other causes – for many pharmaceutical opioid drugs is likely to be significantly lower, regardless of whether the user is in OST or not. The reason for this lower risk is related to the slower onset of action, the impact of sustained release preparations[139], and in the case of partial agonist drugs such as buprenorphine, the ceiling effect for the agonist actions of the formulation.

The risk of fatal overdoses is lower for buprenorphine than for heroin or other full-agonist opioids[17 134 140]. Factors associated with fatalities include intravenous administration, high-dose buprenorphine and especially concomitant use of benzodiazepines, neuroleptics and/or alcohol[9 55 56 58 61 141]. One study has noted that the introduction of high-dose buprenorphine in France coincided with a substantial *decrease* in opioid poisoning mortality [134]. Similar reductions in overdose mortality have been noted in the UK following treatment expansion[142].

A number of international studies have examined deaths associated with methadone[7 8 58-60 134 143]. These studies have identified that a number of deaths have occurred in IDU who had recently commenced methadone where high doses were involved[7 8 14 58-60 134 143]. One Australian study concluded that in the first two weeks after treatment induction, the mortality risk was six times that of heroin users *not* in treatment[15]; thereafter, mortality risk decreases markedly below that of non-treated heroin users[15 144]. In most of these cases, individuals obtain methadone from sources other than the substitution therapy program[116]. Of the methadone-related deaths identified in a study in New Mexico (1998-2002), 22% were due to methadone alone, 24% were due to a combination of methadone and other prescription drugs, 50% were due to the combination of methadone and other illicit drugs and 3% were due to the combination of methadone and alcohol[60].

One factor that significantly increases mortality risk for all opioids (whether heroin or prescription) is the use of multiple depressant drugs. Concurrent use of pharmaceutical opioids and benzodiazepines, with and without alcohol, are commonly associated with unintentional drug overdose deaths[145 146].

## 5.4. Methods and data sources

For the data obtained from regular IDU (via the IDRS), time trends in injection of OST medications were plotted, with consideration of the amount being prescribed. The data are presented as the ratio of the proportion of regular IDU reporting injection of each opioid in the previous six months to the number (per 100 million) of factored units sold in the same six-month period. This meant that the levels of methadone, buprenorphine and buprenorphine-naloxone injection documented among regular IDU were 'standardised' according to background availability (i.e. amounts being prescribed).

Logistic regressions were run to ascertain the predictors of recent injection of OST medication among IDU and OST clients.

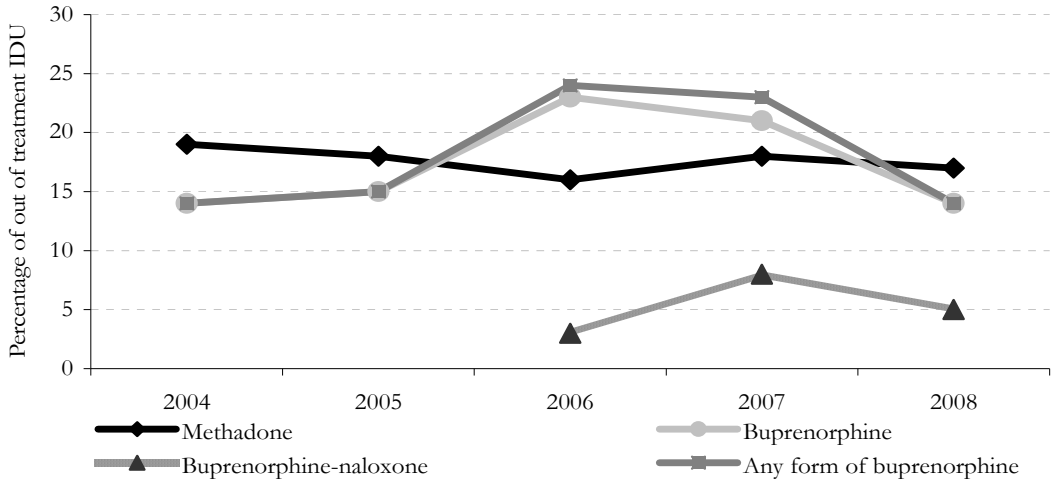
These data are then discussed in the context of reports from KE and authorised prescribers, and population-level indicators such as NSP data collections.

## 5.5. Injection among regular IDU

### 5.5.1. Time trends in injection

Figure 11 presents the overall levels of recent (past six months) injection of OST medications among regular out-of-treatment IDU interviewed for the IDRS from 2004 to 2008. Among the out-of-treatment IDU interviewed, reports of recent buprenorphine injection rose steadily from 14% in 2004 to 24% in 2006. From 2007 to 2008, however, the proportions of IDU reporting recent injection of any form of buprenorphine (including the buprenorphine-naloxone formulation) decreased from 23% to 14%. This decrease coincides with the introduction of the newer buprenorphine-naloxone formulation on the PBS in April 2006, but it also coincides with a decrease in buprenorphine sales over the same period (see Figure 11).

**Figure 11: Proportion of out-of-treatment IDU reporting injection of methadone, buprenorphine and buprenorphine-naloxone in past six months, Australia, 2004-2008**




***Notes:***
*Methadone includes Methadone syrup®, Biodone® and Physeptone®.*

## 5.5.2. Jurisdictional differences

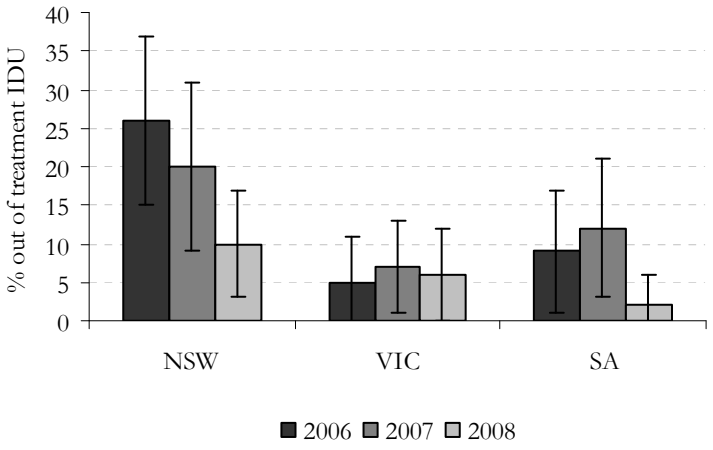
Figure 12 below shows the proportion of out-of-treatment IDU who reported recent injection of methadone, buprenorphine and buprenorphine-naloxone in NSW, VIC and SA (2006-2008). These graphs show the levels of injection of each medication by jurisdiction, but each medication has a different background level of uptake and availability in each jurisdiction (as outlined in Chapter 3), so caution needs to be applied when making comparisons.

These graphs show that over the last three years of monitoring, the trend was towards higher levels of methadone syrup injection among NSW IDU, and higher levels of buprenorphine and buprenorphine-naloxone injection among VIC IDU. Small sample sizes have resulted in wide confidence intervals and these differences between jurisdictions were statistically significant for some years (but not others – see Figure 12). Detailed jurisdictional breakdowns are presented in Appendix 7.

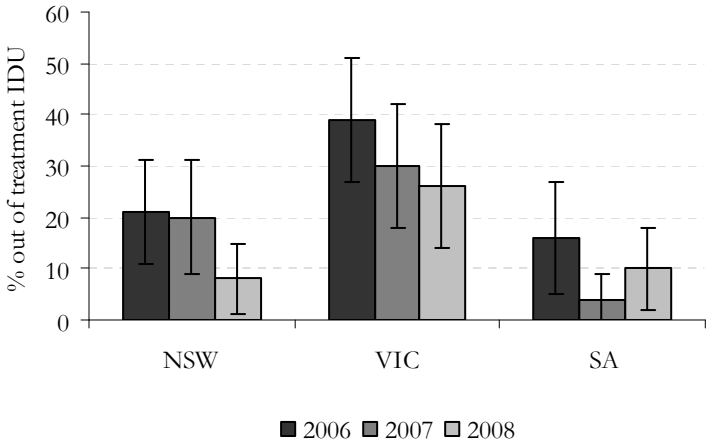
It is notable that the jurisdictions with higher levels of diversion and injection of buprenorphine-naloxone are those where there was much more use of buprenorphine-naloxone (as indicated by sales data described in previous chapter). Even considering the levels of availability indicated by sales data, the overall levels of buprenorphine-naloxone injection appear comparatively lower than for buprenorphine.

**Figure 12: Percentage of out-of-treatment IDU reporting injection of OST medications in the past six months, by jurisdiction, 2006-2008**

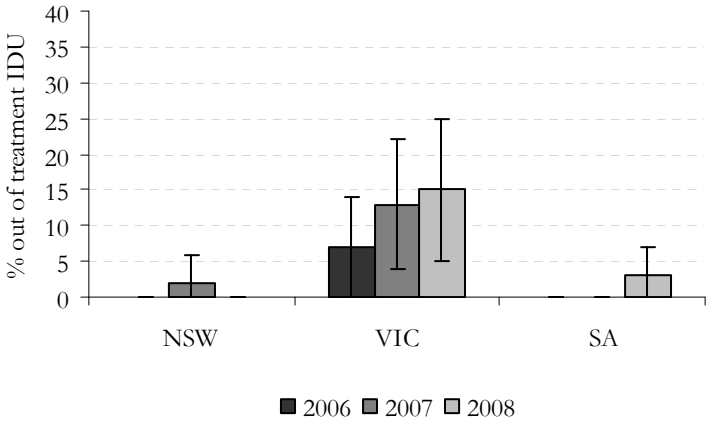
**a. Methadone**




**b. Buprenorphine**




**c. Buprenorphine-naloxone**




***Notes:*** *Methadone includes Methadone syrup®, Biodone® and Physeptone®.*

### 5.5.3. Frequency of injection

Nationally, methadone (all forms - syrup &/or physeptone, licit or illicit) and buprenorphine (licit or illicit) were injected more frequently (i.e. on a median of 10 days each) during the six months preceding interview than buprenorphine-naloxone (median of 5.5 days). There were some jurisdictional differences in frequency of OST medication injection, with IDU in VIC reporting more frequent injection of buprenorphine and IDU in Australian Capital Territory (ACT) and Tasmania (TAS) reporting more frequent injection of methadone (see Table 12 below).

**Table 12: Median number of days (range) injected in the last six months, 2008***

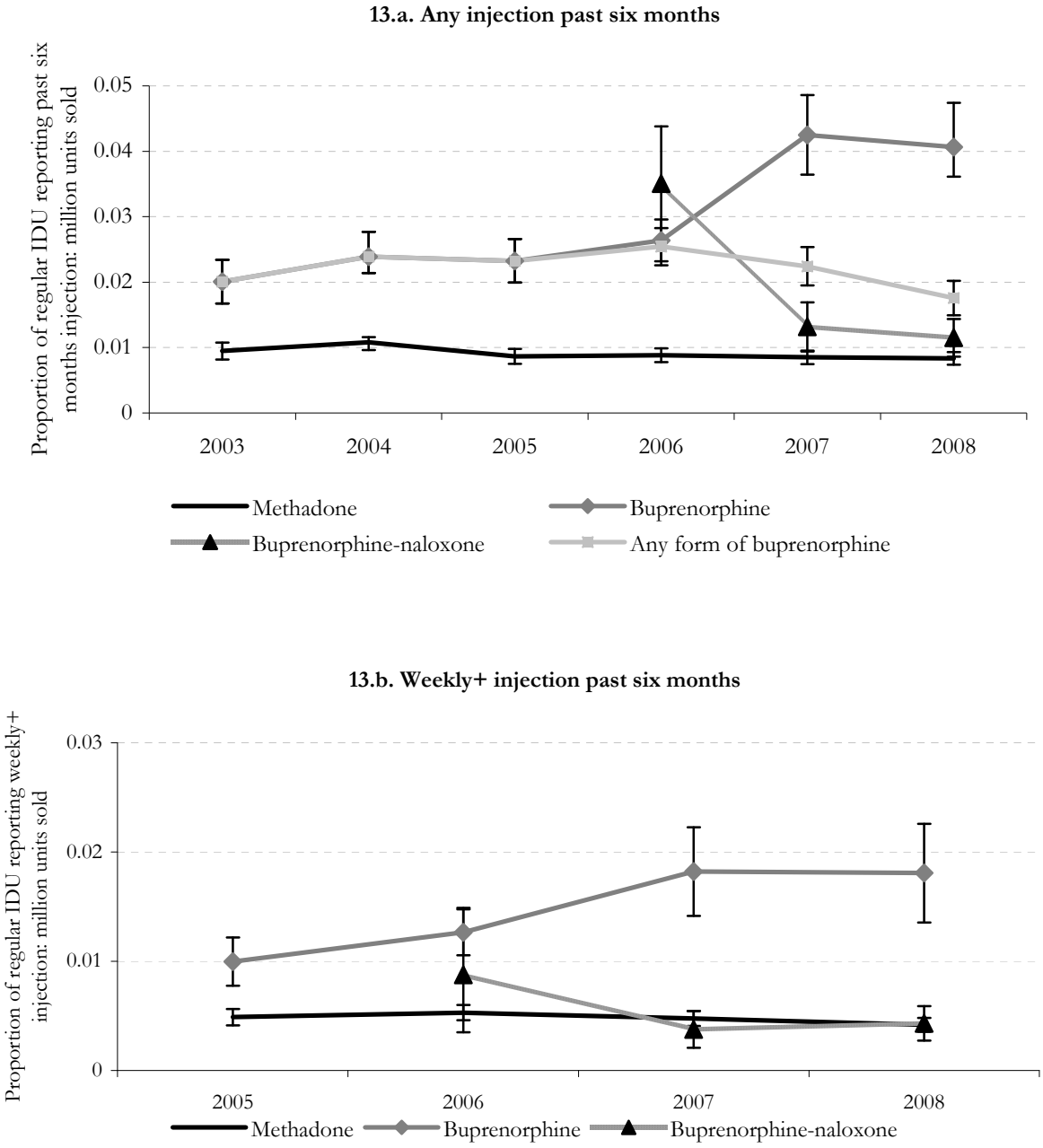
| | NAT** | NSW** | ACT** | VIC** | TAS** | SA** | WA** | NT** | QLD** |
|---|---|---|---|---|---|---|---|---|---|
| Any form methadone*** | 10 (1-180) | 2# (1-48) | 20 (1-48) | n.r. | 17.5 (1-180) | n.r. | 3# (1-72) | 4 (1-180) | 10# (2-48) |
| Buprenorphine | 10 (1-180) | n.r. | 10# (2-180) | 24 (2-180) | n.r. | 3# (1-24) | 12# (12-90) | 4# (1-180) | 10 (1-72) |
| Bup-naloxone | 5.5 (1-180) | n/a | n.r. | 8.5# (1-48) | n.r. | n.r. | n.r. | n/a | 5# (1-180) |

* *Among those who reported injecting illicitly-obtained ORT in the six months preceding interview (max. no. of days = 180).*
** *The following abbreviations have been used: National (NAT); New South Wales (NSW); Australian Capital Territory (ACT), Victoria (VIC); Tasmania (TAS); South Australia (SA); Western Australia (WA); Northern Terrirtory (NT); Queensland (QLD).*
*** *Includes Physeptone.*
\# *Interpret with caution (n<10).*
*n.r. Not reported due to very low numbers (n<5).*

## 5.6. Injection of OST medications among regular IDU adjusted for availability

Figure 13 below presents data on injection of the three OST forms by regular IDU in Australian capital cities, adjusting for the volume of sales of each medication type (expressed as the ratio of the proportions injecting in the past six months per 100 million units sold in the same period). The graphs clearly show that buprenorphine was injected at a higher rate than methadone, adjusted for available volume. In 2006, when buprenorphine-naloxone was first introduced, the adjusted rate of any injection was higher than that for buprenorphine, although weekly or more frequent injection was less common. This had dropped substantially by 2007, and continued to drop in 2008, with buprenorphine-naloxone having a lower level of injection relative to availability, relative to buprenorphine. This difference was particularly marked when weekly or more frequent injection was considered. Interestingly, the ratio for weekly or more frequent buprenorphine injection increased in 2007, and remained at a higher level in 2008. This indicates that although buprenorphine sales decreased, the level of weekly or more frequent injection among regular IDU did not.

**Figure 13: Ratio of injection of OST medication in the past six months by regular IDU: volume of sales of OST medications, 2003-2008**




***Notes:***

*95% confidence interval.*

1. *Past six months*
2. *Regular IDU were selected because of their involvement in central inner-city drug markets in capital cities across Australia. IDUsdata were derived from the total samples of IDU in each year reporting injection of each OST type in the past six months (irrespective of whether they were enrolled in treatment). Data on days of injection only available for 2005 onwards, and could not be aggregated for buprenorphine forms.*
3. *Availability assessed through sales data provided by Reckitt Benckiser. Methadone includes both Methadone syrup® and Biodone®. One 'unit' is an estimated daily dose of 70mg methadone and 12mg of buprenorphine/buprenorphine-naloxone, based upon previous studies of routine Australian prescribing doses[147 148].*

## 5.7. Comparison of out-of-treatment IDU and OST clients

### 5.7.1. Levels of injection

Table 13 shows the proportions of (a) regular IDU not in any form of OST, and (b) clients currently in each form of OST, who reported any and weekly or more frequent injection of each OST during the six months prior to interview. The former group represent a group injecting diverted (i.e. another's) medication; the latter represent a group who are presumably injecting their own medication (i.e. using the medication in a non-adherent manner).

The prevalence of OST injection among out-of-treatment IDU were highest for methadone, followed by buprenorphine, with the smallest proportion of IDU reporting recent injection of buprenorphine-naloxone. Among OST clients, the prevalence of injecting was highest among buprenorphine patients, then methadone, with buprenorphine-naloxone clients reporting the lowest levels of injecting.

**Table 13: Methadone, buprenorphine and buprenorphine-naloxone injection among out-of-treatment regular IDU and OST clients, 2008**

| | **Regular out-of-treatment IDU** 2008 IDRS interviews (n=444) | | **Current OST clients** 2008 interviews with clients in OST (total n=440)[1] | |
|---|---|---|---|---|
| | % | CI[2] (%) | % | CI[2] (%) |
| **Methadone[3]** | | | | |
| % injected in last six months | 23 | 19-27 | 26 | 19-33 |
| % injected weekly or more[4] | 7 | 4-9 | 12 | 4-12 |
| **Buprenorphine** | | | | |
| % injected in last six months | 14 | 10-17 | 33 | 25-40 |
| % injected weekly or more[4] | 5 | 3-7 | 18 | 12-24 |
| **Buprenorphine-naloxone** | | | | |
| % injected in last six months | 5 | 3-8 | 11 | 6-16 |
| % injected weekly or more[4] | 2 | 0-3 | 5 | 1-9 |

***Notes:***

*1 Note that the proportions in this instance refer to those in treatment for that particular form of OST. Sample sizes: methadone n = 153; buprenorphine n=149; buprenorphine-naloxone n=138.*

*2 95% confidence interval.*

*3 The prevalence of monthly and weekly injection of methadone includes Methadone syrup®, Biodone® and Physeptone®. All figures include injection of a participant's own OST medication both licitly and illicitly-obtained products.*

*4 Proportions injecting on >24/180 days.*

### 5.7.2. Predictors of OST injection

A logistic regression model was carried out in 2007 considering predictors of recent injection of OST medications. The following variables were included: sex, age, prison history, jurisdiction of interview, number of months in treatment (OST clients only), heroin use, injection of OST medications (methadone, buprenorphine and buprenorphine-naloxone), injection of other pharmaceutical opioids (morphine and oxycodone), any takeaway doses in the past month (OST clients only), and pharmacy dosing (OST clients only). The detailed results of this analysis are presented in Table 14 (below).

Among both in- and out-of-treatment IDU, the strongest predictors of injection of OST medication were the recent injection of other pharmaceutical opioids. IDU who injected one type of medication were likely to inject a range of medications. Days of heroin use was *not* related to injection of OST, nor was length of time in treatment (for those enrolled in treatment).

There were jurisdictional differences in the injection of OST medications. Among IDU, methadone injection was more likely in NSW (vs VIC, NT and QLD); buprenorphine injection was more likely in ACT (vs NSW) and less likely in NT and SA (vs NSW); and buprenorphine-naloxone injection was more likely in VIC, WA and QLD (vs NSW), possibly reflecting lower levels of buprenorphine-naloxone prescribing in NSW. Among OST clients, methadone injection was more likely in NSW (vs VIC), and buprenorphine injection was more likely in SA (vs VIC).

**Table 14: Predictors of recent[1] injection of OST medication among regular IDU, and among persons enrolled in OST, 2007**

| Regular IDU[2] | Methadone injection | | Buprenorphine injection | | Bup-naloxone injection | |
|---|---|---|---|---|---|---|
| | OR[3] | CI[4] | OR | CI | OR | CI |
| 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 |
| Injection of buprenorphine | 1.7 | 0.9-3.3 | -- | -- | 7.9** | 3.6-17.2 |
| Injection of bup-naloxone | 1.9 | 0.8-4.5 | 7.4** | 3.5-15.9 | -- | -- |
| Injection of morphine | 4.3** | 2.3-7.9 | 1.2 | 0.7-2.1 | 1.1 | 0.5-2.5 |
| Injection of oxycodone | 1.2 | 0.7-2.2 | 1.5 | 0.9-2.6 | 3.3** | 1.5-7.2 |
| Australian Capital Territory[5] | 0.8 | 0.3-2.4 | 4.7** | 1.9-11.5 | 5.3 | 0.5-59.2 |
| Victoria[5] | 0.3* | 0.1-0.8 | 1.5 | 0.7-3.3 | 12.9* | 1.5-113.7 |
| Tasmania[5] | 2.2 | 0.7-6.2 | 0.4 | 0.1-1.3 | --[6] | --[6] |
| South Australia[5] | 0.7 | 0.3-2.0 | 0.2* | 0.1-0.9 | --[6] | --[6] |
| Western Australia[5] | 0.4 | 0.1-1.3 | 0.7 | 0.3-1.9 | 27.5** | 2.8-272.6 |
| Northern Territory[5] | 0.2* | 0.1-0.7 | 0.2** | 0.0-0.6 | 4.7 | 0.2-100.0 |
| Queensland[5] | 0.4* | 0.1-1.0 | 0.9 | 0.4-2.1 | 20.3** | 2.2-185.2 |
| **Persons enrolled in OST[7]** | **Methadone injection** | | **Buprenorphine injection** | | **Bup-naloxone injection** | |
| | OR | CI | OR | CI | OR | CI |
| 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 |
| Pharmacy dosing (vs. 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 |
| Injection of buprenorphine | 6.7 | 0.7-68.0 | -- | -- | 0.7 | 0.1-7.7 |
| Injection of bup-naloxone | --[8] | --[8] | 10.0* | 1.6-62.9 | -- | -- |
| Injection of morphine | 10.7** | 3.0-38.8 | 2.0 | 0.4-10.9 | 15.0* | 1.8-128.5 |
| Injection of oxycodone | 2.3 | 0.6-8.9 | 2.3 | 0.4-13.8 | 0.4 | 0.0-5.5 |
| New South Wales[9] | 21.5** | 3.1-148.8 | 3.1 | 0.2-43.1 | --[10] | --[10] |
| South Australia[9] | 8.2 | 0.8-85.3 | 51.5* | 2.0-1318.9 | 3.2 | 0.0-234.7 |

* Significant p<0.05
** Significant p<0.01

***Notes:***

1 *Past six months.*
2 *IDU currently out of any form of treatment for drug dependence, n=513.*
3 *Odds ratio (adjusted).*
4 *95% confidence interval.*
5 *New South Wales was the reference state for jurisdictional comparisons among IDU.*
6 *These variables were dropped from the model as redundant (no out-of-treatment IDU in these states reported recent injection of buprenorphine-naloxone).*
7 *For OST clients, only those currently in each form of OST were in the regression analyses. Sample sizes: methadone n=157; buprenorphine n=126; and buprenorphine-naloxone n=116.*
8 *This variable was dropped from the model as redundant (among those methadone clients who had injected their methadone, none had recently injected buprenorphine-naloxone).*
9 *Victoria was the reference state for jurisdictional comparisons among OST clients.*
10 *This variable was dropped from the model as redundant (no buprenorphine-naloxone clients in NSW reported recent injection of buprenorphine-naloxone).*

## 5.8. KE reports of OST medication injection

The KE comments did not clearly distinguish between injection of prescribed OST medication from the injection of diverted OST medication. On the whole, however, KE reported that buprenorphine-naloxone was being injected less than methadone and buprenorphine, and substantially less than other pharmaceutical opioids (such as morphine and oxycodone). KE in NSW and SA identified methadone and buprenorphine as the most frequently injected OST medications. KE in VIC perceived buprenorphine as the OST medication most frequently injected in 2008. The injection of buprenorphine-naloxone was observed by KE in all three states, particularly in SA and VIC, but these reports did not increase with the increasing uptake of the medication in these states.

Most KE in NSW were unable to comment with any confidence on any aspect of buprenorphine-naloxone injection. KE in VIC and SA reported buprenorphine-naloxone injection among buprenorphine-naloxone clients (i.e. injection of their own medication, or non-adherence). Other groups that were identified by VIC and SA KE as more likely to inject buprenorphine-naloxone included IDU generally, buprenorphine clients, methadone clients, regular heroin/opioid users and *"buprenorphine-dependent persons either in or out-of-treatment"*.

> *"There is a small group of people who are buying wheel filters regularly and injecting their own buprenorphine-naloxone."* (VIC)

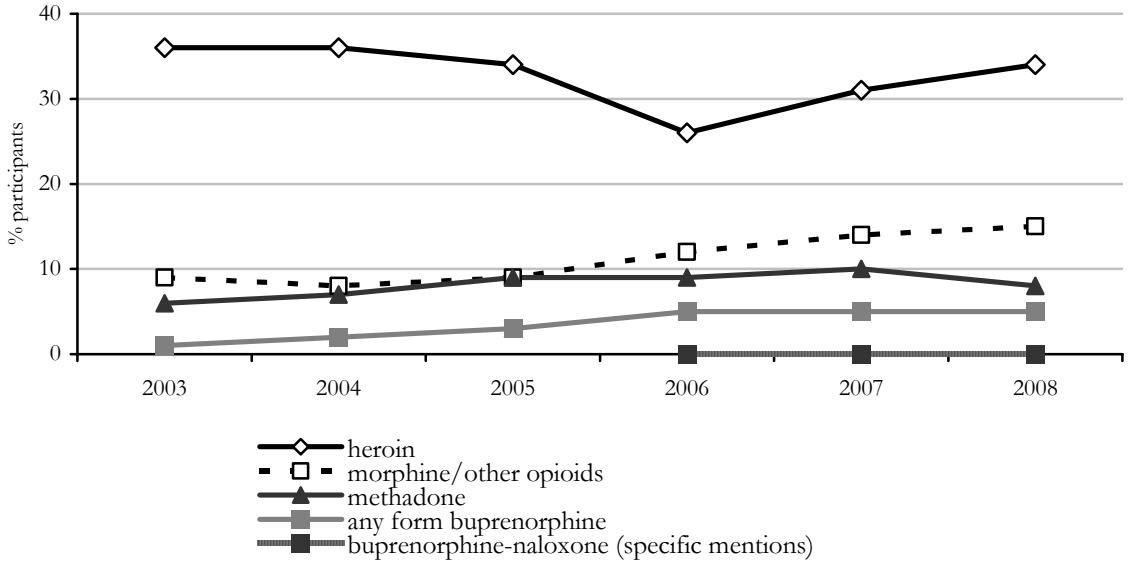
## 5.9. Population-level indicators of OST injection

### 5.9.1. Australian Needle and Syringe Program Survey

The Australian Needle and Syringe Program Survey (NSP Survey) is conducted by the National Centre for HIV Epidemiology and Clinical Research (University of New South Wales). NSP Survey data is collected annually, and all clients attending selected NSPs during the designated survey period are asked to complete a brief, anonymous questionnaire and to provide a capillary blood sample for HIV and HCV antibody testing [149]. Figure 14 (below) presents national data on the drug last injected.

As seen in Figure 14, methadone is reported as the drug last injected by a larger proportion of NSP clients than buprenorphine (any form) in all years. There were low numbers of specific buprenorphine-naloxone mentions. Although buprenorphine-naloxone injection may be underestimated in this survey's data, it is reasonable to assume that levels of injection of this medication have remained low.

**Figure 14: Proportions of annual NSP Survey participants[1] reporting opioids[2] as last drug injected, 2003-2008.**




**Data source: Australian Annual NSP Survey, NCHECR**

***Notes:***

1 *Participants surveyed at participating NSPs on the given survey day (in 2003, N=2,495; in 2004, N=2,035; in 2005, N=1,800; in 2006, N=1,961; in 2007, N=1,912; and in 2008, N= 2,270).*

2 *Morphine/other opioids includes predominantly pharmaceutical opioids. 'Any form buprenorphine' includes both buprenorphine and buprenorphine-naloxone formulations. Buprenorphine-naloxone specific mentions are plotted separately (there were a total of two mentions in 2006 and one mention in 2008). Given that many participant reported "bupe" as last drug injected, and did not specify which formulation, the figures for buprenorphine-naloxone are likely to be under-represented here (J. Iversen, NCHECR, personal communication).*

## 5.9.2. Queensland NSP data

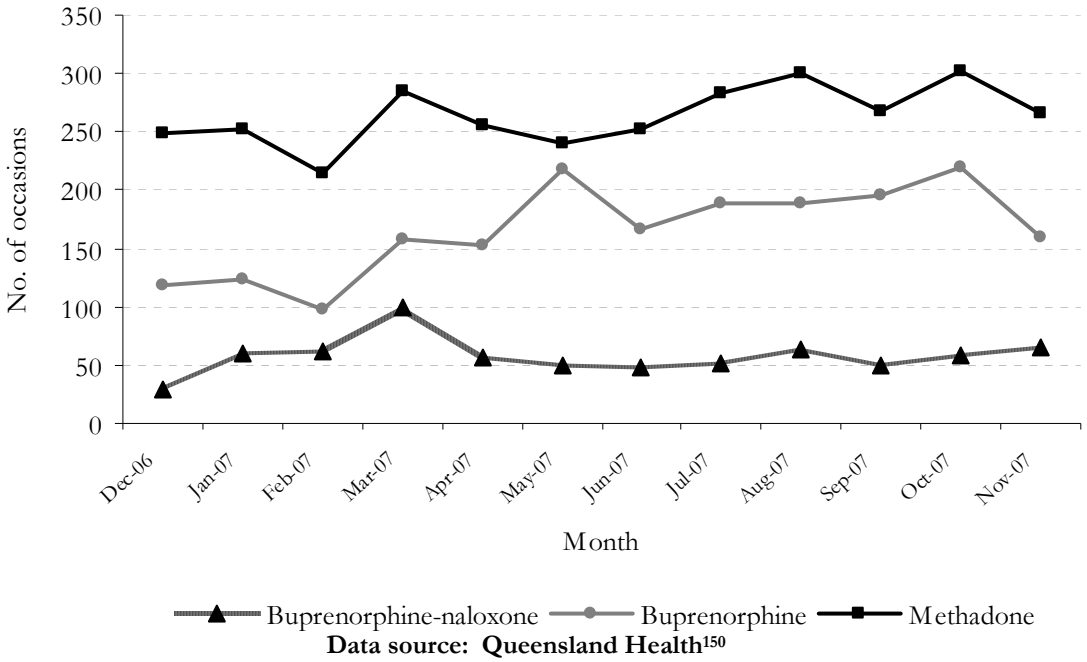
Queensland (QLD) has been regularly monitoring NSP presentations and this data routinely separates methadone, buprenorphine and buprenorphine-naloxone injection (other Australian jurisdictions have not yet established these systems).

To place the injection of OST medications in context in QLD, it is important to consider background availability. The uptake of buprenorphine-naloxone in QLD has followed a similar pattern to that seen nationally (see Figure 3, Chapter 3); from the latter half of 2006, buprenorphine-naloxone sales outstripped those for mono-buprenorphine. More recently, the QLD methadone market share has decreased from around 60% (in 2007) to 50% (in late 2008); buprenorphine/buprenorphine-naloxone increased its market share to approximately half the OST market in this jurisdiction.

Queensland Health has established a minimum data set for monitoring the provision of NSP services. The Queensland Minimum Data Set for NSPs was launched in December 2006, and is working towards enabling the generation of 'real-time' reports. In 2007, 21 NSPs collected the data, and most of these sites were distributing high volumes of injecting equipment[150].

Figure 15 (below) presents the statewide NSP data for QLD for 2006 to 2007 (2008 data were not available at the time of writing this report). Among QLD IDU, methadone injections are reported more frequently than buprenorphine injections. Buprenorphine injections are reported more frequently than buprenorphine-naloxone injections, despite the increased level of buprenorphine-naloxone prescribing.

**Figure 15: Number of NSP service occasions in QLD where OST medications were reported as the last drug injected, December 2006 to November 2007**




**Data source: Queensland Health[150]**

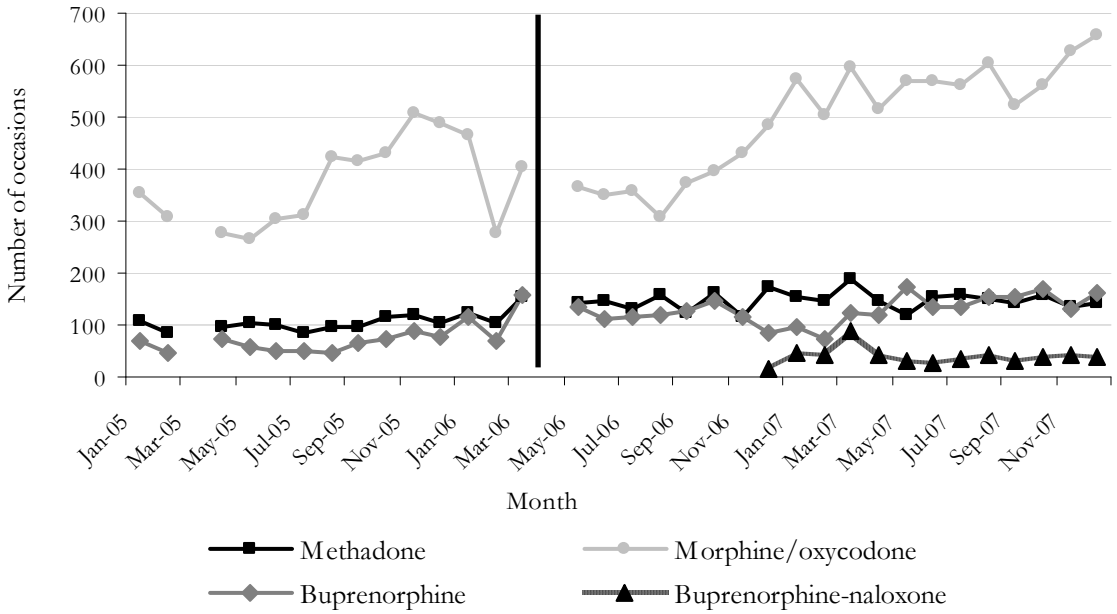
***Notes:*** *QLD NSPs report approximately 8,000-9,000 services occasions per month (in total).*

Similar patterns of OST medication injection are observed in Brisbane NSPs (Figure 16). At the Brisbane Harm Reduction Service, the levels of injection of methadone and buprenorphine among IDU were roughly equivalent, and buprenorphine-naloxone was less frequently mentioned as the last drug injected. At the Biala NSP, the patterns of injecting were very similar to the statewide data.

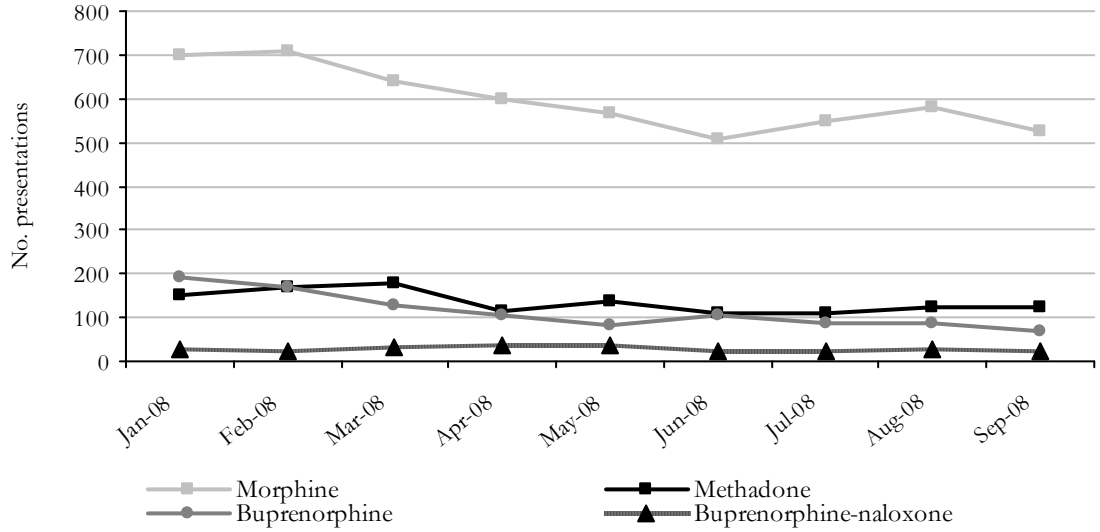
Figures 16.a. and 16.b. also illustrate the scale of the problem of OST medication injection in QLD. Among QLD IDU, OST medications are less frequently injected than other pharmaceutical opioids (predominantly morphine and oxycodone).

**Figure 16: Data from two NSPs in Brisbane, QLD**

**16.a. Number of service occasions at Brisbane Harm Reduction Service where pharmaceutical opioids were the last drug injected, January 2005 to December 2007**




**16.b. Number of service occasions at Biala NSP where pharmaceutical opioids were the last drug injected, January 2008 to December 2008**




**Data source: Queensland Health**

***Notes:*** *Equipment provided by Brisbane Harm Reduction Centre comprises 29% of the total state-wide distribution in Queensland. There are approximately 5,000 to 6,000 presentations a month at this service.*

### 5.9.3. Medically Supervised Injecting Centre data

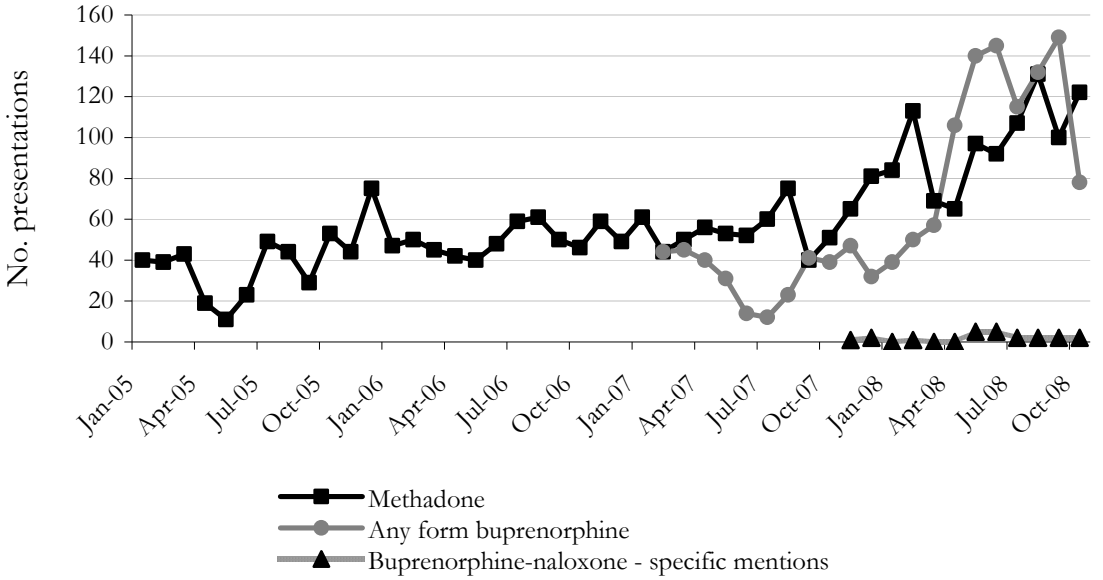
NSW does not have a minimum dataset for NSPs, and data is collected by the individual services for their own monitoring purposes. The Medically Supervised Injecting Centre (MSIC) is located in Kings Cross, Sydney (where there is an established inner-city drug market). The IDU who access the MSIC can be considered a sentinel group of IDU who can provide data on emerging drug trends in NSW (see Figure 17).

As outlined in Chapter 3, there are lower levels of buprenorphine-naloxone being prescribed in NSW, and those clients who are receiving the medication tend to be a selected, stable group of OST clients. The low levels of buprenorphine-naloxone injection (Figure 17.a.) are consistent with these patterns of prescribing. In the latter half of 2008, among MSIC clients, the levels of buprenorphine injection were similar to those for methadone, despite the lower levels of buprenorphine prescribing (relative to methadone) in NSW generally (see Figure 3, Chapter 3).

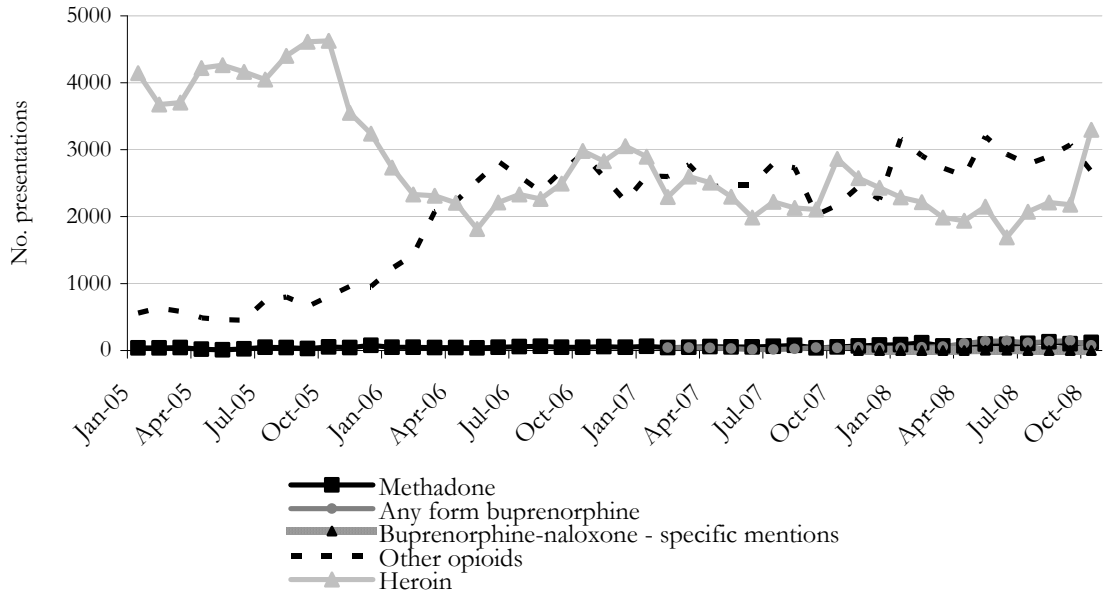
Figure 17.b. indicates that the numbers of OST medication injections are considerably smaller than those observed for heroin and other pharmaceutical opioids.

**Figure 17: Data from the MSIC, Sydney, NSW**

**17.a. Number of presentations where OST medications are reported as the last drug injected, January 2005 to November 2008**




**17. b. Number of presentations where opioids are reported as the last drug injected, January 2005 to November 2008**




***Notes:*** *Approximately 5,000-7,000 injecting episodes per month (in total) are recorded at the Sydney MSIC. 'Any form of buprenorphine' includes the total number of both buprenorphine and buprenorphine-naloxone presentations (specific mentions of buprenorphine-naloxone are plotted separately). MSIC clients are asked which formulation they intend to inject, however many report "bupe" (included in 'any buprenorphine' category). The figures for specific mentions of buprenorphine-naloxone may underestimate the total number of injections occurring, Anecdotal reports indicate that the majority of buprenorphine-naloxone injections are a very small number of individuals injecting their own (rather than diverted) medication (M. Jauncey, MSIC, personal communication).*

## 5.10. Conclusions

Despite the agonist-antagonist formulation, the injection of buprenorphine-naloxone has been reported by IDU, both in and out-of-treatment, and KE. Population-level data (from NSPs) also indicates low levels of buprenorphine-naloxone injection, although there are limitations and caveats that apply to the collection of this data.

Although not eliminated entirely, the levels and frequency of buprenorphine-naloxone injection appear to be less than that for mono-buprenorphine among out-of-treatment IDU. Even when the levels are adjusted for background levels of availability, the levels of buprenorphine-naloxone injection have not increased with the expansion of buprenorphine-naloxone treatment. This finding is even more salient given that the medication is the preferred option for unsupervised dosing of buprenorphine and is potentially more accessible in terms of diversion and injection.

Although small sample sizes limit statistical power, there appear to be jurisdictional differences in both the prevalence and frequency of injection of OST medications. These localised patterns of drug use may be influenced by a number of variables, such as heroin availability, policies for dispensing unsupervised doses of OST medication, and the availability and accessibility of treatment services.

The present study found that current injection of an OST medication, among IDU both in and out-of-treatment, was associated with prior injection of a range of pharmaceutical opioids. This may prove to be a useful clinical indicator in identifying OST clients at increased risk of injecting their prescribed OST medication.

NSP data clearly demonstrated that there were higher levels of injection of pharmaceutical opioids (morphine and oxycodone in particular) than the opioids used in OST. This may reflect the high levels of regulatory controls in the prescribing of OST medications.

# 6. CHARACTERISTICS OF THE MARKET FOR DIVERTED BUPRENORPHINE-NALOXONE

## 6.1. Summary

- *Diversion* is the unsanctioned supply of pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended.
- The rationale for the inclusion of naloxone in buprenorphine-naloxone was that it would deter injection, therefore diversion, of the medication. This assumes that the desirability and street value of pharmaceutical opioids are dependent on the ease with which a medication can be injected (without adverse effects).
- This chapter compares methadone, buprenorphine and buprenorphine-naloxone diversion in Australia, and is the first time the market for illicit buprenorphine-naloxone has been examined in detail. The following indicators of diversion are examined: demand for OST medications, motivations for use, source of diverted medication, and street price of buprenorphine-naloxone. Data sources included interviews with regular (out-of-treatment IDU), OST clients, KE and prescribers.
- There is some demand for diverted OST medications among both IDU and OST clients in Australia, mainly for methadone and buprenorphine, and to a lesser extent, buprenorphine-naloxone. Generally, however, the demand for diverted OST medications is less than that observed for other pharmaceutical opioids such as morphine or oxycodone. Not all diverted medication is injected.
- The most common motivation for using diverted OST medication among out-of-treatment IDU was self-treatment (i.e. treatment of withdrawal symptoms).
- Diverted OST medications are sourced or shared among personal networks and peers. The market is not highly organised or structured. Among those OST clients involved in diversion, OST medications are more commonly given away (no exchange of money) than sold, particularly for buprenorphine-naloxone.
- Buprenorphine-naloxone has a street price that was equivalent to that for mono-buprenorphine in 2008. Consumers in the illicit drug market are not making a distinction between the two buprenorphine formulations.
- There is a market for diverted buprenorphine-naloxone, despite its agonist-antagonist formulation, indicating that the extent to which OST medications are diverted and/or injected will be influenced by a range of variables.

## 6.2. Introduction

As discussed in Chapter 1, *diversion* is defined as the unsanctioned supply of regulated pharmaceuticals from legal sources to the illicit drug market, or to a user for whom the drugs were not intended[49 50]. It does not refer to use of medications by a patient outside the doctor's recommended treatment regime.

OST medications make up a small proportion of the pharmaceutical opioids that leak to the illicit drug market. Australian drug monitoring systems (such as the IDRS) have documented an increasing number of IDU reporting illicit morphine, oxycodone and codeine use[86]. The leakage of OST medication, however, can result in harms at a number of levels. There are risks to individuals such as injection-related injuries and diseases, dependence, overdose and mortality (particularly among opioid-naïve individuals, those with reduced tolerance or when mixed with other CNS depressants such as alcohol or benzodiazepines). Furthermore, the leakage of OST medications can undermine public support for the OST program and jeopardise future investment in and expansion of treatment options.

The rationale for the inclusion of naloxone (in buprenorphine-naloxone) was that it would deter injection, and therefore diversion, of the medication. This assumes that the desirability and street value of pharmaceutical opioids are dependent on the ease with which a medication be injected.

This is the first comparative study of methadone, buprenorphine and buprenorphine-naloxone diversion in Australia, and the first study to examine the market for illicit buprenorphine in detail. This chapter examines the following blackmarket indicators:

- demand for diverted OST medications;
- motivations for use;
- source of diverted buprenorphine-naloxone; and
- street price of diverted buprenorphine-naloxone.

Injection of OST medications may also be considered an indicator for the illicit drug market, but is not discussed here. Chapter 4 discussed injection as a form of non-adherence among OST clients and Chapter 5 discussed injection of diverted medication among out-of-treatment IDU. Not all diverted medication is injected (some is taken orally, sublingually, smoked or snorted) and not all injected medication has been diverted (some individuals inject their own prescribed doses).

## 6.3. Methods and data sources

This chapter draws on data from a number of sources, including the cross-sectional interviews with IDU, OST clients and KE (2007 and 2008), and the postal survey of authorised prescribers (2007). The main source of data is the IDRS interviews with IDU (2006-2008). As discussed in Chapter 2, approximately half the total IDRS sample is in some form of OST (methadone, buprenorphine or buprenorphine-naloxone) in the six months prior to interview. To give the best indication of the illicit market, and use of OST medications among regular IDU not in treatment, the in-treatment group were excluded from the following analyses. Wherever possible, comparisons were made between illicit methadone, buprenorphine and buprenorphine-naloxone, although the main focus of this chapter is on the latter.

Note that the prevalence data reported in this chapter has not been adjusted for background availability of the three medications (as was done for levels of injection among IDU in Chapter 5). Caution therefore needs to be applied when comparing the use of diverted medications.

## 6.4. Demand for diverted OST medications

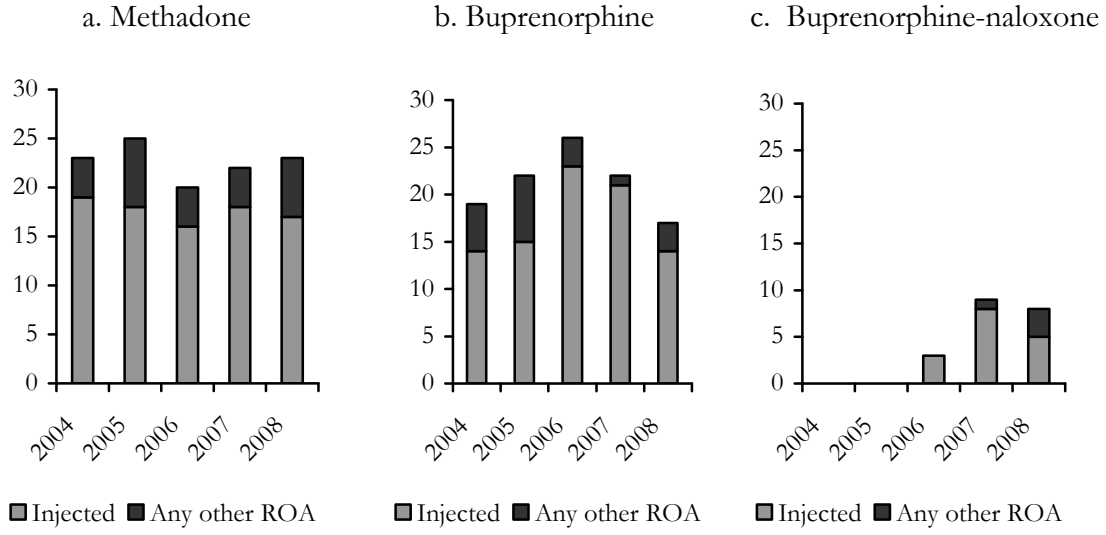
### 6.4.1. IDU reports

In 2008, one in five out-of-treatment IDU reported past six month use of diverted methadone and buprenorphine and these proportions have remained relatively stable since 2004 (see Figure 18 below). When buprenorphine-naloxone was introduced in 2006, a small proportion reported recent use (less than 5%). This proportion increased slightly in 2007, but has remained stable in 2008 (8% in 2008). Recent use of diverted buprenorphine-naloxone was reported by more VIC IDU (24%) than any other jurisdiction (see Appendix 8 for jurisdictional breakdowns).

Nationally, the frequency with which out-of-treatment IDU reported using diverted OST medications was low: a median of eight days for methadone, eight days for buprenorphine, and five days for buprenorphine-naloxone in 2008 (see Appendix 8 for more detail). IDU in VIC reported using diverted buprenorphine-naloxone more frequently (median of 10 days) than the median for the national sample as a whole (median of five days).

Most use of diverted medication was by injection, although a minority of out-of-treatment IDU reported use via other routes of administration (Figure 18). For example, although 24% of out-of-treatment IDU in VIC reported recent use of buprenorphine-naloxone, only 15% reported recent *injection* of the medication (see Appendices 7 and 8 for detailed data).

**Figure 18: Recent use (past six months) of diverted OST medication, by OST-type and route of administration, 2004-2008 (% out-of-treatment IDU)**




***Notes:*** *'Any other ROA' includes routes of administration other than injecting (such as taken orally, sublingually, smoked or snorted).*

### 6.4.2. OST clients' reports

There is some demand for diverted OST medication among methadone and buprenorphine clients, and less demand among buprenorphine-naloxone clients (although there may be different levels of client 'stability' among the three groups given, the NSW threshold for buprenorphine-naloxone is high). A minority (less than 30%) of OST clients in this study supplemented their prescribed doses with medications obtained illicitly (see Appendix 8). Just over a quarter of methadone clients reported recent use of diverted methadone. One-fifth of buprenorphine clients reported recent use of diverted buprenorphine. Fewer buprenorphine-naloxone clients used diverted OST medications in addition to their prescribed doses, than methadone or buprenorphine clients (and there was no clear preference for any one OST-type). Our data were unable to establish OST clients' motivations for using illicitly-obtained medications. The frequency of use, however, is low (less than a median of three out of 180 days for all three medications) (see Appendix 8).

### 6.4.3. KE reports

On the whole, in 2007 and 2008, KE reports corroborated the IDU and OST client self-reports. KE reports indicate that buprenorphine-naloxone is diverted to the illicit market to a lesser extent than methadone or buprenorphine. There was some shift in perceptions from 2007 to 2008: VIC KE reported observing more recent cases of buprenorphine-naloxone diversion (although still less that that observed for buprenorphine) in 2008 than they had in 2007, linking this to the increased availability of the medication. The most common reason given for the lower levels of buprenorphine-naloxone diversion were fear/anxiety among OST clients and IDU regarding the effects of naloxone.

In NSW, the market for illicit buprenorphine-naloxone was seen as non-existent, because of the highly selective patient-group and low levels of prescribing. The perception of KE in NSW was that some buprenorphine-naloxone clients may not be adhering to treatment (i.e. stockpiling for holidays, emergencies or to use later), but were not buying or selling the medication onwards. Several KE in NSW and SA commented that there were other opioids available on the illicit market (e.g. morphine, physeptone, oxycodone, etc), further decreasing the demand for buprenorphine-naloxone. In SA and VIC, KE reported that the demand for buprenorphine-naloxone was less than that for buprenorphine, but that this demand had increased with increased uptake of the medication from 2007-2008.

> *"…there is a preference for buprenorphine but basically users will take what is available, and mostly that is buprenorphine-naloxone now, which has changed from last year. People will take what is available and that is buprenorphine-naloxone…"* (VIC)

In NSW (where there was no perceived market for diverted buprenorphine-naloxone), the only groups identified as likely to use diverted buprenorphine-naloxone were opioid-dependent persons not in treatment who were in withdrawal and buprenorphine clients who had missed a dose. In VIC and SA, a wider range of groups were reported as likely to use diverted buprenorphine-naloxone (such as IDU, buprenorphine clients, buprenorphine-naloxone clients, methadone clients who had missed doses, *"ex-buprenorphine-naloxone clients"*, *"buprenorphine-dependent individuals"*, *"pill users"*, and *"people hanging out"*).

### 6.4.4. OST prescriber reports

Authorised OST prescribers also received reports of a market for diverted OST medications (Table 15), most commonly for methadone and buprenorphine, and less so for buprenorphine-naloxone. Illicit markets for benzodiazepines and morphine were reported more frequently than those for OST medications.

**Table 15: Prescriber reports of buying or selling among their clients***

| | Yes % | No % | Don't know % |
|---|---|---|---|
| *Heard reports of buying or selling:* | | | |
| Methadone (n=278) | 50 | 44 | 6 |
| Buprenorphine (n=262) | 41 | 52 | 7 |
| Buprenorphine-naloxone (n=254) | 23 | 69 | 8 |
| Physeptone (n=249) | 21 | 67 | 12 |
| Morphine (Kapanol, MS Contin, etc) (n=269) | 56 | 36 | 8 |
| Oxycodone (Endone, OxyContin, etc) (n=262) | 51 | 40 | 9 |
| Benzodiazepines (n=270) | 63 | 30 | 7 |

** Among those who prescribers who commented.*

## 6.5. Motivations for using diverted OST medication among regular IDU

The most common motivation for using diverted OST medications was the self-treatment of dependence (particularly among buprenorphine-naloxone injectors) (see Table 16). IDU were asked how frequently they experienced withdrawal symptoms following the injection of the buprenorphine formulations: 21 out of 44 bupenorphine-naloxone injectors had 'never' experienced precipitated withdrawal (48%), compared to 53 out of 94 buprenorphine injectors (56%).

**Table 16: Most commonly reported motivations for using diverted OST medication among out-of-treatment IDU, 2008 (n)**

| | Methadone (n=91) | Buprenorphine (n=46) | Bup-naloxone (n=25) |
|---|---|---|---|
| Self-treatment[1] | 42 (46%) | 26 (56%) | 20 (80%) |
| Intoxication[2] | 23 (25%) | 20 (43%) | 14 (40%) |
| Substitution for other opioids[3] | 20 (23%) | 9 (20%) | 9 (36%) |
| Other | 11 (12%) | 0 (0%) | 0 (0%) |

***Notes:***

[1] *Self-treatment included: alleviate withdrawal; self-manage own treatment for opioid-dependence; supplement dose; can't afford treatment fees; sharing with partner; waitlist for treatment; reluctance to access treatment; reluctance to be "registered"; away from home; and missed a dose.*

[2] *Intoxication included: to obtain an opioid effect; to inject; to get stoned.*

[3] *Substitution for other opioids included: cheaper than other opioids; more available than other opioids; and safer than heroin/other opiates.*

- *Among those IDU who had (i) used diverted OST medications in the past six months; and responded to this question. Multiple responses allowed – percentages do not sum to 100%.*
- *Other motivations included: to treat depression; and to treat methamphetamine dependence.*

## 6.6. Source of diverted OST medications

### 6.6.1. Regular IDU reports

Table 17 (below) highlights the importance of personal networks and peers in the sourcing and sharing of diverted medication. In 2008, out-of-treatment IDU most commonly sourced diverted buprenorphine and buprenorphine-naloxone from friends, acquaintances or a known dealer. About half the IDU believed that the most recent diverted buprenorphine tablet they had obtained was someone else's takeaway dose, and the majority (71%) of this group had purchased the tablet. Diverted buprenorphine-naloxone was also thought to be someone else's takeaway dose and reports were split between having last purchased the tablet (43%) and having been given it for free (48%).

**Table 17: Source of diverted/illicit buprenorphine and buprenorphine-naloxone tablets, 2008 (% out-of-treatment IDU)**

| | Methadone | Buprenorphine | Bup-naloxone |
|---|---|---|---|
| **Main sources[#] (%)** | *n=77* | *n=37* | *n=16* |
| Friends | 53 | 81 | 63 |
| Street dealer | 7 | 14 | 13 |
| Acquaintances | 17 | 19 | 25 |
| Known dealer | 8 | 19 | 19 |
| Unknown dealer | 3 | 3 | 6 |
| Mobile dealer | 1 | 3 | 6 |
| Other | 8 | 0 | 13 |
| **Main method of obtainment (%)** | | *n=42* | *n=21* |
| Purchased | *Not asked* | 71 | 43 |
| Given for free | *Not asked* | 24 | 48 |
| Other | *Not asked* | 5 | 10 |
| **Original source of last purchase (%)** | *n=48* | *n=37* | *n=20* |
| Someone else's takeaway dose | 79 | 54 | 70 |
| Someone else's supervised dose | 8 | 30 | 20 |
| Other | 7 | 3 | 0 |
| Don't know | 6 | 14 | 10 |

[#] *Multiple responses were allowed for this question – sum of percentages exceeds 100%.*

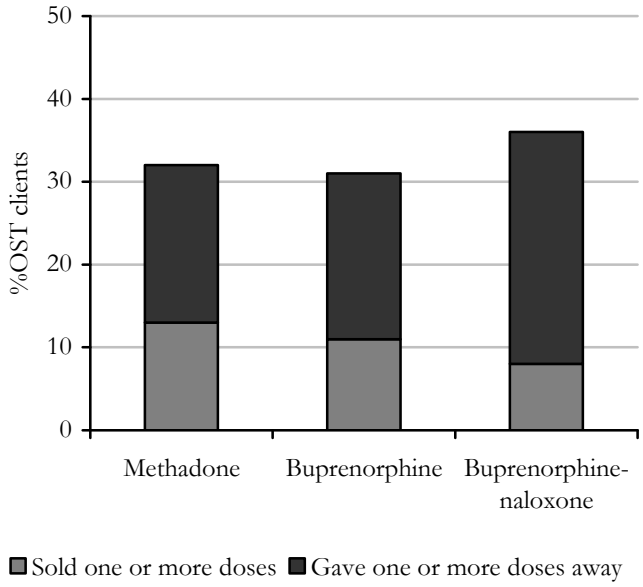
## 6.6.2. OST client reports

Chapter 4 reported the prevalence of diversion among OST clients, and the number of doses diverted per 1,000 doses dispensed. In this section, the prevalence of selling and giving away medication (no exchange of money) are examined separately, to better understand the market for diverted medication.

Overall, the proportions of clients selling their medication did not vary by OST-type (8-13% in 2008) but did vary somewhat between jurisdictions (among the NSW sample, more methadone and less buprenorphine-naloxone clients reported selling doses than clients in the other two jurisdictions) (see Appendix 8 for breakdowns by jurisdiction).

From Figure 19 (below) it appears that the diversion of medications by OST clients may occur through the giving away or sharing of medications (no exchange of money), rather than selling. In general, the proportions of clients reporting giving away their medication was similar across jurisdictions and OST medications, with the exception of a larger proportion of VIC buprenorphine-naloxone clients reporting giving away their medication (Appendix 8).

**Figure 19: Proportions (%) of OST clients who reported selling and/or giving away their prescribed doses in the past six months, by OST type, 2008**




***Note:*** *The above analyses includes all VIC buprenorphine clients interviewed in 2008 (n=51).*

### 6.6.3. KE reports

In NSW, KE reported that methadone syrup and buprenorphine (both supervised and unsupervised doses) were the most frequently diverted OST medications. In SA, supervised and takeaway buprenorphine doses were the main OST of concern. In VIC, supervised buprenorphine was highlighted as the main OST medication of concern.

KE comments indicated that introducing buprenorphine-naloxone may have had unexpected effects on the diversion and injection of methadone and buprenorphine among some OST clients. In VIC, the introduction of buprenorphine-naloxone coincided with a review of takeaway policies resulting in increased access to methadone takeaways, and the perception that there was possibly more diversion of methadone than seen previously. In SA, KE reported that some clients had access to buprenorphine takeaways prior to the combination formulation being introduced, and continued to receive these (permitted in SA policy, and perhaps prescribed by more liberal prescribers). Other clients (who had previously not received buprenorphine takeaways) were willing to forego takeaway doses of buprenorphine-naloxone for either methadone, or their own buprenorphine tablets secreted from the dosing site.

### 6.6.4. Prescriber reports

Prescribers believed that the main source of illicit methadone (92% of n=262 who commented) and illicit buprenorphine-naloxone (77% of n=179 who commented) was the leakage of unsupervised doses. The main source of illicit buprenorphine, however, was believed to be through the removal of supervised doses (62% of n=217 who commented).

## 6.7. Street price of buprenorphine/buprenorphine-naloxone

In the period following the listing of buprenorphine-naloxone on the PBS in 2006, the median street price (as reported by IDU interviewed for the IDRS) for 2 and 8 mg tablets of buprenorphine-naloxone was less than that for equivalent tablets of buprenorphine. After a further 12 months of monitoring, the street price of buprenorphine-naloxone in 2008 was the same as buprenorphine (Table 18). IDU did not make a distinction between the two formulations in terms of price.

Further investigation is needed, but a possible explanation is that buprenorphine-naloxone may be used by IDU on occasions when buprenorphine is not available (this is consistent with the reports of KE: see Appendix 4).

**Table 18: Street price ($) of buprenorphine tablets 2007-2008**

| | 2007 | | | 2008 | | |
|---|---|---|---|---|---|---|
| | **Median price** | **range** | **n** | **Median price** | **range** | **n** |
| Subutex® 2 mg | $10 | $3-30 | 37 | $10 | $5-50 | 29 |
| Suboxone® 2 mg | $6 | $2-25 | 18 | $10 | $5-20 | 15 |
| Subutex® 8 mg | $30 | $7-80 | 88 | $35 | $1-100 | 61 |
| Suboxone® 8 mg | $23 | $4-60 | 24 | $35 | $5-60 | 35 |

***Note:*** *Median price is reported for those IDU who purchased diverted OST medications in the past six months. 2006 data are not reported as very small proportions of IDU reporting purchasing the medication.*

## 6.8. Conclusions

Previous studies have reported that the street price of buprenorphine-naloxone was lower than that for mono-buprenorphine[22 82]. These surveys were conducted within 12 months of the newer formulation being introduced, whereas the present study conducted surveys for three years following widespread introduction of buprenorphine-naloxone. During this time the street price of buprenorphine-naloxone increased; in 2008, it was equivalent to that for mono-buprenorphine. Conducting post-marketing surveillance over a period of more than 12 months is important, as expectancy regarding the aversive effects of naloxone may decrease over time as IDU develop more experience with the medication.

There are a number of scenarios in which buprenorphine-naloxone may be injected without negative effects, and many of these are the same as those in which mono-buprenorphine may be injected (consistent with the two medications having a similar street value). Buprenorphine-naloxone may not have an aversive effect if injected by a person who is (a) an irregular opioid user[68]; (b) a regular user of full-agonists, but currently in withdrawal; or (c) a regular buprenorphine user only.

Although some IDU report using diverted buprenorphine-naloxone, the demand for the agonist-antagonist formulation appears to be less than that for diverted methadone or buprenorphine. The demand for diverted OST medications, in turn, is substantially less than that for other pharmaceutical opioids, such as morphine and oxycodone.

It is often assumed that when OST medications leak from OST programs, they are bought or sold. In reality, there is a lot of sharing of medication between friends or partners. The selling of OST medications happens infrequently.

# 7. DISCUSSION AND CONCLUSIONS

Preventing diversion and injection of the pharmaceutical opioids used in OST reduces harms to the individual (such as dependence, injection-related injuries and diseases and overdose) and protects the integrity of the OST program. Reports of buprenorphine or methadone injection can undermine public support for OST. This in turn may limit future investment and development, and hinder efforts to make OST more attractive and accessible.

Agonist-antagonist formulations (such as buprenorphine-naloxone) are seemingly simple and potentially cost-effective strategies for minimising the diversion and injection of pharmaceutical opioids[42 75 78 151 152]. There is limited post-marketing data, however, examining the impact of agonist-antagonist formulations upon real-life injecting practices. This is the first detailed study comparing the levels of methadone, buprenorphine and buprenophine-naloxone injection among two populations; IDU in and out-of-treatment. Unlike previous post-marketing studies of buprenorphine-naloxone (e.g. [22 82 153]), this study draws on additional data from KE and prescribers, and examines population-level indicators of OST medication injection. The three OST medications were monitored over a three year period following the widespread uptake of buprenorphine-naloxone.

The present study's methodology was largely informed by that of Schuster and colleagues in the US, who also used multiple data sources to monitor buprenorphine and buprenorphine-naloxone over a longer time-period[83]. There are, however, two key points of difference; the present study interviewed out-of-treatment IDU and examined the frequency with which IDU (both in and out-of-treatment) injected OST medications. This is also the first time the levels of methadone, buprenorphine and buprenorphine-naloxone injection have been examined among IDU, adjusting for background availability of each medication. These findings will inform Australian OST policy and have international relevance.

Post-marketing studies conducted to date have concluded that the buprenorphine-naloxone formulation has a lower *abuse liability* than the mono-buprenorphine product [22 82 83], although this term is used simultaneously to imply less injection of the medication and a lower street value. This study examined the issues of diversion and injection separately; individual behaviours carry risks of differing severity and require different policy responses.

## 7.1. Key findings

*(i) Is there injection of the agonist-antagonist formulation - buprenorphine-naloxone - following its large-scale introduction into treatment programs for opioid dependence?*

A minority of IDU, both in and out-of-treatment, reported recent injection of buprenorphine-naloxone, despite the agonist-antagonist formulation. Buprenorphine-naloxone injection was also documented in KE and prescriber reports, and population-level indicators (such as NSP data).

*(ii) To what extent is buprenorphine-naloxone injected compared to existing OST medication formulations, and in particular compared to the mono-buprenorphine product, among those receiving treatment and among out-of-treatment IDU?*

Among OST clients, fewer buprenorphine-naloxone clients reported injecting their medication than methadone or buprenorphine clients. The number of buprenorphine-naloxone doses injected (adjusted for the total number of doses dispensed) was less than that for mono-buprenorphine, but equivalent to that for methadone. A similar pattern was observed among out-of-treatment IDU; fewer IDU reported recent injection of diverted buprenorphine-naloxone, compared to methadone and buprenorphine. Adjusting for background availability, the levels of buprenorphine-naloxone injection were less than those for mono-buprenorphine (despite rapid expansion of buprenorphine-naloxone prescribing in Australia), but were similar to those for methadone syrup. These patterns of OST medication injection among IDU and OST clients were consistent with the reports of KE, OST prescribers and NSP data.

Although there are some jurisdictional differences in uptake, national buprenorphine-naloxone sales outstrip those for mono-buprenorphine (there are some jurisdictional differences). The vast majority of unsupervised buprenorphine doses are the agonist-antagonist formulation. Given that buprenorphine-naloxone is, therefore, the more accessible medication in terms of injection, the finding that it is injected less than the mono-buprenorphine product is an important one.

*(iii) Is diverted buprenorphine-naloxone less attractive in illicit markets?*

Despite its agonist-antagonist formulation, diverted buprenorphine-naloxone has some value in illicit markets. A study conducted in Finland found that the street price of buprenorphine-naloxone was approximately half that of mono-buprenorphine[82]. This survey of IDU, however, was conducted less than 12 months after the new formulation was introduced. The present study found that the street price of buprenorphine-naloxone increased from 2007 to 2008, and in 2008, was equivalent to that for mono-buprenorphine. With an additional year of experience with the medication, consumers in the market for diverted buprenorphine did not distinguish between the two formulations in terms of price. This demonstrated the importance of longer-term monitoring of new medications. This finding also indicated that the ease with which a medication can be injected (without adverse consequences) was not the only factor to influence its value in illicit markets.

Although the two buprenorphine formulations are similar in street price, our findings indicated that buprenorphine-naloxone was less attractive than both methadone and buprenorphine in illicit markets. The proportion of IDU injecting diverted OST medications, however, was substantially smaller than those injecting other pharmaceutical opioids (such as morphine and/or oxycodone). This implies that the infrastructure, supervision and careful monitoring of patients in OST have been successful in preventing widespread diversion and injection of the medications used. There is a need to remain vigilant, however, particularly in light of international reports of new opioid-dependent cohorts dependent on pharmaceutical opioids[154-162]. In the US, prescription opioid deaths now outnumber those for heroin[163-165]. The harms associated with the medications used in OST, however, are likely to be lower than those for other pharmaceutical opioids due to the slower onset of action; sustained release preparations; and in the case of buprenorphine, the ceiling effect of its agonist actions[116].

*(iv) What influences the diversion and/or injection of buprenorphine-naloxone?*

The most common motivation for using diverted buprenorphine-naloxone (among out-of-treatment IDU) was self-treatment of dependence, particularly withdrawal symptoms[22 83]. This is consistent with the findings that substantial proportions of out-of-treatment buprenorphine-naloxone injectors reported *never* experiencing precipitated withdrawal following injection of buprenorphine-naloxone.

The addition of naloxone to sublingual buprenorphine tablets reduces the extent to which the medication is injected, by limiting the circumstances in which it can be injected. The inclusion of naloxone does not act as a deterrent in all situations, however. Clinical studies of buprenorphine-naloxone have demonstrated that the agonist-antagonist formulation was equivalent to mono-buprenorphine if taken sublingually, but could precipitate an uncomfortable withdrawal syndrome if injected by someone who is full-agonist dependent[65-67 69 71 72]. Buprenorphine-naloxone may not have an aversive effect, however, if injected by a person who is (a) an irregular opioid user[68 73 74]; (b) a regular user of full-agonists who is experiencing severe withdrawal symptoms; or (c) a regular buprenorphine user only[70].

The strongest predictors for injection of OST among IDU in and out-of-treatment, was a prior history of injecting other prescription opioids, particularly morphine. Those most at risk of injecting OST medications were those with a recent history of injecting a range of pharmaceuticals: prior history of injecting prescription opioids may prove an important clinical indicator in risk assessments conducted with OST clients.

Localised patterns of drug use, or 'drug cultures', can develop among small groups of personal networks. This study, and previous studies, identified high levels of buprenorphine injection in some suburbs of Melbourne[20 39]. These 'hot spots' of buprenorphine injection may reflect differences in the practice of supervised dosing and may indicate the need for local, targeted responses. Alternatively, the higher levels of buprenorphine injection in VIC might, more generally, reflect a lower-threshold, more accessible model of treatment. By rapidly expanding OST provision through increased buprenorphine prescribing in primary care settings, the VIC model may be attracting a more marginalised group of clients who would not have been in treatment otherwise.

The extent to which buprenorphine-naloxone is diverted and/or injected is not simply a function of its drug formulation. Naloxone acts as a deterrent only in a specific set of circumstances: when the person is a regular, dependent user of full-agonist opioids. Not all use of diverted medication was by injection and some IDU consumed the drug as it was intended to be taken (sublingually). In addition, the extent to which an opioid medication is diverted and/or injected is influenced at a number of levels. Environmental variables may include heroin availability, fluctations in heroin price and/or purity, the availability of other (more desirable) pharmaceutical opioids, and the levels of background availability of OST medications. Treatment variables also play a role, such as insufficient OST places, accessibility/cost of treatment, dose adequacy, dissatisfaction with treatment medication's effects, theft or "standovers", and differences in the extent to which supervised doses are directly observed. The individual variables that influenced diversion and injection include: ambivalence about treatment, a strong preference for (or difficulty stopping) injecting, willingness to help a friend in withdrawal, and concerns about being "registered". The price an individual is willing to pay for diverted buprenophine-naloxone will also depend on their motivations (e.g. seeking intoxication versus self-treating dependence) and whether or not

they are in withdrawal and, therefore, experiencing a level of discomfort. The policy implications for these various motivations differ.

## 7.2. Implications for OST in Australia

The past 30 years of methadone experience in Australia has informed many strategies to minimise the likelihood and severity of harms associated with OST such as risk assessment, supervision of doses, restriction of unsupervised dosing, and restriction of equipment used to inject methadone syrup (butterfly infusion kits). There is also an understanding among prescribers that an individual patient's behaviour can never be predicted with certainty. Some level of non-adherence can be expected, as occurs in all areas of medicine. Experience also suggests that some diversion and injection of medications will occur among OST clients, and are to some extent (in the case of injection) tolerated. This study's findings suggest that supervised administration of doses does not prevent all non-adherent behaviours. Some buprenorphine and buprenorphine-naloxone clients removed supervised doses from the dosing site, and buprenorphine clients reported the highest levels of injection despite this group reporting higher levels of supervision. The OST program faces two key challenges: agreeing whether there is an 'acceptable' level of diversion and injection; and evaluating the differing harms associated with different opioid formulations.

Among the OST clients in this study, larger proportions received unsupervised methadone than unsupervised buprenorphine or buprenorphine-naloxone. Many Australian clinicians appeared willing to accept a level of risk associated with methadone, despite the potential for overdose. Buprenorphine-naloxone is a safer medication in terms of overdose, and its potential for diversion and injection appears to be, at worst, the same as that for methadone (and may be less in some circumstances). There may be a case for relaxing the current level of regulation for buprenorphine-naloxone to allow for further expansion of low-threshold treatments in primary care settings.

To address a large unmet demand for the treatment of opioid dependence in France, from 1995 all registered medical doctors were permitted to prescribe buprenorphine without any special education or licensing[33]. This led to a dramatic increase in the number of opioid dependent people in OST, compared to the more restrictive requirements of methadone maintenance[33]. Although buprenorphine injection has emerged in France over the past 10 years, mortality arising from opioid overdose has declined substantially (by 79%) since the widespread introduction of buprenorphine[33]. In addition, buprenorphine injection may be associated with fewer injection-related HIV risk behaviours among some groups of IDU[114 115 166]. Some of the public health benefits may be seen as contingent upon the French system of health and social services. However, the French model raises questions about the value of restrictive regulations imposed on buprenorphine treatment in Australia and other countries[33].

Buprenorphine and buprenorphine-naloxone are safer in overdose than methadone syrup, but the risks increase with concurrent use of depressants such as alcohol and benzodiazepines; injection of the tablets (especially when secreted in the mouth); or use by opioid-naïve individuals. The risks of buprenorphine/buprenorphine-naloxone injection among OST clients may be "manageable" and could be reduced with dose adjustment, treatment of comorbid mental health concerns, and a reduction in the use of alcohol and other drugs[117]; however, more research is needed.

The attractiveness of OST for some dependent opioid users may be compromised by overly restrictive requirements[48 96 167]. Methadone requires daily, and buprenorphine often requires daily or second-daily, attendance at a dispensing clinic or pharmacy. This limits a client's movements and their ability to work, especially if extended travel is involved. Some treatment services may also require regular supervised urine samples and high levels of security at the clinic, contributing to the treatment's unattractiveness. Patients often have clear ideas about which treatment they want and dissatisfaction in being allocated an unwanted treatment is one common reason for early drop-out of randomised controlled trials [44]. It is important that a range of treatment options be available and patients be informed about these options. Supervised administration of medication is costly and inconvenient to clients and pharmacists. Increased provision of unsupervised buprenorphine-naloxone doses for stable patients may prove an attractive addition to the OST program.

Given that the injection of buprenorphine-naloxone may not precipitate withdrawal among buprenorphine-maintained individuals, the present study's findings of lower levels of injection among the buprenorphine-naloxone clients need to be interpreted with caution. The lower levels of injecting may be an artefact of jurisdictional treatment policies. As buprenorphine-naloxone is the preferred medication for unsupervised dosing, it is reasonable to expect a larger proportion of clinically stable clients among the group receiving this medication.

Alternatively, anxiety about the effects of naloxone among opioid-dependent individuals may be driving the lower levels of buprenorphine-naloxone injection. Open communication and frank discussion of all aspects of drug use and medication are needed to maximise treatment outcomes. If the effects of naloxone are overstated, OST clients may lose trust in the information given to them, and be less likely to share open accounts of their drug use, particularly harmful patterns use of use such as injection of their doses. Some KE (and their clients) reported the perception that buprenorphine-naloxone has been used as a punitive measure in some jurisdictions. These perceptions may impact on the ability of buprenorphine-naloxone to attract and retain people in treatment.

Responses that diminish harm related to non-adherence with OST, including diversion, are necessary, but punitive restriction upon patients and prescribers are unlikely to be effective. Responses need to be guided by the dual maxims of minimising harm and maximising therapeutic benefits. 'Optimally-designed' drug diversion control programs have three goals: (i) to limit access to only those with a legitimate need for the drug; (ii) to track and identify cases where control over this access is compromised; and (iii) to minimise the effect of these controls on legitimate medical practice[168].

Evidence strongly suggests that higher OST doses are more effective in retaining patients in treatment, and reducing misuse, diversion and other opioid use[44]. There is continued debate about the need for varied OST medications to assist different patients (e.g. heroin, morphine) who may not be adequately held by standard OST medications such as methadone and buprenorphine[169-174]. There is also debate about the need for injectable forms of OST for those clients unable to cease injecting[175-182]. This group is at risk of disengaging with treatment services through removal and injection of their dose secretly, potentially eroding trust between clinicians and clients. Finally, diversion to assist other users obviously indicates a need for more treatment places of sufficient attractiveness to retain more users in treatment[44].

## 7.3. Implications for future research

Injecting behaviour, in itself, is rarely the focus of treatment, despite OST clients citing difficulty stopping injecting as the main motivation for non-adherence with OST. Route of administration has been acknowledged in tobacco cessation with the development of nicotine inhalers. Development of interventions for addressing injecting behaviour (psychosocial treatments and injectable forms of OST) and evaluations of their effectiveness are needed.

Further studies are also needed to evaluate clinical practices, such as whether the dilution of unsupervised methadone doses reduces injection, whether crushing buprenorphine tablets decreases the likelihood of clients removing supervised doses from the dosing site, and whether there is better treatment adherence among clients receiving higher doses of OST medications.

The evidence base for determining the severity of non-adherent behaviours, and differentiating between 'low', 'medium' and 'high risk' patients needs further research. The development and evaluation of new interventions to maximise adherence in OST are also needed.

The emergence of illicit markets for other opioid analgesics (such as morphine and oxycodone) in Australia also warrants further research that brings together the fields of opioid dependence and pain management.

## 7.4. Study limitations

Each data source used in this report has its strengths and limitations. The methodology was based on a number of cross-sectional surveys (not cohort studies) and convenience (not random) sampling, which limited the extent to which inferences can be drawn about the wider opioid-dependent population and changes in patterns of drug use among individuals over time. The following caveats apply to the current post-marketing surveillance studies outlined in this report:

- The IDRS intentionally recruits a sentinel group of IDU who inject regularly and are entrenched in inner-city drug markets, as this is the group most able to comment on emerging illicit drug trends. As such, the group cannot be taken as representative of all Australian IDU.
- Both the IDU and OST client samples were recruited from metropolitan areas, and the patterns of drug use reported may differ in remote or rural areas. These surveys are subject to the limitations of self-report (although self-report is sufficiently valid and reliable enough to describe patterns of drug use[88]).
- In recruiting OST clients, the study targeted recruitment strategies to reflect the treatment characteristics of NSW, VIC and SA, and ensure representation of public/private prescribers and clinic/pharmacy dispensing. A change in recruiting organisations in VIC led to concerns about representativeness, and subsequent analyses were adjusted for potential biases.
- Given the limitations that apply to the OST client sample, caution is needed in generalising the rates of non-adherent behaviours to the wider treatment

population in Australia. Rates of non-adherence may vary in different treatment populations.

- The response rate for the authorized prescriber survey was low, but the minority of prescribers who did participate prescribed to a majority of OST clients in Australia. Both the KE and prescriber reports may be subject to expectancy biases regarding the aversive effects of naloxone in the buprenorphine-naloxone formulation.
- The current study was unable to control for the number of takeaway doses dispensed (i.e. we did not collect data on the proportion of doses injected that were unsupervised doses). The study could not evaluate the dilution of methadone syrup takeaways (mandated in VIC and SA OST policy) or the crushing of supervised buprenorpine tablets (mandated in VIC).
- Finally, national indicators (such as prescription, NOPSAD and NSP data) do not routinely separate the buprenorphine/buprenorphine-naloxone formulations or the proportions of supervised/unsupervised medication dispensed.

The comparison of multiple data sources (the surveys of IDU, OST clients, KE and prescribers, and population-level indicators of injection) minimizes the potential biases and serves to validate the self-report of OST clients and IDU. Although there are limitations, the present study provides a detailed evaluation of buprenorphine-naloxone and its impact on injecting behaviour in real-life settings. Few studies have published data in this area to date.

## 7.5. Conclusions

Agonist-antagonist formulations, such as buprenorphine-naloxone, may diminish abuse liability by injection, but will not deter all injection. The inclusion of naloxone has limited the circumstances in which the buprenorphine can be injected, but has not led to a lower street price in Australia. This implies that the market for diverted medications is complex. There continues to be a place for other measures to reduce diversion and injection: agonist-antagonist formulations cannot replace risk assessment; careful patient selection for unsupervised dosing; and ongoing patient monitoring. These remain essential strategies for ensuring the safety and integrity of OST.

Post-marketing surveillance of new medications needs to be conducted over a sufficient time period to detect changes that occur with increased uptake of the medication and experience among clinicians and patients. Ongoing surveillance of the injection of OST medications, and other pharmaceutical opioids, is needed in Australia.

Finally, the findings of this study might change if key variables were to change: less regulated, widespread prescribing of buprenorphine-naloxone; the introduction of new drug formulations; or the removal of the mono-buprenorphine product from the market.

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# APPENDIX 1: Study outputs

The following papers and presentations arose from the study by the time of publication. The investigators intend to publish further (more detailed) papers from the post-marketing surveillance studies in the peer-reviewed literature.

**Conference presentations:**

Larance, B. The diversion and injection of Opioid Treatment Program (OTP) medications following the introduction of buprenorphine-naloxone. Opioid Treatment Program Policy Meeting, jointly convened by AChAM and NDARC. RACP, Sydney, 16 February 2009.

Larance, B., Degenhardt, L., Mattick, R., Ali, R., Bell, J., Lintzeris, N., & Winstock, A. The diversion and injection of buprenorphine-naloxone: Preliminary findings from the post-marketing surveillance studies. APSAD Conference 2008, Sydney, 24-27 November 2008

Mattick, R. P. Suboxone Post-marketing Surveillance. National Drug and Alcohol Research Centre Annual Symposium, Sydney, 31 July - 1 August 2008.

Larance, B., Degenhardt, L., Mattick, R., Ali, R., Bell, J., Lintzeris, N., & Winstock, A. The diversion and injection of OST following the introduction of buprenorphine-naloxone: Preliminary findings from surveillance studies in Australia. Presented at Europad 2008 (European Opiate Addiction Treatment Association conference), Sofia, Bulgaria, 29-31 May 2008.

Larance, B., Degenhardt, L., Mattick, R., Ali, R., Bell, J., Lintzeris, N., & Winstock, A. Surveillance studies monitoring the extent of diversion and injection of buprenorphine-naloxone in Australia: Preliminary findings. Harm Reduction 2008 (IHRA conference), Barcelona, Spain, 11-15 May 2008.

Larance, B. The introduction of Suboxone: Monitoring the extent of diversion and related harms. Paper presented at Meeting New Challenges: APSAD Conference 2006, Cairns, 5-8 November 2006.

Larance, B. The introduction of buprenorphine-naloxone (Suboxone) in Australia: A comparative study of diversion and injection. SPHCM Postgraduate Research Student Conference, Sydney, 27 October 2006.

**Papers:**

Degenhardt, L., Larance, B., Bell, J., Winstock, A., Lintzeris, N., Ali, R., Scheuer, N., & Mattick, R. (2008). Injection of OST in Australia following the introduction of a mixed partial agonist-antagonist opioid medication (in press). MJA.

Larance, B., Degenhardt, L., Lintzeris, N., Winstock, A., Bell, J., & Ali, R.. (2008). Adherence, non-adherence and diversion: A proposal for better-defining behaviours related to the use of pharmaceutical opioids (submitted).

O'Brien, S., et al (2008) Australian prescribers' perceptions of the diversion and injection of OST: a national postal survey (in preparation).

# APPENDIX 2: Patterns of drug use and alternative routes of buprenorphine administration among out-of-treatment IDU

**A.2.1. Patterns of drug use reported by regular (out-of-treatment) IDU, 2008 (% IDU)**

| | Ever used | Used in last 6 months | Median days used in last 6 months[1] | Ever injected | Injected in last 6 months | Median days injected last 6 months[1] |
|---|---|---|---|---|---|---|
| Heroin[2] | 85 | 51 | 60 | 83 | 50 | 55 |
| Methamphetamine | | | | | | |
| Powder | 91 | 50 | 10 | 88 | 48 | 7 |
| Base | 48 | 21 | 6 | 46 | 21 | 6 |
| Crystalline | 74 | 48 | 12 | 71 | 47 | 12 |
| Cocaine | 64 | 16 | 6 | 45 | 13 | 6 |
| Cannabis | 96 | 78 | 180 | - | - | - |
| Ecstasy | 68 | 24 | 2 | 27 | 10 | 2 |
| Benzodiazepines[3] | 75 | 59 | 48 | 20 | 10 | 12 |
| Physeptone tablets[3] | 38 | 17 | n/a | 30 | 14 | n/a |
| Morphine[3] | 77 | 55 | 72 | 71 | 53 | 72 |
| Oxycodone[3] | 54 | 31 | 7 | 43 | 27 | 6 |
| Methadone syrup[3] | 63 | 23 | 8 | 40 | 17 | 12 |
| Buprenorphine [3] | 45 | 17 | 10 | 31 | 14 | 10 |
| Buprenorphine-naloxone[3] | 14 | 8 | 5 | 7 | 5 | 5.5 |

***Notes:***

*1 Among those who reported use/injection in the last six months.*

*2 Excludes 'homebake' form of heroin.*

*3 Includes both prescribed and illicitly-obtained medications.*

**A.2.2. Alternative routes of buprenorphine/buprenorphine-naloxone administration, 2007-2008 (% IDU)**

| | Buprenorphine | | | | Buprenorphine-naloxone | | |
|---|---|---|---|---|---|---|---|
| | **2005** | **2006** | **2007** | **2008** | **2006** | **2007** | **2008** |
| **Snorting** | | | | | | | |
| Ever (lifetime) | 0.2 | 0.2 | 0.4 | 0.7 | # | 0 | 0 |
| Recent* | 0.2 | 0 | 0.2 | 0.5 | # | 0 | 0 |
| **Smoking** | | | | | | | |
| Ever (lifetime) | 0.5 | 2.7 | 0.9 | 1.4 | 0 | 0.2 | 0.2 |
| Recent* | 0.5 | 0.7 | 0.4 | 0.5 | 0 | 0.2 | 0 |

** In the last six months.*
*# not asked in 2006*

# APPENDIX 3: Buprenorphine/buprenorphine-naloxone policies in SA, VIC and NSW

The following table summarises the policies supporting the introduction of buprenorphine-naloxone in SA, VIC and NSW at the time of the 2007 and 2008 OST client interviews. Since this time, both the VIC and NSW policies have undergone minor revisions.

| | SA | VIC | NSW |
|---|---|---|---|
| **Prescriber authorisation** | If a prescriber is approved for buprenorphine, no additional authorisation is required for buprenorphine-naloxone. | If a prescriber is approved for buprenorphine, and is prescribing within the policy on levels of supervision, no additional authorisation is required for buprenorphine-naloxone [104] [183].<br>To prescribe buprenorphine-naloxone with minimal supervision (i.e. outside of the standard guidelines), prescribers must apply for a permit from Drugs and Poisons Regulation Group and complete specialised training. | All prescribers are required to complete the Buprenorphine-naloxone Advanced Prescribers' Training Module to obtain authorisation for buprenorphine-naloxone. |
| **New admissions** | Buprenorphine-naloxone is encouraged for all new buprenorphine patients. | Not specified – left to the prescriber to decide based on their assessment of the patient. | All new buprenorphine admissions are commenced on mono-buprenorphine. Buprenorphine-naloxone only introduced when patients have been stable on mono-buprenorphine for 3 months, and they request takeaways. |
| **Crushing of tablets for supervised administration** | | Both buprenorphine and buprenorphine-naloxone tablets are to be broken into small pieces resembling granules for supervised administration.[104] | NSW policy does not specify the crushing of buprenorphine/buprenorphine-naloxone tablets for supervised administration. |
| **Takeaway formulations** | Both mono-buprenorphine and buprenorphine-naloxone are available as takeaway medication. Mono-buprenorphine takeaways are only permitted if received buprenorphine takeaways prior to the introduction of buprenorphine-naloxone; patient is at 6-day per week pharmacy; or, the patient is pregnant, breastfeeding or has an identified allergy to naloxone. | Only buprenorphine-naloxone is available as a takeaway medication. Buprenorphine may be supplied as a takeaway where a patient is pregnant, breastfeeding, or when there is an identified allergy to naloxone [104]. | Only buprenorphine-naloxone is available as a takeaway medication. Buprenorphine may be supplied as a takeaway where a patient is pregnant, breastfeeding, or when there is an identified allergy to naloxone. |

| | SA | VIC | NSW |
|---|---|---|---|
| **Number of takeaways** | **0-2 months:** In general, no access to takeaway doses, and patients should attend 7-day pharmacy where possible. May be eligible for one takeaway dose per week (for Sundays), and public holidays if no other arrangement can be made.<br>**2-9 months:** Patients may be eligible for up to 6 takeaway doses per month.<br>**9-18 months:** Patients may be eligible for up to 12 takeaway doses per month.<br>**18mths+:** Patients may be eligible for 18 takeaway doses per month. | Three levels of supervised dosing in VIC OST policy:<br>**HIGH:** Daily supervised doing; no takeaways.<br>**MED:** At least 2 continuous months of stable treatment; 1-2 takeaways. of buprenorphine-naloxone per week (minimum 5 days of supervised dosing).<br>**LOW:** At least 6 continuous months of stable treatment; 3-5 takeaways. of bupernorphine-naloxone per week (minimum 2 days supervised dosing)[104].<br>Patients must attend a minimum of 2 days supervised dosing per week, regardless of length of time in treatment. [104]. Once a stable dose of buprenorphine has been reached, prescribers review patients at least monthly or more frequently throughout the first two years.<br>A maximum of 28 days supply of burpenorphine-naloxone ("minimal" supervision) can be prescribed through the permit approval system (see Prescriber Authorisation, above). | Alternate-day dosing is encouraged as an alternative to takeaways.<br>**0-3 months:** No access to takeaway doses, except in exceptional circumstances.<br>**3-4 months:** Patient observed no less than every second day. If stable and no contraindications, eligible for a maximum of 2 takeaway doses of buprenorphine-naloxone per week (not consecutive).<br>**4-5 months:** Patient observed no less than every third day. If stable and no contraindications, eligible for a maximum of 4 takeaway doses of buprenorphine-naloxone per week.<br>**6-8 months:** Patent observed weekly. If stable and no contraindications, 7 days of dispensed buprenorphine-naloxone can be prescribed.<br>**8-12 months:** Patient observed fortnightly. If stable and no contraindications, 14 days of dispensed buprenorphine-naloxone can be prescribed.<br>**12-24 months:** If patient remains stable and no contraindications, 28 days of dispensed buprenorphine-naloxone can be prescribed[103]. |
| **Assessment of client stability** | | VIC policy provides a structured stability assessment checklist for determining the appropriate level of supervised dosing [104]. | NSW policy describes absolute contraindications and specifies drug-use and psychosocial indicators of stability [103]. It provides a suggested *'Suitability for takeaways assessment form'* [103]. |

# APPENDIX 4: KE views of the implementation of buprenorphine-naloxone in their jurisdiction (NSW, VIC and SA)

## A4.1 Limitations

The limitations of buprenorphine-naloxone as reported by KE varied widely between, as well as within, states. Many KE found it difficult to evaluate the impact of buprenorphine-naloxone, as they were still early on in their experience with the medication (this was particularly the case in NSW, but also mentioned by KE in SA). The most common criticisms of buprenorphine-naloxone in NSW were that it is being prescribed in an overly cautious manner, and that there are few trained prescribers and therefore low level of uptake of the medication.

> *"[Buprenorphine-naloxone has had] no impact at all, buprenorphine-naloxone isn't even on the radar in NSW, and the people on buprenorphine-naloxone are those who are very stable…"* (NSW)

KE also noted that OST is dominated by methadone syrup in NSW, probably because it is familiar, enables faster dosing and is easier to supervise (with respect to consumption) than buprenorphine/buprenorphine-naloxone tablets.

KE in VIC more frequently reported the limitations of buprenorphine-naloxone as being related to OST clients' reluctance or refusal to accept the medication. Some of the reasons given for client reluctance included:

- client preference for methadone;
- unable to get started on or not being held by buprenorphine/buprenorphine-naloxone;
- buprenorphine-naloxone dosage not equivalent to buprenorphine dose;
- dislike of the strong lemon flavour;
- the requirement of switching back to buprenorphine if on a dose <2mg and subsequently losing access to takeaways;
- side-effects of buprenorphine-naloxone;
- anxiety/fear of naloxone;
- misunderstanding of what buprenorphine-naloxone is and how it works;
- the disruption of transferring stable buprenorphine clients to a new medication; and
- a desire to continue injecting buprenorphine (among a small group of clients).

Among SA KE the limitations of buprenorphine-naloxone related to the medication not being used to its full potential, e.g.:

- the introduction of buprenorphine-naloxone did not bring extra benefits to existing buprenorphine clients, as the policy did not increase the number of takeaways;
- there is no cost-saving for clients; and
- there is still a need to supervise the dosing of buprenorphine-naloxone (among high risk clients), and this may not always happen:

> *"we know that some pharmacies are not good at supervising doses even if required to, basically it is easier to supervise a liquid being swallowed than tablet being dissolved".* (SA)

KE in all three jurisdictions reported that the acceptability of buprenorphine-naloxone among OST clients was being compromised by the perception of "punitive actions" of treatment providers, specifically:

- the decision made by some prescribers/pharmacies to only prescribe/dispense buprenorphine-naloxone;
- the transfer of clients to buprenorphine-naloxone without prior warning or consultation;
- the perception that the addition of naloxone is a strategy to exert control over clients; and
- the transfer of buprenorphine clients who persistently remove doses/divert their medication to buprenorphine-naloxone.

> *"…the self-worth of people and feelings of control decreased as clients perceived they had little say in being transferred to buprenorphine-naloxone…the chemist says 'sorry we no longer dispense that here, you have to go somewhere else, but there is no where else [for them] to go without travelling out of the area"* (VIC)
>
> *"I disagree with the way buprenorphine-naloxone is used in a punitive fashion by some prescribers…if clients are suspected of diversion or injection they are switched to buprenorphine-naloxone, like it's a punishment"* (SA)

KE in NSW and VIC reported potential financial pressures associated with buprenorphine-naloxone treatment were also a limitation, specifically:

- the expectation (in NSW) that clients will be able to afford to pay up-front for a long script of buprenorphine-naloxone takeaways at private clinics; and
- pharmacies charging a daily rate for dispensing, despite the client not picking up doses everyday.

The two limitations specifically associated with the buprenorphine-naloxone formulation as reported by KE were that it still has some agonist actions (even if slightly attenuated when injected) in some groups of users, and the medication cannot be used in pregnancy. In addition, KE reports indicate that buprenorphine-naloxone has not eliminated diversion and injection entirely.

## A4.2 Benefits

In general, the key benefit of buprenorphine-naloxone reported by KE in NSW was the comparatively large number of takeaway doses for a select few people stable in treatment for the long-term. Retaining the high threshold for buprenorphine-naloxone treatment was seen as necessary for maintaining this outcome:

> *"…[I] don't like connotations of low uptake comments about the New South Wales use of Suboxone…It may be that it shouldn't be higher. Maybe this is the appropriate level of uptake".*

The key benefits for KE in SA and VIC related to the perception that buprenorphine-naloxone had reduced the extent of buprenorphine injection, either because it is less attractive to inject or due to the uptake of the newer formulation leading to less availability of the mono-buprenorphine product.

The potential of buprenorphine-naloxone to lead to increased access to takeaways for a larger number of clients was seen as beneficial in VIC and NSW, but less so in SA (where there has not been an increase in the number of takeaways available for buprenorphine-naloxone). Many KE listed the advantages of increased takeaways (rather than the advantages of buprenorphine-naloxone per se), including:

- a treatment option that allows people to lead a more normal life;
- increased treatment satisfaction;
- retention in treatment; and
- greater chance of securing and maintaining employment.

> *"The takeaways available are the most important advantage… not being chained to a pharmacy, especially for clients who work…a lot of working clients have switched to buprenorphine-naloxone and reports back have been very positive. A lot of chemists will not dispense buprenorphine now because of the inconvenience of supervising clients. It would be great if there were more takeaways, for example, a month's supply, it would give more freedom to work, travel, etcetera.." (VIC)*

Several KE mentioned that doctors, pharmacists and other treatment providers feel more confident and less anxious about providing buprenorphine-naloxone (and takeaways) over buprenorphine, due to:

- perceptions of it being a safer medication;
- perceptions of less intravenous use and injection-related harms; and
- the perception that injected medication is less likely to have been secreted from the mouth.

The KE in SA were more cautious in their accounts of the impact of buprenorphine-naloxone on buprenorphine diversion and injection, although it was generally thought to be a good addition to the OST program:

> *"…Buprenorphine-naloxone does have merit and is worthwhile, perhaps not as much as we first thought but there is still a place for it".* (SA)

# APPENDIX 5: Buprenorphine clients, Victoria, 2007 and 2008

### A.5.1. Geographic spread of buprenorphine clients recruited in Melbourne, Victoria, 2007-2008

| Local Government Area (LGA) | 2007<br>n | 2008<br>n |
|---|---|---|
| Bayside | ≤3* | - |
| Brimbank | - | ≤3* |
| Darebin | ≤3* | - |
| Frankston | - | 5** |
| Greater Dandenong | 5 | 5 |
| Maribyrnong | ≤3* | 11** |
| Melbourne | - | ≤3* |
| Moonee Valley | ≤3* | ≤3* |
| Moreland | - | ≤3* |
| Port Phillip | 5 | 17 |
| Stonnington | - | 5 |
| Yarra | 16 | ≤3* |
| **Total** | **36** | **51** |

**Notes:**

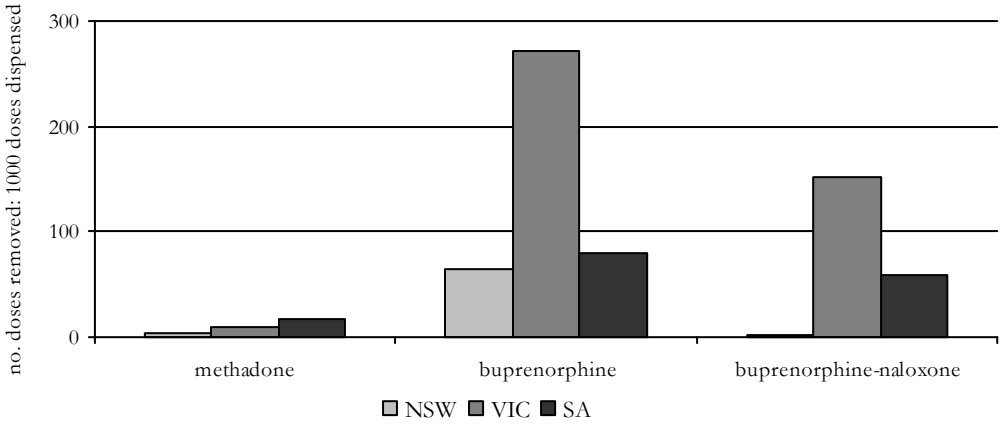
* *To protect participant confidentiality, '≤3' indicates that three, or fewer than three, participants resided in this LGA.*

** *n=5 participants from Frankston and n=11 participants from Footscray (Maribyrnong above) were excluded from the main analyses and their patterns of drug use discussed separately.*

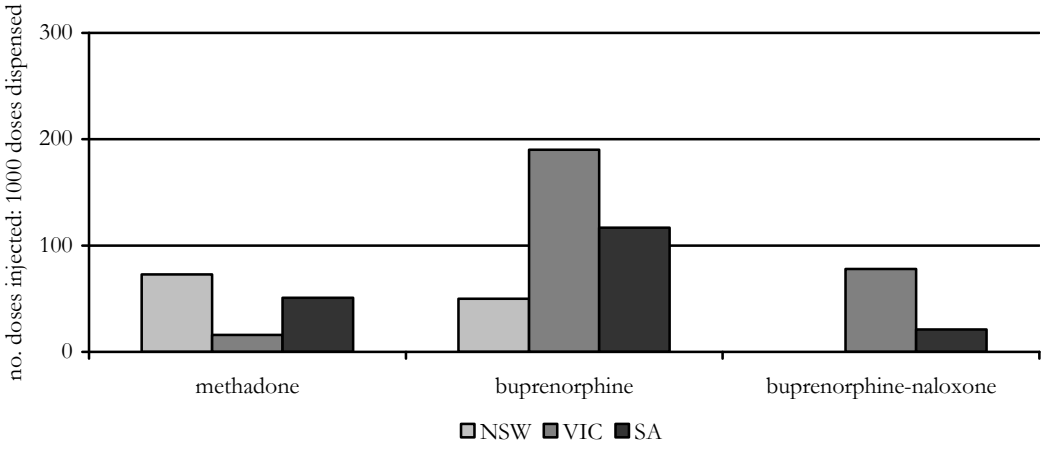
# APPENDIX 6: Frequency of non-adherent behaviours per 1,000 doses dispensed, by jurisdiction

**A.6.1. Frequency of non-adherent behaviours (removing supervised doses, injecting doses and diverting doses) per 1,000 doses dispensed[1], by OST-type, by jurisdiction, 2008**

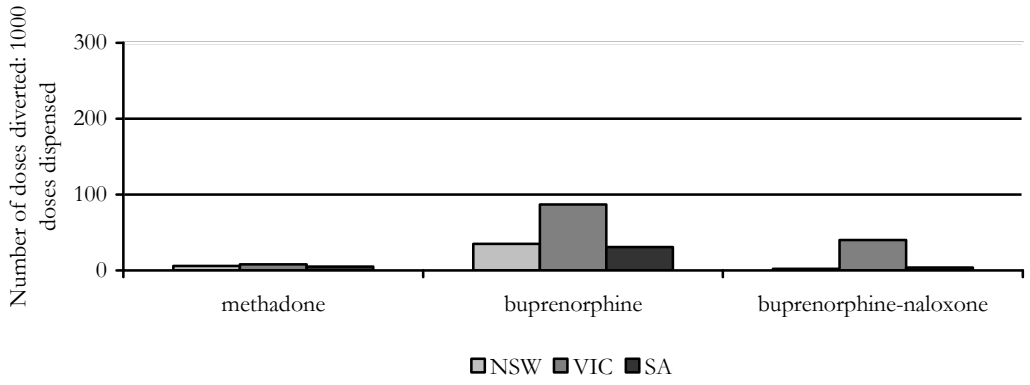
**A.6.1.a. Removal of supervised doses**




**A.6.1.b. Injection of doses**



## A.6.1.c. Diversion of doses




***Notes:***

[1] *Based on total number of daily doses dispensed in the past 180 days to participants in that form of treatment (methadone n=153, buprenorphine n=133, buprenorphine-naloxone n=138). 'Days of use' (of prescribed OST) was used as best available proxy in preference to 'days in treatment' to adjust for second- and third-daily dosing regimes.*

*'Supervised doses removed' includes the total number of all or part of a supervised dose removed from the dosing site in the past six months, adjusted per 1,000 supervised doses dispensed only (i.e. corrected for number of takeaways received).*

*'Doses injected' includes the total number of supervised and unsupervised doses injected in the past six months, adjusted per 1,000 doses dispensed.*

*'Doses diverted' includes the total number of supervised and unsupervised doses that were sold or given away in the past six months, adjusted per 1,000 doses dispensed.*

*The above analyses adjusted for outliers among the buprenorphine clients interviewed in Victoria in 2008 (n=35).*

*Data not collected in 2007.*

# APPENDIX 7: Use of diverted OST medications among IDU and OST clients

**A7.1. Recent use (past six months) of diverted OST medications among out-of-treatment IDU, by jurisdiction, 2006-2008 (%)**

| **2006 IDRS interviews** | **NAT** N=448 | **NSW** n= 58 | **ACT** n=48 | **VIC** n=59 | **TAS** n= 44 | **SA** n=45 | **WA** n= 57 | **NT** n=76 | **QLD** n= 61 |
|---|---|---|---|---|---|---|---|---|---|
| Methadone | 20 | 31 | 33 | 9 | 34 | 16 | 19 | 12 | 13 |
| Buprenorphine | 26 | 26 | 48 | 39 | 5 | 18 | 32 | 12 | 28 |
| Bup-naloxone | 3 | 0 | 2 | 7 | 0 | 0 | 11 | 0 | 7 |
| **2007 IDRS interviews** | **NAT** N=453 | **NSW** n=56 | **ACT** n=35 | **VIC** n=60 | **TAS** n= 49 | **SA** n=49 | **WA** n=49 | **NT** n=72 | **QLD** n=83 |
| Methadone syrup | 22 | 25 | 29 | 15 | 47 | 22 | 20 | 15 | 16 |
| Buprenorphine | 22 | 23 | 51 | 32 | 10 | 6 | 25 | 6 | 29 |
| Bup-naloxone | 9 | 2 | 9 | 18 | 0 | 0 | 20 | 1 | 19 |
| **2008 IDRS interviews** | **NAT** N=444 | **NSW** n=61 | **ACT** n=30 | **VIC** n=54 | **TAS** n=43 | **SA** n=58 | **WA** n=67 | **NT** n=79 | **QLD** n=52 |
| Methadone syrup | 23 | 15 | 33 | 19 | 56 | 10 | 13 | 28 | 23 |
| Buprenorphine | 17 | 10 | 27 | 28 | 5 | 16 | 10 | 17 | 29 |
| Bup-naloxone | 8 | 2 | 13 | 24 | 2 | 3 | 8 | 3 | 14 |

**A7.2. Median number of days (range) out-of-treatment IDU had used illicitly-obtained OST in the last six months, 2008[1]**

| | **NAT** | **NSW** | **ACT** | **VIC** | **TAS** | **SA** | **WA** | **NT** | **QLD** |
|---|---|---|---|---|---|---|---|---|---|
| Methadone | 8 (1-180) | 6[2] (1-49) | 20 (1-48) | 4 (1-40) | 15 (2-72) | 9[2] (1-24) | 9[2] (1-72) | 4 (1-180) | 5 (2-48) |
| Buprenorphine | 8 (1-180) | 3[2] (1-126) | 10[2] (2-180) | 33 (2-180) | n.r. | 3[2] (1-24) | 12[2] (1-90) | 7 (1-180) | 5 (1-72) |
| Bup-naloxone | 5 (1-180) | n.r. | n.r. | 10 (1-65) | n.r. | n.r. | n.r. | n.r. | 4[2] (1-180) |

*1 Among those who reported using the medication in the six months preceding interview (max. no. of days=180).*
*2 Interpret with caution, small sample size (n<10).*
*n.r. Not reported due to very low numbers (n<5).*

**A7.3. Recent use (past six months) of illicitly-obtained OST medications among methadone, buprenorphine and buprenorphine-naloxone clients, by jurisdiction, 2007-2008 (%)**

| | 2007 interviews | | | | 2008 interviews | | | |
|---|---|---|---|---|---|---|---|---|
| | SA | VIC | NSW | TOT | SA | VIC | NSW | TOT |
| **Methadone clients** | n=50 | n=50 | n=57 | n=157 | n= 51 | n= 49 | n= 53 | n=153 |
| Methadone syrup | 26 | 16 | 15 | 22 | 28 | 19 | 30 | 26 |
| Buprenorphine | 6 | 6 | 0 | 4 | 2 | 8 | 4 | 5 |
| Buprenorphine-naloxone | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 |
| **Buprenorphine clients** | n= 29 | n= 36 | n= 61 | n=126 | n= 61 | n= 51 | n= 37 | n=149 |
| Methadone syrup | 0 | 14 | 5 | 6 | 5 | 4 | 3 | 4 |
| Buprenorphine | 24 | 17 | 21 | 21 | 11 | 29 | 16 | 20 |
| Buprenorphine-naloxone | 7 | 8 | 8 | 8 | 0 | 14 | 3 | 6 |
| **Bup-naloxone clients** | n=41 | n=64 | n=11 | n=116 | n= 55 | n= 63 | n= 20 | n=138 |
| Methadone syrup | 12 | 8 | 0 | 9 | 11 | 11 | 5 | 10 |
| Buprenorphine | 20 | 16 | 9 | 16 | 11 | 13 | 16 | 13 |
| Buprenorphine-naloxone | 12 | 16 | 0 | 13 | 11 | 19 | 5 | 14 |

**A7.4. Median number of days OST clients had used diverted (illicitly-obtained) OST[1] in the last six months, by jurisdiction, 2007-2008**

| | 2007 interviews | | | | 2008 interviews | | | |
|---|---|---|---|---|---|---|---|---|
| | SA | VIC | NSW | TOT | SA | VIC | NSW | TOT |
| **Methadone** | n=18 | n=18 | n=17 | n=53 | n=22 | n=18 | n=19 | n=59 |
| Median (range) | 3 (1-24) | 1.5 (1-30) | 3 (1-60) | 2 (1-60) | 3 (1-48) | 3 (1-48) | 3 (1-48) | 3(1048) |
| **Buprenorphine** | n=18 | n=19 | n=14 | n=51 | n=11 | n=25 | n=15 | n=51 |
| Median (range) | 7.5 (1-30) | 4 (1-30) | 2.5 (1-48) | 3 (1-48) | 2 (1-60) | 5 (1-120) | 3 (1-20) | 3 (1-120) |
| **Bup-naloxone** | n=7 | n=13 | n=5 | n=25 | n=7 | n=19 | n=3 | n=29 |
| Median (range) | 2 (1-3) [2] | 3 (1-90) | 1 (1-2) [2] | 2 (1-90) | 2 (1-30)[2] | 2 (1-90) | n.r.[3] | 2 (1-90) |

***Notes:***

*1 Among those who reported using illicitly-obtained products in the six months preceding interview (max. no. of days=180).*

*2 Interpret with caution – small numbers (n<10).*

*n.r. Not reported due to very small numbers (n<5) .*

# APPENDIX 8: Diversion of doses of prescribed OST medication among OST clients

**A8.1. Sold a dose of their current OST medication in the last six months, by jurisdiction, 2008 (% OST clients)**

| | 2008 | | | |
|---|---|---|---|---|
| | SA | VIC | NSW | TOTAL |
| Methadone (n=153) | 12 | 8 | 19 | 13 |
| Buprenorphine (n=149) | 14 | 14 | 8 | 11 |
| Buprenorphine-naloxone (n=137) | 9 | 10 | 0 | 8 |

*Note that the proportions listed above are among those clients receiving that particular form of OST, and includes all 2008 VIC buprenorphine clients (n=51).*

**A8.2. Gave away (for free) or shared their OST medication, by jurisdiction, 2008 (% OST clients)**

| | 2008 | | | |
|---|---|---|---|---|
| | SA | VIC | NSW | TOTAL |
| Methadone (n=153) | 18 | 20 | 19 | 19 |
| Buprenorphine (n=149) | 16 | 24 | 20 | 20 |
| Buprenorphine-naloxone (n=137) | 16 | 42 | 15 | 28 |

*Note that the proportions listed above are among those clients receiving that particular form of OST, and includes all 2008 VIC buprenorphine clients (n=51).*

**A8.3. Number of doses diverted by OST clients in past six months per 1,000 daily doses dispensed[1], by OST-type, by jurisdiction, 2008**

| | Methadone | | | | Buprenorphine | | | | Bup-naloxone | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NSW | VIC | SA | TOT | NSW | VIC | SA | TOT | NSW | VIC | SA | TOT |
| No. doses sold | 3 | 1 | 3 | **2** | 14 | 28 | 22 | **20** | 0 | 12 | 1 | **6** |
| No. doses given away | 3 | 7 | 3 | **4** | 21 | 51 | 9 | **27** | 2 | 28 | 3 | **14** |

- *Based on total number of daily doses dispensed in the past 180 days to participants in that form of treatment (methadone n=153, buprenorphine n=149, buprenorphine-naloxone n=138). Estimates of the number of daily doses dispensed are based on the number of days 'used' for each prescribed OST medication. The study considered two proxies for number of daily doses dispensed; the number of days 'used' for each prescribed OST medication was fractionally lower than the reported number of days in treatment, so the former measure was used. The above ratios, therefore, may over-estimate how frequently behaviours occur (i.e. these behaviours may occur less frequently per 1,000 doses dispensed).*
- *These figures include all 2008 VIC buprenorphine clients (n=51).*

# APPENDIX 9: Injection of OST medications among IDU and OST clients

**A9.1. Recent (past six months) injection of diverted OST medications among out-of-treatment IDU, by jurisdiction, 2006-2008 (% IDU)**

| **2006 IDRS** | **NAT** | **NSW** | **ACT** | **VIC** | **TAS** | **SA** | **WA** | **NT** | **QLD** |
|---|---|---|---|---|---|---|---|---|---|
| | N=448 | n=58 | n=48 | n=59 | n=44 | n=45 | n=57 | n=76 | n=61 |
| Methadone syrup | 16 | 26 | 31 | 5 | 32 | 9 | 16 | 8 | 10 |
| Buprenorphine | 23 | 21 | 40 | 39 | 5 | 16 | 32 | 9 | 25 |
| Bup-naloxone | 3 | 0 | 2 | 7 | 0 | 0 | 11 | 0 | 5 |
| **2007 IDRS** | **NAT** | **NSW** | **ACT** | **VIC** | **TAS** | **SA** | **WA** | **NT** | **QLD** |
| | N=453 | n=56 | n=35 | n=60 | n=49 | n=49 | n= 49 | n=72 | n= 83 |
| Methadone syrup | 18 | 20 | 29 | 7 | 43 | 12 | 18 | 10 | 15 |
| Buprenorphine | 21 | 20 | 51 | 30 | 10 | 4 | 25 | 6 | 28 |
| Bup-naloxone | 8 | 2 | 6 | 13 | 0 | 0 | 20 | 1 | 19 |
| **2008 IDRS** | **NAT** | **NSW** | **ACT** | **VIC** | **TAS** | **SA** | **WA** | **NT** | **QLD** |
| | N= 444 | n=61 | n=30 | n=54 | n=43 | n=58 | n=67 | n=79 | n=52 |
| Methadone syrup | 17 | 10 | 33 | 6 | 56 | 2 | 8 | 20 | 17 |
| Buprenorphine | 14 | 8 | 23 | 26 | 5 | 10 | 8 | 10 | 25 |
| Bup-naloxone | 5 | 0 | 10 | 15 | 2 | 3 | 8 | 0 | 10 |

**A9.2. Recent (past six months) injection of OST medications among methadone, buprenorphine and buprenorphine-naloxone clients, by jurisdiction, 2007-2008 (% OST clients)**

| | 2007 interviews | | | | 2008 interviews | | | |
|---|---|---|---|---|---|---|---|---|
| | SA | VIC | NSW | TOT | SA | VIC | NSW | TOT |
| **Methadone clients** | n=50 | n=50 | n=57 | n=157 | n=51 | n=49 | n=53 | n=153 |
| Methadone syrup | | | | | | | | |
| Prescribed/licit | 24 | 4 | 32 | 20 | 22 | 14 | 42 | 26 |
| Someone else's/illicit | 16 | 2 | 18 | 12 | 14 | 6 | 28 | 16 |
| Any form (licit or illicit) | 26 | 2 | 37 | 23 | 26 | 14 | 47 | 29 |
| Buprenorphine | | | | | | | | |
| Prescribed/licit | 0 | 4 | 2 | 2 | 0 | 2 | 2 | 1 |
| Someone else's/illicit | 6 | 4 | 0 | 3 | 0 | 6 | 2 | 3 |
| Any form (licit or illicit) | 6 | 6 | 2 | 5 | 0 | 4 | 4 | 3 |
| Buprenorphine-naloxone | | | | | | | | |
| Prescribed/licit | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Someone else's/illicit | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Any form (licit or illicit) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Buprenorphine clients** | n=61 | n=36 | n=29 | n=126 | n=37 | n=51 | n=61 | n=149 |
| Methadone syrup | | | | | | | | |
| Prescribed/licit | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Someone else's/illicit | 0 | 3 | 3 | 2 | 3 | 2 | 2 | 2 |
| Any form (licit or illicit) | 0 | 3 | 3 | 2 | 3 | 2 | 2 | 2 |
| Buprenorphine | | | | | | | | |
| Prescribed/licit | 45 | 26 | 18 | 26 | 30 | 45 | 25 | 33 |
| Someone else's/illicit | 14 | 14 | 15 | 14 | 8 | 24 | 13 | 15 |
| Any form (licit or illicit) | 45 | 28 | 26 | 31 | 30 | 47 | 30 | 36 |
| Buprenorphine-naloxone | | | | | | | | |
| Prescribed/licit | 5 | 0 | 0 | 2 | 0 | 8 | 0 | 3 |
| Someone else's/illicit | 7 | 0 | 7 | 5 | 0 | 8 | 0 | 3 |
| Any form (licit or illicit) | 7 | 0 | 12 | 7 | 0 | 12 | 0 | 4 |
| **Bup-naloxone clients** | n=41 | n=64 | n=11 | n=108 | n=55 | n=63 | n=20 | n=138 |
| Methadone syrup | | | | | | | | |
| Prescribed/licit | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Someone else's/illicit | 7 | 2 | 0 | 3 | 4 | 2 | 5 | 3 |
| Any form (licit or illicit) | 7 | 2 | 0 | 3 | 2 | 2 | 5 | 2 |
| Buprenorphine | | | | | | | | |
| Prescribed/licit | 12 | 2 | 18 | 7 | 2 | 6 | 0 | 4 |
| Someone else's/illicit | 15 | 9 | 0 | 10 | 6 | 6 | 15 | 7 |
| Any form (licit or illicit) | 17 | 11 | 18 | 14 | 7 | 11 | 15 | 10 |
| Buprenorphine-naloxone | | | | | | | | |
| Prescribed/licit | 10 | 11 | 0 | 10 | 6 | 19 | 0 | 11 |
| Someone else's/illicit | 5 | 5 | 0 | 4 | 2 | 7 | 5 | 4 |
| Any form (licit or illicit) | 12 | 11 | 0 | 10 | 6 | 18 | 5 | 11 |