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Mortality related to naltrexone in the treatment of opioid dependence: A comparative analysis

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MORTALITY RELATED TO NALTREXONE IN THE TREATMENT OF OPIOID DEPENDENCE: A COMPARATIVE ANALYSIS

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EXECUTIVE SUMMARY

Background:

Naltrexone is an opiate antagonist, meaning that it blocks the actions of opioids such as heroin in the body. It is registered in Australia for use as an oral maintenance treatment for heroin dependence, and tablets are administered on a daily basis. Provided a person continues to take naltrexone daily, the effects of any opioids taken are blocked or substantially reduced.

However, one of the effects of naltrexone is that it effectively removes tolerance to opioid drugs. Tolerance is the effect that occurs after repeated administrations of a drug, and results in a given dose of a drug having less effect than previously, or a higher dose of a drug being required to get the same effect. Because naltrexone blocks the actions of opioids, naltrexone rapidly removes a person's tolerance to opioids so that a given dose of opioids would have more effect than previously. The lack of naltrexone, not its presence, exposes a naltrexone-maintained patient to risk of opioid overdose. If naltrexone treatment is ceased, individuals may be at risk of opioid overdose if they choose to return to opioid use. There have been no attempts to quantify the mortality rate associated with naltrexone treatment.

Naltrexone implants are an unregistered form of naltrexone treatment which can be accessed through the Therapeutic Goods Administration "Special Access Scheme". Their efficacy in the treatment of opioid dependence is yet to be supported by randomised controlled trial evidence and they have been associated with death and other serious adverse events, both in Australia and overseas.

Buprenorphine and methadone are also used as maintenance pharmacotherapies in the treatment of opioid dependence. These drugs have opioid agonist actions (as do heroin and morphine). These treatments have also been associated with death, primarily in the period soon after treatment commences. These deaths are similar to deaths from opioid overdose, in that methadone or buprenorphine (together with any other depressant drugs that may be present) cause death primarily by respiratory failure or the complications that develop in a coma related to central nervous system depression.

It is important to note at the outset that naltrexone-related deaths are more difficult to monitor than deaths associated with either buprenorphine or methadone. Not only is naltrexone typically not detected at autopsy, but coroners, police and medical professionals are also unlikely to be

aware of the relevance of (or be informed about) a recently terminated episode of naltrexone treatment in the investigation of the circumstances surrounding a death. This report is a first attempt to quantify the mortality associated with oral naltrexone treatment for heroin dependence in Australia. It also compares the resulting rates with those associated with buprenorphine and methadone treatment.

It should be noted that mortality rates associated with implanted naltrexone treatment were not able to be estimated in this study due to lack of national data on the numbers of patients receiving naltrexone implant treatment. As a result, our picture of naltrexone-related death in Australia remains incomplete. We recommend that this lack of data be addressed.

Results:

Oral naltrexone-related deaths

Searches of the National Coronial Information System (NCIS) revealed 32 deaths related to the use of oral naltrexone in the period 2000-2003 in Australia. This number is an underestimate since the majority of known naltrexone-related deaths in Western Australia (WA) and Queensland (QLD) were not detected in our searches.

When expressed as deaths per number of treatment episodes, it was estimated that naltrexone had a mortality rate of 10.1 per 1000 treatment episodes. If the mean treatment retention in naltrexone treatment was estimated at 3 months (rather than two months, as assumed in the above estimate), the mortality rate for naltrexone treatment increased to 15.2 deaths per 1000 treatment episodes.

Naltrexone was associated with a mortality rate of 22.1 per 100 person years during the period of high risk (2 weeks post-treatment), and 1 per 100 person years during the period of low risk (during treatment).

While we did not specifically search for deaths related to naltrexone implants, two fatal cases were identified in the search period, one in Western Australia and one in Queensland. These cases were not included in the above naltrexone mortality rates.

Comparison with methadone- and buprenorphine-related deaths

NCIS searches revealed 1 buprenorphine-related death and 282 methadone-related deaths during the same time frame.

The mortality rate for naltrexone was four times higher than for methadone when calculated as deaths per number of episodes of treatment, and substantially higher than for buprenorphine. The estimated mortality rate was 0.02 per 1000 treatment episodes for buprenorphine and 2.7 per 1000 episodes for methadone.

When considering deaths per periods of high and low risk, the mortality related to naltrexone was approximately seven times that of methadone during the period of high risk and three times the rate during the period of low risk. Naltrexone treatment was associated with a mortality rate of 22.1 per 100 person years during the period of high risk (two weeks following treatment cessation) and 1 per 100 person years during the period of low risk (during treatment). Buprenorphine mortality rates were not expressed in terms of periods of high and low risk due to the low number of deaths detected with this search method.

Conclusions:

Deaths related to oral naltrexone maintenance treatment have occurred in Australia. However, this study found that identifying naltrexone-related death was difficult, and it will remain so as long as coronial databases do not systematically receive and record treatment data in a detailed fashion. The estimates produced in this study are underestimates, since a significant number of known naltrexone deaths reported elsewhere were not detected in our NCIS searches. Because naltrexone-related deaths are not captured in a systematic way, consideration of our results must take into account the various assumptions made and their potential to bias estimates of mortality.

This study also found that the mortality related to oral naltrexone treatment was higher than that for buprenorphine and methadone, two of the most common forms of pharmacotherapy for opioid dependence in this country. Deaths were also related to buprenorphine and methadone treatment, but whether estimated as deaths per 1000 treatment episodes or per 100 person years of risk, the death rate for naltrexone was higher and we believe the estimate provided here is a conservative one.

These mortality rates are plausible given the pharmacology of these drugs. Naltrexone is a treatment that provides blockade of opioid effects during treatment and a sudden reduction in tolerance to all opioids. Buprenorphine and methadone, in contrast, provide tolerance to all other opioids during treatment. It is not surprising, then, that there is a higher potential for more deaths to occur post-treatment in the case of naltrexone. It is also not surprising that more deaths occur during treatment induction with buprenorphine and methadone (where opioid levels are rising), than in naltrexone (where there is an opioid blockade in place).

The mortality rates suggest that oral naltrexone treatment, as it is provided in Australia, can place recipients at significant risk of death, and at higher risk than buprenorphine and methadone. However, it should be noted that naltrexone treatment is a useful option in some well-motivated patient subgroups that form a minority of the opioid-dependent population.

Implant technologies have been proposed as alternative methods for delivering naltrexone. A number of potential issues also relate to this form of treatment, and rigorous research is certainly required to carefully examine the potential for this delivery system to represent a viable treatment option for opioid-dependent persons. Specifically, these issues are: the lack of randomised controlled trial evidence of naltrexone implant efficacy in the treatment of opioid dependence; considerable inter and intra-subject variability in the blood levels of naltrexone resulting from an implant (and so the level of opioid blockade); the lack of good monitoring of adverse events relating to the use of naltrexone implants; and the acceptability of the naltrexone implant preparation to patients and medical professionals. Due to lack of data on the number of people receiving naltrexone implants, this study was unable to include naltrexone implant deaths in estimates of naltrexone-related mortality. Our incidental discovery of two deaths related to naltrexone implants suggests that this formulation of naltrexone also carries with it a mortality risk. The current inability to measure naltrexone implant-related death is an issue that needs to be investigated as a matter of priority.

In comparing mortality rates associated with these pharmacotherapies, it is important to draw the reader's attention to the rates of mortality for active heroin users. It has been estimated that mortality rates for heroin-dependent persons not in treatment are in the vicinity of 0.9 per 100 person years of risk, very similar to the mortality rate of a person in naltrexone treatment (during the period of low risk) calculated in this study. While maintained in methadone or buprenorphine treatment after the initial induction stages, opioid-dependent people are at lower risk of dying. Clearly, an important aspect of methadone and buprenorphine treatment for opioid dependence is the improvement of treatment retention rates.

The mortality risks associated with oral naltrexone treatment, particularly following treatment cessation, warrant serious attention. This is especially the case considering that the majority of unselected opioid-dependent persons will return to opioid use soon after leaving naltrexone treatment. It is recommended that future trials of all treatments for opioid dependence include monitoring of post-treatment mortality risk, as is estimating the rate of naltrexone implant-related mortality. In order to more effectively monitor the use of this drug for the treatment of opioid dependence, and because of the risk of mortality, it may be appropriate to consider naltrexone for scheduling.

1. INTRODUCTION

The treatment of opioid dependence has received considerable research and clinical attention, not least because opioid dependence is associated with significant morbidity and mortality. Treatment is not without its risks, however, and it is important to consider the magnitude of such risks when considering its implementation.

This report seeks to examine the mortality risks of naltrexone (an opioid antagonist) in the treatment of opioid dependence, and compare it to the mortality associated with two other pharmacotherapies for opioid dependence, buprenorphine and methadone.

1.1. Opioids and opioid receptors

Opioids produce their effects in the body through three major receptor subtypes: mu (μ), delta (δ) and kappa (κ). Most of the familiar opioids such as morphine, methadone, and fentanyl, are μ-opioid agonists and produce analgesia and euphoria. Drugs acting at either μ or δ receptors cause respiratory depression (White & Irvine, 1999).

The main pharmacological effects of an opioid such as morphine include analgesia, euphoria and sedation, respiratory depression and cough suppression, nausea and vomiting, pupillary constriction, and reduced gastrointestinal motility (causing constipation) (Rang, Dale, & Ritter, 1995).

1.1.1. Tolerance

Tolerance is a common response to repetitive use of the same drug and is defined as a reduction in response to the drug after repeated administrations. This tolerance applies not only to the drug being administered, but to other drugs with a similar structure and mechanism of action (O'Brien, 1996). This is termed "cross-tolerance" and has the practical application of a patient maintained on one opioid (such as methadone) being tolerant to the effects of other opioids (such as heroin). Tolerance to opioids develops rapidly after first administration, and can be detected within 12 to 24 hours of a dose of morphine (Rang et al., 1995). It is commonly seen in patients using opioids for pain relief and in people using heroin for its euphoric and sedative effects. Tolerance to the different pharmacological effects of opioids does not occur at the same rate, so it is possible that a person who can take up to 50 times the normal analgesic dose of morphine may have little respiratory depression but show marked pupillary constriction and constipation (Rang et al., 1995). In animals, the development of tolerance to respiratory

depression is relatively slow compared to other opioid effects and there is some evidence that this is also true in humans (White & Irvine, 1999). Based on the different rates of tolerance, one model has proposed that experienced opioid users may be at higher risk of fatal opioid overdose, since the difference between an intoxicating and lethal dose may reduce over time (White & Irvine, 1999). Consistent with this theoretical view, a study of 953 heroin-related fatalities in NSW, Australia, between 1992 and 1996 confirmed that older, more experienced opioid users made up the majority of fatal overdose cases (Darke, Ross, Zador, & Sunjic, 2000).

After a period of abstinence from opioids, a person's tolerance rapidly reduces to that of an opioid-naïve person, so they experience a much greater opioid effect at a given dose than when opioid-dependent. This has been shown to be a significant risk factor for overdose death in situations when opioid dependent persons have been relatively opioid free, such as the two weeks following release from prison (Bird & Hutchinson, 2003; Darke et al., 2000; Seaman, Brettle, & Gore, 1998). The loss of tolerance for the different opioid effects is likely to be non-uniform, and the actual rate of loss is not yet known (White & Irvine, 1999).

1.1.2. Opioid overdose

Heroin and methadone are the major opioids implicated in fatal opioid overdose (W. Hall, 1999; W. D. Hall, Degenhardt, & Lynskey, 1999). Heroin (diacetylmorphine) exerts its activities on the opioid receptor through its metabolites, including 6-monoacetylmorphine (6-MAM) and morphine. The activity of methadone, on the other hand, is predominantly through methadone itself (White & Irvine, 1999).

The presentation of a person experiencing an opioid overdose ranges from being in a stupor to a profound coma. Blood pressure and body temperature falls, and the skin becomes cool and clammy. The respiratory rate drops from the normal 12 to 15 breaths per minute (Ganong, 1997) to as low as two to four breaths per minute; lungs fill with fluid, impairing gas exchange; and cyanosis (blueing of the mucous membranes and lips) may occur. The person's pupils reduce in size to pinpoints, skeletal muscles become flaccid, the jaw relaxes and the tongue may block the airway. Infants and children may experience convulsions. Death, if it occurs, is nearly always due to respiratory failure or the complications that can develop during a coma, such as aspiration of vomitus. Potentially fatal complications such as pneumonia may also develop (Reisine & Pasternak, 1996). In fatal opioid overdoses, heroin use is presumptively diagnosed based on the patient's history. Morphine is commonly detected in post-mortem body fluids, and additional autopsy findings may include pulmonary oedema.

The amount of opioids required to cause a fatal opioid overdose depends on the individual's level of tolerance to opioids. An opiate-naïve person could experience toxicity and death at oral opiate doses of between 40 to 60mg of methadone (Reisine & Pasternak, 1996), while an opiate-dependent person would require a much higher dose to reach toxic levels. Central nervous system depressant drugs such as alcohol, benzodiazepines and other opioids potentiate respiratory depression, increasing the risk of death (Darke & Zador, 1996; Warner-Smith, Darke, Lynskey, & Hall, 2001).

Estimates of mortality related to opioid overdose among opioid dependent persons have ranged from 0.5 to 3 per 100 person years (Frischer, 1998; Frischer, Hickman, Kraus, Mariani, & Wiessing, 2001; Larson, 1992). A weighted average mortality rate of 0.43 per 100 person years (95% confidence interval 0.25 to 0.64) was calculated from 34 different cohort studies, predominately consisting of subjects in treatment for opioid dependence (Degenhardt, Hall, Lynskey, & Warner-Smith, 2004). Treatment with drugs such as methadone confers a degree of cross tolerance to opioids and so protects against overdose, reducing the mortality rate (Frischer, 1998; Frischer et al., 2001). In a longitudinal NSW-based study, that followed entrants to a Sydney methadone clinic prior to 1979, the overdose mortality rate for subjects who were *not* in methadone treatment was 0.9 per 100 person years (Capelhorn, Dalton, Halder, Petrenas, & Nisbet, 1996).

1.2. Naltrexone actions, treatment and mortality risk

1.2.1. Action

Naltrexone hydrochloride is an orally well-absorbed opioid antagonist with no agonist properties (Reisine & Pasternak, 1996). It acts at the mu opioid receptor to inhibit the effects of opioids at that receptor (Kirchmayer, Davoli, & Verster, 2004). Peak plasma concentrations of naltrexone in blood plasma are reached within 1 to 2 hours and the duration of action approaches about 24 hours after an oral dose. Its metabolite, 6-beta-naltrexol, is a weaker antagonist with a longer half-life, so some antagonist action remains after approximately 48 hours (Reisine & Pasternak, 1996) or even up to 72 hours (Arnold-Reed et al., 2003). Despite both compounds having relatively short half-lives, the duration of naltrexone blockade is much longer. An oral dose of 50mg naltrexone has been shown to produce 80% inhibition of opioid binding for 72 hours (Lee et al., 1988). Naltrexone has few actions besides its opioid-blocking properties (J. Bell et al., 2003). If given to an opioid-dependent subject, naltrexone will precipitate prolonged symptoms of withdrawal (Reisine & Pasternak, 1996).

Discontinuation of naltrexone treatment produces very few symptoms, and the drug has very little or no potential for abuse (Reisine & Pasternak, 1996). However, it has been speculated that chronic administration of antagonists such as naltrexone increases the density of μ, δ and ϰ receptors in the central nervous system in a type of homeostatic compensation (Lesscher et al., 2003; Parkes & Sinclair, 2000). Rodent models have demonstrated that this "up-regulation" is accompanied by an increase in opioid agonist potency, or functional supersensitivity (Hyytia, Ingman, Soini, Laitinen, & Korpi, 1999; Lesscher et al., 2003). In humans, up-regulation of opioid receptors has been suggested to have the potential to enhance the risk of opioid overdose in people receiving naltrexone treatment (Miotto, McCann, Rawson, Frosch, & Ling, 1997). However, it is unclear whether the receptor up-regulation actually has any discernable clinical impact. One study found no effects of two weeks of oral naltrexone treatment upon the effects of a small dose of morphine on respiratory depression (in normal volunteers), and concluded that naltrexone maintenance was unlikely to induce hypersensitivity to opioids (Cornish et al., 1993). This study does not appear to have been replicated.

1.2.2. Naltrexone treatment

Naltrexone hydrochloride is used as an adjunctive therapy in relapse prevention in former opioid-dependent individuals. It also is used in the treatment of alcohol dependence and a number of other conditions (Kirchmayer et al., 2004).

Naltrexone may help motivated individuals remain abstinent, but it is not a drug that will reduce a patient's desire to use opioids, and a patient's motivation to remain drug-free may vary over time (J. Bell et al., 2003).

A Cochrane review of the efficacy of naltrexone treatment concluded that the methodological quality of available studies was generally poor, and there was insufficient evidence to evaluate the efficacy of this treatment for opioid dependence (Kirchmayer et al., 2004). The evidence at present suggests naltrexone may be more appropriate for opioid users who are committed to long term abstinence (J. Bell et al., 2003), or those participants who face severe consequences if they do not achieve opioid abstinence, such as health care professionals (G. K. Hulse, O'Neil, Hatton, & Paech, 2003; Kirchmayer et al., 2004; Ling & Wesson, 1984). In a recent Australian treatment study of heroin dependent persons, 97 of 317 (31%) participants screened pre-withdrawal for enrolment in naltrexone treatment proceeded to enter naltrexone treatment post-withdrawal; of these enrolled subjects, only 32% were retained in treatment at 12 weeks (Tucker, Ritter, Maher, & Jackson, 2004).

It is usual to commence naltrexone maintenance treatment after the patient has remained opioid-free for at least 5 days (for shorter acting opioids) to 10 days (for methadone) to reduce the chances of precipitating a severe withdrawal (J. Bell et al., 2003). The initial dose is 25mg, and, if no withdrawal signs occur, the patient is given 50mg per day thereafter. Length of treatment is not specified but the drug is stated to be most effective when taken as a part of a comprehensive occupational rehabilitation program or other conditions that support continued compliance (J. Bell et al., 2003). Maintenance of therapeutic levels in the blood using oral naltrexone requires regular dosing, but non-compliance with treatment often occurs (Arnold-Reed et al., 2003). Because the drug is non-dependence-forming, it is considered easier for patients to miss doses than those in agonist maintenance treatments (Digiusto et al., 2004).

The Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) studies included studies that involved the treatment of 324 persons with naltrexone. The majority of those treated with naltrexone had undergone detoxification prior to starting treatment. Naltrexone was generally provided on a takeaway basis, and 7-14 tablets (i.e.: 1-2 weeks supply) were given at a time.

Naltrexone implants

In order to improve compliance with treatment, several groups have explored alternate methods of administration of the drug, including implants and depot preparations (Foster, Brewer, & Steele, 2003; G. Hulse & O'Neil, 2002; G. K. Hulse et al., 2003). However, these devices are not currently registered for use in Australia and no randomised controlled trials for their use in the treatment of opioid dependence have yet been published.

Evidence of effectiveness

A paper discussing two cohorts of British patients receiving naltrexone implants (n=101) reported heroin use outcomes at one and three months post-implantation, which were confirmed by telephone self-report from patients and their families in 66% of cases (Foster et al., 2003). At three months, 23% of subjects had relapsed to regular opioid use and "several" had tested out the blockade of naltrexone by using opioids, although details of this opioid use were not explored systematically.

A non-randomised, non-controlled study of 156 Spanish patients receiving naltrexone implants and psychosocial support therapy reported opioid-free urine test results at 6 and 12-month

follow-up interviews, for the 55% and 21% participants, respectively, who were followed up (Carreno et al., 2003).

Coverage

There is evidence to suggest that there are marked individual variations in plasma concentrations of naltrexone following implants, and, further, that there is considerable intra-individual variation in plasma levels (Olsen, Christophersen, Frogopsahl, Waal, & Morland, 2004). This suggests that different individuals, when given the same dose of naltrexone, may have different levels of protection against opioid agonists. It also suggests that, at different times, the same individual may have different levels of protection. This is an issue of obvious concern given the risk faced by patients if they relapse to opioid use.

A case study of blood naltrexone levels in five patients receiving sequential naltrexone implants also demonstrated great intra- and inter-personal variability (G. Hulse, Arnold-Reed, O'Neil, Chan, & Hansson, 2004). Blood levels of above 2ng/ml naltrexone, and 10ng/ml 6-β-naltrexol, were considered "adequate implant coverage": naltrexone levels dropped below 2ng/ml for two subjects[1], and over half of the samples tested for 6-β-naltrexol were below 10ng/ml. Opioid use during treatment was not reported, but participants remained "non heroin-dependent" (G. Hulse et al., 2004). The criteria for "adequate coverage" were lower than other authors have suggested: levels of 10-30ng/ml blood naltrexone are considered fully effective in antagonising the euphoric effects of 25mg intravenous heroin; 2ng/ml only has 87% efficacy (Hamilton et al., 2002). If 10ng/ml blood naltrexone was taken as the criterion, only four of 46 samples (9%) provided adequate coverage (G. Hulse et al., 2004).

Adverse events

Serious adverse events have been recorded following use of naltrexone implants. These include pulmonary oedema, drug toxicity, withdrawal, aspiration pneumonia, variceal rupture and death. A case series (n = 6) from New York and Pennsylvanian emergency departments in a two-year period included two fatalities (Hamilton et al., 2002). Over a three year period, the US Food and Drug Administration noted an additional 10 deaths in patients with a recent naltrexone pellet implantation (Hamilton et al., 2002).

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[1] It should be noted that the blood sampling frequency in this study was not consistent between subjects, so it is possible that additional instances of low blood naltrexone could have been missed

Local tissue reactions to implants also occur: in an estimated 15% of subjects in the British cohort study mentioned above (Foster et al., 2003); in two out of ten patients in a small pharmacokinetics study (Olsen et al., 2004); and seven out of 156 participants from the Spanish study described above (Carreno et al., 2003).

1.2.3. Mechanism of death

There are three ways in which a naltrexone-related death may occur: opioid overdose while receiving oral naltrexone treatment; opioid overdose after cessation of naltrexone treatment; and toxicity to naltrexone itself. Naltrexone or its metabolites would probably be detected in the autopsy toxicology in the first and last cases, but not in the second. Of these three types, opioid overdose after cessation of naltrexone treatment is the most likely to occur because of poor compliance with treatment and high rates of relapse to opioid use. The absence of naltrexone in post-mortem toxicology makes these deaths particularly difficult to identify.

Overdose risk while receiving naltrexone treatment

Opioid overdose while receiving naltrexone treatment is unlikely, but it is not impossible. The blockade caused by naltrexone at the opioid receptors is surmountable if particularly high amounts of opioids are taken to try and overcome the blockade, meaning there may be a risk of fatal opioid overdose (J. Bell et al., 2003). However, in practice, while someone is maintained upon regular daily doses of naltrexone the risk of opioid overdose is very low (Digiusto et al., 2004).

Overdose risk after cessation of naltrexone treatment

The greatest danger with naltrexone treatment is the increased risk of death from opioid overdose in patients who return to opioid use after being treated with naltrexone (J. Bell et al., 2003). Initiation on naltrexone requires a period of abstinence from opioids, which results in the loss of tolerance to opioids. An individual with low opioid tolerance is more likely to overdose at lower doses of opioids and so is at greater risk of acute opioid intoxication and death, especially if they return to their pre-abstinence levels of opioid use. The National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) studies showed that post-treatment overdoses in patients leaving naltrexone treatment occurred at eight times the rate of patients who left agonist treatments such as buprenorphine and methadone (Digiusto et al., 2004). Accordingly, it was recommended that clinicians alert naltrexone patients to the risks of opioid overdose after ceasing naltrexone use (Digiusto et al., 2004). The possibility that an increase in

the number of opioid receptors (in response to naltrexone treatment) also contributes to the risk of opioid overdose - over and above this lack of tolerance - is not well supported yet (Warner-Smith et al., 2001).

A number of Australian studies have reported on the risk of opioid overdose after cessation of naltrexone treatment. One small study (n=30) of naltrexone-accelerated detoxification as induction onto naltrexone maintenance treatment, reported that one patient died of heroin overdose and two other patients reported non-fatal overdoses after misjudging their own levels of tolerance, despite repeated warnings (J. R. Bell et al., 1999). The patient who died appeared to do so two weeks after their supply of naltrexone maintenance would have been exhausted. NEPOD pooled the data from 13 different clinical trials of pharmacotherapies for opioid dependence conducted across Australia (n=1244) (R. P. Mattick et al., 2004), including the above study. An analysis of serious adverse events in these studies showed that there were 24 overdoses (fatal and non-fatal), after leaving naltrexone treatment, equivalent to 39 per 100 person years. Forty-four percent of these overdoses occurred within the first two weeks after stopping naltrexone treatment and three of these overdoses proved fatal. Three non-fatal overdoses also occurred during naltrexone treatment, although naltrexone subjects were six times more likely to experience an opioid overdose post-treatment than during treatment (95% CI: 2 to 30, p=0.0012). The authors emphasise that these data highlight the need for clinicians to warn their naltrexone patients of the risks of opioid overdose, particularly after treatment ceases (Digiusto et al., 2004; Ritter, 2002).

A case-control study using data linkage methods in Western Australia compared 21 cases of fatal heroin overdoses with prior exposure to naltrexone, with 71 cases of fatal heroin overdose without prior naltrexone exposure, to examine the issue of enhanced sensitivity to opioids following naltrexone treatment (Arnold-Reed et al., 2003). The researchers found no differences in blood morphine levels between the two groups (irrespective of whether overdoses were acute or delayed), suggesting that enhanced sensitivity to opioids may not have played a factor in naltrexone-related opioid overdoses in these cases (Arnold-Reed et al., 2003). Regardless of this finding, however, it remains the case that 21 cases of naltrexone-related heroin overdoses occurred in this state alone during a two year period.

No population-based estimates of the rates of fatal overdose following naltrexone treatment were identified in this review. The NEPOD study estimate of 2.8 deaths per 100 person years of observation (Digiusto et al., 2004) is the only comparator for the current estimate of naltrexone-related mortality.

Naltrexone toxicity

There is limited clinical experience with naltrexone toxicity in humans. The current Australian clinical guidelines for naltrexone note that the drug can be toxic to the liver in high doses, and the margin of separation between an apparently safe dose of naltrexone and a dose causing hepatic injury is fivefold or less (J. Bell et al., 2003). Experience with patients receiving naltrexone for alcohol dependence has demonstrated that abnormal liver function test results are rare (Croop, Faulkner, & Labriola, 1997), and there is little evidence of naltrexone causing clinically significant liver disease or exacerbating pre-existing disease (Brewer & Wong, 2004).

1.3. Buprenorphine actions, treatment and mortality risk

1.3.1. Action

Buprenorphine hydrochloride is a partial opioid receptor agonist (Lintzeris et al., 2001) with effects similar to opioids such as morphine but with less toxicity. The drug has high affinity for opioids receptors (Lintzeris et al., 2001) and a slow rate of dissociation from these receptors, resulting in a long duration of action (R. P. Mattick et al., 2004). Buprenorphine has a flattened dose-response cure, so that doses above about 16mg prolong the duration of the effect but do not increase the peak opioid respiratory depressant effect (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). The respiratory depressant effect of buprenorphine appears to be less than for full opioids such as methadone, and consequently there is a lower risk of opioid overdose (R. P. Mattick et al., 2004).

The first effects of buprenorphine are experienced between 30 and 60 minutes after sublingual administration, peak plasma concentrations of buprenorphine are reached within 1-2 hours, and clinical effects last for approximately 12 hours for low doses (2mg) and 48-72 hours for higher doses of between 16 and 32mg (Lintzeris et al., 2001).

1.3.2. Buprenorphine treatment

Buprenorphine is used both in the management of opioid withdrawal and as a maintenance therapy for opioid-dependent patients 18 years and older, although caution should be exercised for patients with high risk poly-drug use, concomitant medical or psychiatric conditions, chronic pain and for patients transferring from methadone maintenance treatment (Lintzeris et al., 2001). In withdrawal, buprenorphine provides good symptomatic relief, little adverse effects, little rebound withdrawal on discontinuation and has higher treatment retention than clonidine

(Gowing, Ali, & White, 2004; Lintzeris, Bell, Bammer, Jolley, & Rushworth, 2002). As a maintenance therapy for opioid dependence, buprenorphine has similar efficacy to methadone (R.P. Mattick, Kimber, Breen, & Davoli, 2003), but in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project, buprenorphine had a lower retention in treatment in the first six months compared to methadone, possibly due to low induction doses of buprenorphine (R. P. Mattick et al., 2004). Buprenorphine has been registered since 2000 in Australia for both withdrawal and maintenance treatment (R. P. Mattick et al., 2004).

Buprenorphine comes in sublingual preparations of 0.4mg, 2mg and 8mg strengths under the commercial name of "Subutex" (Reckitt Benckiser). Instead of receiving a daily sublingual dose, it is possible for some patients to receive their dose on alternate days or even thrice weekly (Lintzeris et al., 2001). Doses as irregularly as two days per week have been reported by some authors to have comparable efficacy to daily dosing in terms of treatment retention, opioid abstinence and reductions in HIV risk behaviour (Marsch, Bickel, Badger, & Jacobs, 2005).

1.3.3. Mechanism of death

While buprenorphine alone is less likely than heroin, methadone or morphine to cause respiratory depression in high doses, fatal respiratory depression is still possible, particularly if it is co-administered with other drugs that have inhibitory effects on respiration (White & Irvine, 1999). In the context of the current study, a buprenorphine-related death would be highly likely to have buprenorphine detected in autopsy toxicology (assuming it was tested for), probably in combination with alcohol and benzodiazepines.

The mortality rate attributed to buprenorphine in France, where it can be prescribed by any general practitioner, has been estimated at 0.24 per 1000 patients (Auriacombe, Franques, & Tignol, 2001). Virtually all cases of buprenorphine-associated deaths have involved the concomitant administration of other respiratory-depressant drugs, usually benzodiazepines and/or alcohol (Lintzeris et al., 2001).

1.4. Methadone actions, treatment and mortality risk

1.4.1. Action

Methadone is the most common treatment for opioid dependence in Australia, and is a potent synthetic opioid agonist characterised by a long and highly variable half-life (Henry-Edwards et

al., 2003; White & Irvine, 1999). Methadone has good oral bioavailability, is taken as a daily oral dose, with effects qualitatively similar to morphine (discussed earlier).

The pharmacokinetics of methadone are highly variable between individuals, but generally the onset of effects commences 30 minutes after drug ingestion, and blood methadone levels continue to rise for three to four hours after dosing (Henry-Edwards et al., 2003). A person commencing methadone treatment will only reach stable levels of blood methadone (or "stabilise") after a period of 3-10 days, and methadone blood levels will continue to rise in the first week of dosing, falling slowly between doses (Henry-Edwards et al., 2003).

1.4.2. Methadone treatment

In general, methadone and buprenorphine treatment in Australia involve supervised administration – the patient attends a clinic or pharmacy daily, taking medication under direct observation. Jurisdictional guidelines permit "take-away doses" under certain conditions.

Particular caution should be exercised when assessing patients with the following conditions for methadone treatment: high risk poly-drug use, alcohol dependence, reduced opioid tolerance, psychiatric illness (that may impair the person's ability to give informed consent, or if the patient is at high risk of self-harm), chronic pain and some concomitant medical problems (Henry-Edwards et al., 2003).

1.4.3. Mechanism of death

Some psychotropic drugs, such as benzodiazepines and alcohol, may increase the actions of methadone by contributing to its respiratory depressant effect. Other drugs may interact with methadone by either increasing or decreasing its metabolism (Henry-Edwards et al., 2003).

In the context of this study, a methadone-related death would be highly likely to have methadone detected in autopsy toxicology, either as the only drug or in combination with others, such as alcohol and benzodiazepines.

In a study of an Australian maintenance program in the early 1970s, the death rate during methadone maintenance treatment was one third of the death rate outside treatment, suggesting it had a protective effect (Capelhorn, Dalton, Cluff, & Petrenas, 1994).

Overdose risk during first weeks of methadone treatment

The risk of methadone overdose is particularly high around the time of induction onto methadone treatment. In people on methadone programs in NSW in 1994, there were 70.4 deaths per 1000 per year in the first two weeks of methadone treatment, compared to 0.72 deaths per 1000 per year among those who continued beyond 2 weeks (Capelhorn & Drummer, 1999). The critical risk factors – which cannot always be readily identified before initiating treatment - are low opioid tolerance, slow methadone clearance, and concomitant use of benzodiazepines or alcohol. In patients with these risk factors, methadone blood levels can progressively build over the first several days of treatment, leading to fatal respiratory depression. Methadone overdose can be difficult to identify, as toxic effects occur many hours after ingestion. Death often occurs at home during sleep (Henry-Edwards et al., 2003).

Overdose risk after cessation of methadone treatment

While overdose deaths are lower in methadone treatment than out of treatment (Capelhorn et al., 1994), only a few studies have investigated the overdose death rate in the period shortly after ceasing a methadone treatment episode. The Australian NEPOD studies recorded no opioid overdoses (fatal or non-fatal) after treatment cessation in the 805 subjects who had entered methadone or buprenorphine treatment (Digiusto et al., 2004).

A cohort of 5,200 Amsterdam methadone patients was observed during and up to one year after methadone treatment episodes between 1986 and 1998 (Buster, van Brussel, & van den Brink, 2002). Overdose deaths in the first two weeks after cessation of a methadone treatment episode (0.24 deaths per 100 person years) were no different from overdose rates occurring any time after treatment. Overdose rates in the first two weeks of methadone treatment were 0.6 deaths per 100 person years compared to the whole in-treatment overdose mortality rate of 0.23 deaths per 100 person years (Buster et al., 2002). The authors noted that the majority of the heroin users in this study used non-injecting routes of administration, which may have contributed to lower overdose mortality (Buster et al., 2002).

In contrast to the findings above, another cohort study of 827 Amsterdam methadone patients found that leaving treatment was related to higher overdose mortality in the 77% of the cohort with a history of injecting drug use, but not in the complete cohort (Langendam, van Brussel, Coutinho, & van Ameijden, 2001). The overdose rate for the whole study was 0.63 deaths per 100 person years. The dichotomous variable of "in" or "out" of methadone treatment at the

time of death used in this study was not able to capture deaths occurring soon after methadone treatment cessation.

Deaths involving diverted methadone

The current methadone clinical guidelines note that between one third and two thirds of all methadone-related deaths occur among persons using diverted methadone (Henry-Edwards et al., 2003). Take-away doses have also been implicated in overdose deaths of people not in treatment, including some cases where small children have drunk methadone (Sunjic & Zador, 1999).

1.5. Aims of this study

The aims of the current study were to:

1. estimate the number of persons receiving oral naltrexone for the treatment of opioid dependence in the calendar years of 2000 to 2003 inclusive;
2. examine data from the National Coronial Information System (NCIS) on the number of deaths related to oral naltrexone between 2000 and 2003;
3. examine the characteristics of cases where naltrexone was thought to be related to death;
4. calculate estimated mortality rates of oral naltrexone in terms of deaths per number of treatment episodes and periods of high and low mortality risk; and
5. compare these mortality rates for oral naltrexone with rates calculated for methadone and buprenorphine treatment using the same methods.

2. METHOD

2.1. Data on persons receiving treatment

Naltrexone was registered by the Therapeutic Goods Administration (TGA) for the maintenance treatment of opioid dependence in 1999, and is not currently publicly subsidised. Buprenorphine was registered in 2000 for the treatment of opiate maintenance and detoxification. The Pharmaceutical Benefits Advisory Committee (PBAC) recommended in 2001 that buprenorphine be subsidised as a treatment for opioid dependence, and it has been made available in all Australian jurisdictions for this purpose.

Methadone is the primary pharmacotherapy for the treatment of opioid dependence in Australia, and is publicly funded through the Pharmaceutical Benefits Scheme (PBS). Methadone maintenance treatment has been available in Australia since 1969 and is now an established form of treatment in all jurisdictions, although the Opioid Pharmacotherapy Program (using methadone and buprenorphine) was only introduced in the Northern Territory in 2002.

2.1.1. Naltrexone treatment episodes

Naltrexone is not a Schedule 8 drug, so it may be prescribed by any medical practitioner without registering the patient. Naltrexone for the treatment of opioid dependence is not publicly funded, and is available only by private prescription, whereas naltrexone prescribed for alcohol dependence is subsidised under the PBS.

Data were obtained on the number of prescriptions for oral naltrexone, by month, from the Australian Government Department of Health and Ageing. These estimates of naltrexone prescriptions include prescriptions written through public hospitals (K. Klaucke, Australian Government Department of Health and Ageing, personal communication). It should be noted that these estimates do not include unregistered naltrexone implants accessed through the Therapeutic Goods Administration (TGA) "special access scheme". Efforts were made to obtain both sales data from the company supplying naltrexone in Australia, and TGA data on the number of persons receiving naltrexone implants, but such data were not made available for use in this study. Accordingly, we have only estimated oral naltrexone-related mortality, not mortality for all forms of naltrexone treatment.

We received expert clinical advice from a range of sources on the average retention in oral naltrexone treatment (R. Ali, M. Montebello, A. Quigley, personal communication). The

consensus was that the mean prescription period would be between two and three months (given that one month's doses would be prescribed each time). The mean of two months was used for the major estimates in this work; three months was used in a sensitivity analysis. Estimates of three month naltrexone retention from the Australian NEPOD studies range from 2% after conventional inpatient detoxification to 33% in self-selected abstinent patients (R. P. Mattick et al., 2004). Retention rates from clinical experience rather than research were used for this study, as they were considered more relevant to the general use of naltrexone in the clinical setting.

It is important to note that higher retention (i.e. a greater number of prescriptions per client) is likely among particularly well-motivated client groups, such as opioid-dependent medical professionals (Ling & Wesson, 1984; Roth, Hogan, & Farren, 1997). The proportion of such persons receiving naltrexone was not estimated in the current study (the number is likely to be very small), so it is possible that we have overestimated the number of naltrexone treatment episodes as a result. This will lead to a relative underestimate of the mortality rate associated with naltrexone treatment for opioid dependence.

2.1.2. Methadone and buprenorphine treatment episodes

Both buprenorphine and methadone are registered Schedule 8 drugs, and as such can only be prescribed in the treatment of opioid dependence by medical practitioners specifically trained as buprenorphine or methadone prescribers. The authorised prescriber requires an individual patient authority for each patient, and in NSW the Pharmaceutical Services Branch (PSB) maintains a database of all patient authorities, including total number of treatment episodes and whether the episodes are current or not. On a national level, only the numbers of current methadone and buprenorphine treatment episodes at June 31st were available for each year.

To calculate the total national number of episodes of treatment for methadone or buprenorphine between January 2000 and the end of December 2003, we used data from the NSW Health PSB to calculate the percentage of treatment episodes current on June 31st, 2003. We then applied this percentage of current episodes to the national data to give the number of treatment episodes nationally 2000-2003 for methadone and buprenorphine.

2.2. Definitions of deaths related to opioid pharmacotherapy

2.2.1. Naltrexone

These cases include deaths involving both prescribed and illicit naltrexone, despite very few cases involving non-prescribed naltrexone. Any deaths involving implanted naltrexone that happened to be detected during our searches were noted, but not used in the calculation of mortality rates. No specific searches were conducted for implant deaths.

Definition of known naltrexone-related death:

1. Naltrexone specifically mentioned in the coroner's finding as a contributing or causal factor in the person's death; or
2. Opioid overdose within two weeks after the cessation of known naltrexone maintenance treatment[2]; or
3. A death very closely temporally associated (approximately 24 hours) with taking naltrexone, in a person who did not normally take naltrexone treatment; or
4. Death caused by opioid overdose in a person known to be in current naltrexone treatment.

Definition of probable naltrexone-related death:

Some uncertainties about the relatedness of naltrexone, considering other drugs detected by autopsy, or (more commonly) it was not known how recently naltrexone treatment was stopped before the occurrence of the opioid/mixed drug overdose.

Definition of possible naltrexone-related death:

It is conceivable that naltrexone exposure might have made the death more likely, either if the death occurred soon after a dose of naltrexone or as a result of reduced opioid tolerance produced by induction onto naltrexone treatment. Records lack sufficient information to be more certain about the relatedness of naltrexone treatment.

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[2] The interval after treatment cessation has been limited to two weeks before the death, as treatment cessation prior to this time is less likely to be noted by the coroner.

2.2.2. Buprenorphine

These cases include deaths involving both prescribed and illicit buprenorphine because of the high number of cases where the source of the buprenorphine was unknown.

Definition of known buprenorphine-related death:

1. Specifically mentioned by coroner or autopsy pathologist as causal or a contributing cause in the death; or
2. Death from multiple or opioid drug toxicity where buprenorphine was one of the drugs detected at autopsy or in toxicology.
3. Opioid overdose within two weeks of the cessation of known buprenorphine maintenance treatment.[3]

Definition of probable buprenorphine-related death:

There were some uncertainties about the relatedness of buprenorphine in a multiple or opioid drug toxicity death considering other drugs detected by autopsy, or it was not known how recently buprenorphine treatment was stopped before the occurrence of the opioid/mixed drug overdose.

Definition of possible buprenorphine-related death:

It is conceivable that buprenorphine exposure might have made the death more likely, such as if the death occurred soon after a dose of buprenorphine, or fatal injuries were made more likely by buprenorphine exposure. Records lack sufficient information to be more certain about the relatedness of buprenorphine treatment.

2.2.3. Methadone

These cases include deaths involving both prescribed and illicit methadone because of the high number of cases where the source of the methadone was unknown.

[3] The interval after treatment cessation has been limited to two weeks before the death, as treatment cessation prior to this time is less likely to be noted by the coroner.

Definition of known methadone-related death:

1. Specifically mentioned by coroner or autopsy pathologist as causal or a contributing cause in the death, or

2. Death from multiple or opioid drug toxicity where methadone was one of the drugs detected at autopsy or in toxicology.

3. Opioid overdose within two weeks of the cessation of known methadone maintenance treatment.[4]

Definition of probable methadone-related death:

There were some uncertainties about the relatedness of methadone in a multiple or opioid drug toxicity death considering other drugs detected by autopsy, or it was not known how recently naltrexone treatment was stopped before the occurrence of the opioid/mixed drug overdose.

Definition of possible methadone-related death:

It is conceivable that methadone exposure might have made the death more likely, such as if the death occurred soon after a dose of methadone, or fatal injuries were made more likely by methadone exposure. Records lack sufficient information to be more certain about the relatedness of methadone treatment.

2.3. The National Coronial Information System (NCIS)

The NCIS is a hazard identification system and research tool used for government agencies and researchers with an interest in public health and safety, death and injury surveillance, and policy development. It includes all coronial cases in Australia from July 2000 (except for Queensland, which commenced in January 2001). It contains a drugs module with information on deaths related to alcohol, illicit drugs, pharmaceuticals and poisons.

Coronial cases that would be registered in the system include cases where the death has been sudden and unexpected, or violent and unnatural. This includes all suicides, homicides, traffic

[4] The interval after treatment cessation has been limited to two weeks before the death, as treatment cessation prior to this time is less likely to be noted by the coroner.

fatalities, work-place fatalities, drownings, product-related fatalities, sporting fatalities and adverse events in hospitals.

The NCIS is managed by the Monash University National Centre for Coronial Information (MUNCCI). Data entry is undertaken locally by coronial clerks in each of the Coroner's Offices around Australia and the data is then up-loaded to the NCIS on a regular basis.

2.3.1. Database strengths

The NCIS drugs module is able to identify key risk factors and monitor outcomes in an effort to reduce preventable deaths and facilitate health care decision-making. The quality assurance program includes both a Senior Project Officer who visits the state and territory coronial offices and a Quality Assurance Officer based at MUNCCI. Their role is to investigate completeness, timeliness, validity and reliability of data.

2.3.2. Database limitations

Local data entry from the eight Australian jurisdictions results in occasional coding errors, missing fields and documents not attached to records. The quality assurance program listed above aims to minimise this problem.

Some inter-state differences were found in the quality of coronial records. In NSW, coronial findings are also only recorded when an inquest has been held, unlike states such as Victoria, where there is either an inquest or in-chambers finding handed down for all cases, including natural cause deaths. As a result, there are much fewer findings documents associated with NSW cases than in other states. The content of findings documents also varied from state to state. For example, all Victorian findings are created using a form or template, whereas NSW findings differ quite substantially in quality and content from each other. NSW findings are not always self-contained and can rely on other information contained within other documents in the paper coronial file (M. Hoy, NCIS, personal communication). Records from Queensland only contain police reports at this stage, and without the coroner's judgment or toxicology results it is difficult to judge the relatedness of a substance to a death in this state. NSW records lack toxicology reports but this has less impact as NSW autopsy reports contain a brief summary of toxicology results. These differences between coronial records make comparisons in the mortality rates between jurisdictions beyond the capacity of this study, and we have elected to only consider national mortality rates.

We are only able to view cases that were "closed" by both the state coroner and NCIS. It takes a varying amount of time between the date of death and case closure. South Australian cases take an average of two months for case closure, whereas both NSW and the ACT take an average of over 11 months to close their cases (R. Thornton, NCIS, personal communication). We decided to limit our analysis to death cases occurring between 2000 and 2003, to account for the delay in a case becoming closed. Accordingly, the number of persons in the various pharmacotherapy treatments was limited to 2000-2003 data.

Table 1: Percentages of closed coronial cases by state and year (at 01/03/2005)

State	Percentage cases closed in NCIS				
	2000	**2001**	**2002**	**2003**	**2004**
ACT	100%	99%	96%	87%	41%
NSW	97%	83%	83%	73%	44%
NT	100%	100%	99%	92%	59%
QLD	N/A	55%	87%	71%	10%
SA	98%	99%	98%	96%	86%
TAS	100%	99%	98%	94%	74%
VIC	99%	97%	93%	87%	56%
WA	58%	82%	83%	70%	33%

Source: R. Thornton, Coronial Liaison Officer, NCIS

The time taken for an individual case to be closed depends on the level of investigation required for each death, and it is not expected that a poisoning-type death (such as an opioid overdose) would be any different from the average time taken for a case to be closed.

2.3.3. Searching the NCIS

The "Coroner's Screen" search tool was used to search the database for keywords, and these keywords were different for each type of drug-related death. The search was conducted for each of the four different types of documents accessible through the NCIS; findings, autopsy reports, police reports and toxicology reports, and it was also conducted for each Australian state and territory.

Once the search has been performed, the results are presented in a table of summary information and individual case details can be viewed by clicking on the links. Individual case details are linked to their relevant finding, autopsy reports, police report and toxicology report. The majority of cases have a complete set of reports attached, but as discussed in 2.3.2, there are some systematic differences between the jurisdictions.

2.4. NCIS searches

2.4.1. Naltrexone

The keywords "naltrexone" and "revia" were both used in the search. Revia is the commercial name of naltrexone hydrochloride tablets (produced by Orphan Australia Pty Ltd).

The quality and depth of the police reports in the NCIS database are quite variable between the different cases. They can range from a single line stating "an inquest was requested" to over a page with a detailed description of what happened, how the body was encountered, witness reports, and medications found at the scene. Not all reports have been thoroughly proof-read and spelling and grammar mistakes appear. A number of variations in the spelling of "naltrexone" were noted, including "maltrexone", "naltrexane", "naltrixon" and "naltrion".

In the ACT, where all toxicology reports included the word "naltrexone", along with the names of many other drugs, the records had to be searched individually to determine the relatedness of naltrexone to the death.

2.4.2. Buprenorphine

The keywords "buprenorphine", "subutex" and "temgesic" were used. Subutex is the commercial preparation of buprenorphine hydrochloride (0.4mg, 2mg or 8mg) used in the treatment of opiate dependence (produced by Reckitt Benckiser Pty Ltd). Temgesic, produced by the same manufacturers, contains buprenorphine hydrochloride in a smaller dose used for acute, moderate to severe pain. While not registered for use in the treatment of opiate dependence, this use is possible.

Spelling variations "beupomorphine", "bufrenorphine", "bupromorphine" were noted in police records, finding documents and toxicology records.

2.4.3. Methadone

The keywords "methadone" and "biodone" were used. Other methadone formulations such as physeptone appeared in the toxicology and/or autopsy reports as "methadone" rather than the commercial name, so were not included in the keyword searches. Due to the limited time frame of the project and the large numbers of NCIS records mentioning methadone, the search approach was necessarily different for methadone-related deaths. Searches were first only conducted for coroner's findings documents in all states, the data source most likely to detect a

methadone-related death. As Northern Territory findings routinely report when methadone is not detected, records from this state were hand searched to find methadone-related deaths. Queensland records only had police reports available, so these were searched instead. This made the quality of Queensland information much lower than those records coming from the other jurisdictions.

In NSW there were abnormally small numbers of findings documents mentioning methadone compared to other states, due to low numbers of deaths going to the coroner (see section 2.3.2), so autopsy reports were also searched for this state. As many autopsies routinely stated "methadone not detected" (or a similar phrase), the number of records were restricted by only considering deaths caused by "external causes", and then hand searching the records. This means that any deaths where methadone may have contributed to a death by natural causes were not found.

Spelling variations seen in the findings and autopsy documents were less common with methadone than the other two pharmacotherapies, and included "methodone". It was also not commonly reported in files whether the methadone dose was prescribed under a methadone treatment program at the time of death.

Findings documents also do not appear to have standardised ways of reporting the primary cause of death. For instance, a death caused by methadone overdose only may be reported as "methadone toxicity", "toxic effects of methadone", "toxicity to methadone", "effects of methadone", "overdose of methadone", "raised methadone level", and many others. Of the 81 deaths that were known to be methadone-related in Victoria between 2000 and 2003, there were 25 different ways of listing the primary cause of death in the official findings documents (see Appendix 2 for a full list). This means that a search based on a particular cause of death, such as "methadone toxicity" would only capture a minority of methadone-related deaths.

2.5. Calculation of mortality rates

2.5.1. Mortality rates as deaths per treatment episodes

Mortality rates were first calculated as mortality per 1,000 treatment episodes to account for the different rates of prescribing of naltrexone, methadone and buprenorphine. This calculation is made irrespective of the treatment duration, and does not consider differential periods of risk across treatments. As the risk of mortality appears to vary across the treatment episode, it was also decided to express mortality rates in terms of high and low risk periods of death.

2.5.2. Mortality rates considering periods of high and low risk of death

Deaths associated with pharmacotherapies do not occur at a consistent rate over the treatment episode. In methadone treatment, the person is at higher risk of dying during the first week of treatment (Zador & Sunjic, 2000), but in naltrexone treatment the major risk period is after treatment has been stopped. This high risk period for deaths exiting naltrexone treatment has been considered to be two weeks long in the NEPOD studies (Digiusto et al., 2004), so this approach was adopted here. Deaths occurring later than two weeks post-treatment were also considered less likely to have prior naltrexone treatment mentioned in coronial reports.

It should be noted that persons recently ending a treatment episode of methadone and buprenorphine are also at risk of death. Only one such death was detected in using this search method (occurring in the week following a closed episode of prison methadone treatment), so post-treatment deaths for methadone or buprenorphine are not considered in the following mortality rate calculations.

As only one death related to buprenorphine was found, mortality rates in periods of high and low risk were not calculated for buprenorphine.

Naltrexone

Assumptions are:

a) Persons in naltrexone treatment are at high risk of dying in the two weeks following the end of a treatment episode.

b) Persons currently receiving naltrexone treatment are at lower risk of dying while they remain in treatment than if they stopped treatment.

c) The average period of time in naltrexone treatment is 60 days (R. Ali, M. Montebello and A. Quigley, personal communication).

Methadone

Assumptions are:

a) Persons in methadone treatment are at high risk of dying in the first week of a treatment episode.

b) The mean retention in methadone treatment is 6.6 days in the first week of treatment and the median time in treatment is 7 days in NSW. We assume that this retention is consistent at the national level.

c) Persons in methadone treatment are at lower risk of dying in the remaining period of time in treatment than they were in the first week.

d) The mean retention in methadone treatment is 236 days and the median retention is 142 days in NSW and we assume that this retention is generally consistent at the national level.

3. RESULTS

3.1. Estimated number of treatment episodes

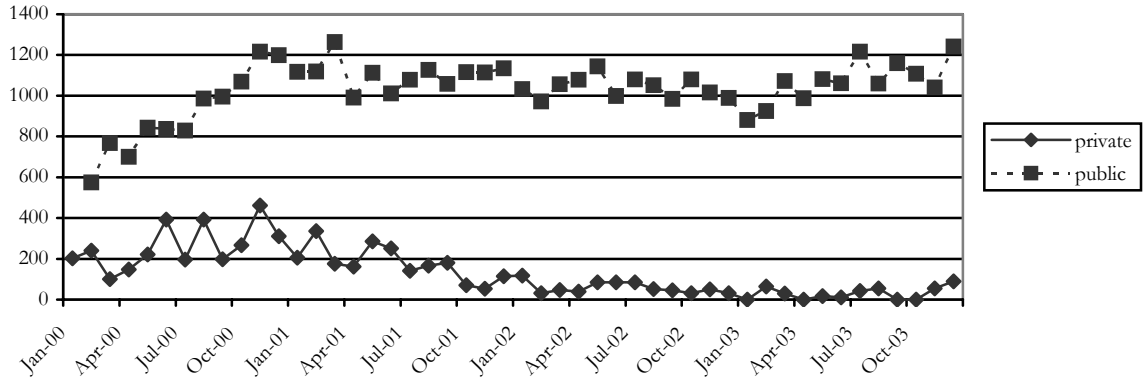
The number of treatment episodes was estimated only for the period between the calendar years of 2000 and 2003 inclusive, to allow for the time lag for closure of NCIS cases (discussed in section 2.3.2).

3.1.1. Naltrexone

We have assumed that all private naltrexone prescriptions were for opioid dependence treatment and all public naltrexone prescriptions were for alcohol dependence treatment. A discussion of this assumption and its potential to bias estimates of mortality is included in Appendix 1.

A total of 6,337 private naltrexone prescriptions were filled in Australia between 2000 and 2003 (Figure 1). Each naltrexone prescription provides one month of medication at the recommended dose of 50mg/day (MIMS Online, 2005), and a treatment episode may include more than one prescription. The estimated number of persons receiving naltrexone treatment for opioid dependence depends upon the mean treatment retention (and so on the number of prescriptions per treatment episode). If it is assumed that mean treatment retention is two months, then the number of persons who received naltrexone treatment was 3,169. If treatment retention is assumed to be three months, then approximately 2,112 persons received naltrexone treatment for opioid dependence between 2000 and 2003.

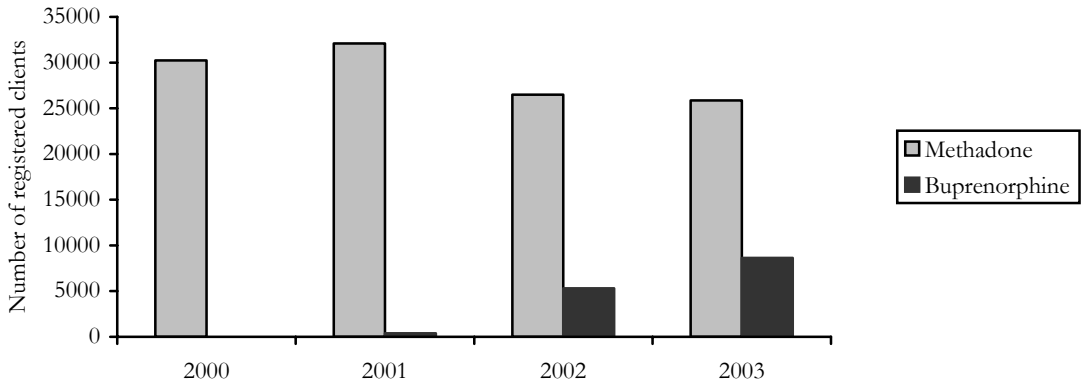
Figure 1: Number of naltrexone prescriptions dispensed, 2000-2003



3.1.2. Buprenorphine

In NSW there were 1,929 episodes of buprenorphine treatment on June 30th, 2003. There were a total of 11,145 buprenorphine treatment episodes estimated to have occurred in NSW between January 2000 and December 2003. National data kept by the Australian Government Department of Health and Ageing were only available for the number of current treatment episodes on June 30th (Figure 2). By making the assumption that the same proportion of treatment episodes was current on June 30th 2003 in the rest of Australia, it was estimated that there were 49,948 episodes of buprenorphine treatment in Australia between 2000 and 2003. This assumption is considered in further detail in Appendix 1.

Figure 2: National pharmacotherapy client numbers as at June 30th, 2000-2003



Source: Australian Government Department of Health and Ageing

3.1.3. Methadone

In NSW there were 13,985 episodes of treatment still running as at June 30th, 2003. A total of 55,408 treatment episodes occurred in NSW between January 2000 and December 2003.

Using the same method as above, it was estimated that there were 102,615 episodes of methadone treatment in Australia between 2000 and 2003.

3.2. Estimated number of deaths

Table 2 shows the total number of detected deaths related to naltrexone, buprenorphine and methadone during the study period, as well as the estimated number of treatment episodes and mortality rate per 1,000 treatment episodes. Table 3 also shows the jurisdictional breakdown of deaths related to the three pharmacotherapies. Appendix 3 lists the cases, relevant details of treatment and manner of deaths.

Naltrexone was the least common pharmacotherapy for opioid dependence. Using a mean treatment episode length of two prescriptions (two months), there were an estimated 3,169 treatment episodes during the study period. A total of 32 deaths among opioid-dependent persons were related to naltrexone during the study period. A little less than half of these (n =15) were known naltrexone deaths; the relatively higher number of "probable" or "possible" deaths reflects difficulties ascertaining treatment status and determining the relation of naltrexone treatment to the death for this form of treatment. The mortality rate was 10.1 deaths per 1,000 episodes (95% confidence interval: 6.9 to 14.3 deaths per 1,000 episodes).

There were almost 50,000 treatment episodes for buprenorphine during the study period. Only one death was related to buprenorphine use; this death occurred after the injection of a number of buprenorphine tablets, and the treatment status of the deceased was unknown. The mortality rate was 0.02 per 1,000 episodes (95% CI: 0.0005 to 0.1 per 1,000 episodes).

As can be seen, methadone was the most common treatment for opioid dependence during the study period. Not surprisingly, deaths related to methadone were also the most numerous, totalling 282 between 2000 and 2003. Of the methadone-related deaths, most (91%) were considered deaths "known" to be due to methadone (alone or in combination with other drugs). Of the 258 known deaths, 92 (36%) occurred among persons whose treatment status was unknown, and 53 (21%) occurred after the use of illicit (diverted) methadone. The rate of mortality (including all thought to be related at least in part to methadone) was 2.7 per 1000 treatment episodes (95% CI: 2.4 to 3.1 per 1,000 episodes).

The mortality rate for naltrexone expressed in deaths per treatment episodes was substantially higher than for the other two treatment modalities. It was 505.0 times higher than the rate for buprenorphine, and 3.7 times higher than the mortality rate for methadone. Comparisons with buprenorphine death rates should be viewed with caution because of the low number of deaths detected with this search method.

Table 2: Deaths related to naltrexone, buprenorphine and methadone, estimated number of treatment episodes, and mortality rate per 1000 episodes, Australia 2000-2003

	Number treated[1] 2000-2003	Known deaths	Probable deaths	Possible deaths	Total related deaths 2000-2003	Total mortality rate (per 1000 episodes)
Naltrexone	3169	15	4	13	32	10.1 (95% CI: 6.9, 14.3)
Buprenorphine	49,948	1 (1, 0)	0 (0, 0)	0 (0, 0)	1 (1, 0)	0.02 (95% CI: 0.0005, 0.1)
Methadone	102,615	258 (92, 53)	5 (2, 0)	19 (11, 0)	282 (105, 53)	2.7 (95% CI: 2.4, 3.1)

Numbers refer to: Total deaths (deaths where treatment status unknown, deaths where illicit medication used)

1. Refers to the estimated number of treatment episodes.

If the mean number of scripts for naltrexone treatment was three per episode, then a total of 2,112 episodes occurred during the study period. This raises the mortality rate to 15.2 per 1000 naltrexone treatment episodes. This consequently increases the rate relative to the other treatment modalities to 5.6 times higher than methadone, and 760.0 times higher than the mortality rate for buprenorphine.

3.2.1. Mortality rates for naltrexone and methadone considering periods of high and low risk of death

Naltrexone

Searches of NCIS suggested that 32 naltrexone-related deaths occurred. Of these deaths, five cases had naltrexone or its metabolite detected at autopsy, so it was assumed that these deaths occurred during the naltrexone treatment episode (the period of "low risk"), and the 27 remaining deaths occurred in the high risk period of two weeks after naltrexone treatment[5].

[5] It was assumed that all naltrexone-related deaths - where naltrexone was not detected or tested for at autopsy - occurred outside of treatment.

The period of time at high risk for the 3169 episodes of naltrexone treatment was 122 person years, so the mortality rate during the period of high risk (two weeks following treatment cessation) was 22.1 per 100 person years.

If the mean period of time in treatment (i.e. "low risk period") was taken to be 60 days, the total period of lower risk is 521 person years of lower risk. As 5 people were estimated to have died during this period of lower risk, the mortality rate was 1 per 100 person years (Table 3).

Methadone

How long a person had been in methadone treatment before a methadone-related death occurred was not well recorded in the NCIS. Instead, using the figure that 21% of deaths in people receiving methadone treatment occur within the first week of methadone treatment (Zador & Sunjic, 2000), then 59 people died during this high risk period of time. Assuming patients remained in treatment for at least 7 days, the period of time at high risk for the 102,615 episodes of methadone treatment is then 718,305 person days or 1,968 person years. As the actual retention in treatment during the first week in NSW was calculated at 6.6 days, this appears to be a reasonable assumption. Methadone deaths occurred at the rate of 3.0 per 100 person years of risk in the high risk period of treatment.

If the mean period of time in methadone treatment is 236 days, the period at lower risk is 229 days or 64,380 person years of lower risk. If 222 deaths occurred during this period, the mortality rate is 0.34 per 100 person years of lower risk.

The different methods of expressing mortality rates are summarised in Table 3. The naltrexone-related mortality rate is 3.7 times that of methadone if expressed as deaths per number of treatment episodes; 7.4 times that of methadone if expressed as deaths per person years of high risk exposure; or 2.9 times that of the methadone-related mortality rate when expressed as deaths per person years of low risk exposure. In the latter case it should be noted that only five naltrexone-related deaths occurring in the low risk period contributed to this estimate.

It is important to note that reports received from experts in the field and previous literature (Arnold-Reed et al., 2003) indicate that the WA and QLD estimates of naltrexone-related deaths are significant underestimates. The likely extent of this underestimate is discussed in Appendix 1.

Table 3: Mortality rates per 1000 treatment episodes and per person-years of exposure (stratified into periods of high and low risk of death), Australia 2000-2003

	Deaths/ No of episodes	Deaths/ person-years of exposure	
		High risk period	Low risk period
Naltrexone	10.1 per 1000 episodes	22.1 per 100 person years	1 per 100 person years
Buprenorphine	0.02 per 1000 episodes	Not calculated	Not calculated
Methadone	2.7 per 1000 episodes	3.0 per 100 person years	0.34 per 100 person years

3.2.2. Deaths involving naltrexone implants

In addition to the 32 oral naltrexone-related deaths identified in the present study, two deaths involved the use of naltrexone implants. Since this study was unable to receive official estimates of the number of patients receiving naltrexone implants, naltrexone implant-related mortality rates were not investigated. Implant deaths were not searched for in the NCIS, but these two cases (found incidentally) are included for illustration.

The first death, occurring in Queensland, was what appeared to be an opioid overdose with a fast onset because the needle was found in the hand of the victim post-mortem. The victim had a current naltrexone implant but no toxicology records were available. As the cause of death was apparently an opioid overdose, it appears that the implant was not producing therapeutic levels of naltrexone at the time of death.

The second death occurred in Western Australia, and this time naltrexone was detected in toxicology in addition to amphetamine, propranolol, doxepin, diazepam and paracetamol. The victim had experienced stomach pain around the site of the naltrexone implant for two days prior to their death from a combined drug effect.

Table 4: Number of deaths related to naltrexone, buprenorphine and methadone by jurisdiction

State	Oral naltrexone-related deaths				Buprenorphine-related deaths				Methadone-related deaths			
	Known	**Probable**	**Possible**	**Total**	**Known**	**Probable**	**Possible**	**Total**	**Known**	**Probable**	**Possible**	**Total**
NSW	10 (0, 3)	1	8	**19**	0	0	0	**0**	111 (52, 16*)	1	7 (6, 0)	**119**
Vic	0	3	1	**4**	0	0	0	**0**	81 (18, 20*)	2 (1, 0)	3 (1, 0)	**86**
SA	1	0	0	**1**	0	0	0	**0**	5 (4, 0)	0	0	**5**
ACT	1	0	1	**2**	0	0	0	**0**	8 (1, 4*)	0	1 (1, 0)	**9**
Tas	0	0	0	**0**	0	0	0	**0**	20 (3, 10)	0	0	**20**
NT	0	0	0	**0**	0	0	0	**0**	2 (2, 0)	0	1	**3**
Qld	1	0	0	**1**	0	0	0	**0**	6 (1, 1)	2 (1, 0)	6 (2, 0)	**14**
WA	2	0	3	**5**	1 (1, 0)	0	0	**1**	25 (11, 2)	0	1 (1, 0)	**26**
Total	15	4	13	**32**	1 (1, 0)	0	0	**1**	258 (92, 53)	5 (2, 0)	19 (11, 0)	**282**

Numbers refer to: Total deaths (deaths where it was unknown if medication was licit or illicit, deaths where illicit medication used).

In all cases where a single number is presented, all deaths occurred with known licit medication.

* In one case (NSW and ACT) or two cases (Vic), the person was receiving methadone maintenance treatment and appeared to take additional illicit methadone as well.

4. DISCUSSION

Assuming that the mean naltrexone treatment episode involved two naltrexone prescriptions, there were an estimated 10.1 deaths per 1,000 episodes of naltrexone treatment for opioid dependence. If on the other hand, treatment episodes were longer and each client received a mean of three month's prescriptions, then the mortality rate increases to 15.2 deaths per 1,000 episodes. This mortality rate for naltrexone was at a minimum four times higher than for methadone (2.7 per 1,000 treatment episodes), and substantially higher than for buprenorphine (0.02 per 1,000 episodes).

Since risk of death is not constant across a treatment episode, mortality rates can also be expressed in terms of periods of risk. Naltrexone mortality was estimated as 22.1 deaths per 100 person years of high risk (two weeks post-treatment) and one death per 100 person years of low risk (during treatment). Methadone mortality was 3.0 deaths per 100 person years of high risk (during the first week of treatment) and 0.34 deaths per 100 person years of low risk (during the rest of the treatment episode, assuming mean treatment retention is 236 days). This makes the mortality rate for naltrexone approximately seven times that of methadone during the period of higher risk. During the period of lower risk, the mortality rate for naltrexone was estimated as at approximately three times that of methadone.

4.1. Implications of these mortality rates

Naltrexone treatment in Australia had higher mortality rates than either methadone or buprenorphine treatment. Most of the mortality for naltrexone occurred in the two week period of high risk after treatment ceased, whereas only one death occurred in the two week period after cessation of methadone treatment. Depending on the method of calculation, naltrexone mortality rates were between three to seven times higher than those for methadone. Naltrexone mortality while in treatment (low risk period) was very similar to the mortality of Australian heroin-dependent users not in treatment (0.9 deaths per 100 person-years; (Capelhorn et al., 1996). The mortality rate of buprenorphine was extremely low, with only one buprenorphine-related death identified during the study period.

These rates suggest that naltrexone treatment for opioid dependence is associated with significant risk of mortality, primarily because of the short duration of treatment and highly elevated risk of death following cessation of treatment. These rates do not suggest that access to naltrexone for the general population of opioid-dependent persons should be expanded,

although the treatment may be of value in particularly well-motivated populations who remain in treatment, such as opioid-dependent medical professionals (Ling & Wesson, 1984; Roth et al., 1997). Warning subjects of the risks of opioid overdose following naltrexone treatment cessation is an extremely important part of the current Australian naltrexone treatment guidelines and should remain so, but its effectiveness in reducing overdose following cessation of treatment is uncertain.

4.1.1. Naltrexone implants

It is the cessation of naltrexone treatment, through lack of compliance or the termination of a treatment episode, which presents the main period of risk of death for patients. It follows, then, that sustained release modes of naltrexone treatments such as implants might present an alternative. The evidence supporting naltrexone sustained release implant efficacy and acceptability to date has been lacking, but we understand that the first Australian randomised controlled study of naltrexone implants is underway at the present time in Western Australia. We hope this study can start to address the lack of rigorous evidence.

It is important that the research addresses a number of questions. Firstly, it has been shown that there is considerable inter- and intra-subject variability in the blood levels of naltrexone resulting from an implant (Olsen et al., 2004). Naltrexone implants must be able to reliably provide a protective level of blood naltrexone, particularly considering the numbers of subjects who have been reported to "test the blockade" of their implants with opioids (Foster et al., 2003). If consistent levels of naltrexone are not produced, those patients with an implant may have false confidence in the ability of the implant to block the administration of opioids, and may be at risk of overdose. One naltrexone implant-related death found incidentally in this study occurred under such circumstances.

Secondly, there needs to be good monitoring of the levels of adverse events resulting from naltrexone implants. Patients can and do die as a result of complications from naltrexone implants, as seen in one case found in this study, and previously published reports (Hamilton et al., 2002; Oliver, 2005). Other adverse events have included pulmonary oedema, prolonged withdrawal, drug toxicity, variceal rupture, aspiration pneumonia, and injuries when patients have attempted to remove the implant themselves (Hamilton et al., 2002; Oliver, 2005).

Thirdly, acceptability of the preparation must be considered for both patients and any general practitioners who may be responsible for inserting the implants. Patients may forget oral naltrexone tablets at times, but they also can choose to cease treatment at any time, despite the

risk of fatal opioid overdose associated with this. There have been reports of patients attempting to remove their own implants, with harmful consequences (Oliver, 2005). Naltrexone implants must also be changed on a regular basis, and do not necessarily provide a consistent blockade (G. K. Hulse & Tait, 2003). An implant recipient will be at risk when their implant begins to provide only sub-therapeutic levels of naltrexone (and before the next implant is inserted), and the time at which this occurs will vary from patient to patient. It is also possible that some general practitioners will not be inclined to provide the surgical procedure required to insert the implant in the patient's abdomen, restricting the number of prescribers willing to provide this formulation of the drug.

Despite our best efforts, we were unable to obtain data on the number of persons receiving naltrexone implant treatment. This lack of information made estimating mortality rates associated with naltrexone implants impossible, and is an important issue to address.

4.2. Limitations of the present study

The methods of this study required a number of assumptions to be made, which may have biased estimates of mortality for the three pharmacotherapies. These assumptions and their likely impact on mortality are discussed in detail in Appendix 1.

In quoting mortality rates for naltrexone, buprenorphine and methadone, we have assumed that all deaths were related to a course of treatment. We know this is not the case, since at least 53 (19%) of methadone-related deaths were mentioned to have involved diverted medication and 105 (37%) of methadone-related deaths had an unknown treatment status at the time of death. As the NCIS does not routinely identify whether a person was in treatment with a particular drug at the time of their death, we have chosen to include all pharmacotherapy-related deaths, whether involving prescribed or diverted medication. As more methadone is likely to be diverted than is naltrexone, this will have the effect of overestimating the mortality related to methadone treatment in comparison with naltrexone. The difference between methadone and naltrexone mortality rates is likely to have been attenuated by this bias.

We have compared the mortality rates associated with naltrexone - a medication resulting in low opioid tolerance where the majority of deaths occur after treatment - with methadone and buprenorphine, medications resulting in continued high opioid tolerance where the majority of deaths occur during the early stages of treatment. These are very different treatments that are likely to attract patients with different goals (abstinence versus maintenance) and even different socioeconomic statuses (private naltrexone treatment is more expensive). Despite these

differences, it is important for clinicians to compare the mortality associated with treatments before offering a particular therapy. Comparisons of post-treatment adverse events related to naltrexone, methadone and buprenorphine treatment in the NEPOD studies showed that overdoses in patients leaving naltrexone treatment occurred at eight times the rate of those leaving methadone and buprenorphine treatment (Digiusto et al., 2004). In this study, 27 deaths in the two weeks following naltrexone treatment were identified, compared to no deaths following buprenorphine treatment and one death following methadone treatment.

The estimates of methadone and buprenorphine-related deaths appear reasonably consistent with estimates from cohort studies in Australia and elsewhere (Auriacombe et al., 2001; Capelhorn et al., 1994; Capelhorn et al., 1996; Capelhorn & Drummer, 1999). That our two methods of calculating mortality rates gave similar results also gives us greater confidence in our findings. Notably, a relatively large number of methadone-related deaths occurred among persons who had either diverted methadone, or for whom treatment status was unknown. This finding suggests a clear need to examine the extent of diversion of methadone in Australia.

It is highly likely that the mortality rate associated with naltrexone treatment is significantly underestimated, for a number of reasons. First, knowledge of a deceased person's prior naltrexone status and its possible relevance in their death was required to be noted by the police, the coroner, or the pathologist. Second, other evidence strongly suggests that in Western Australia the number of cases related to naltrexone treatment was seriously underestimated: one case series mentioned 21 deaths in a period of two years (Arnold-Reed et al., 2003), compared to the five cases in Western Australia during the period of four years we were able to identify in the current study. Third, personal communications with experts in the field suggested that the number of cases in Queensland was also considerably lower than they had expected based upon their knowledge of events in that state. In these ways, we feel that the current study has provided an extremely conservative estimate of mortality associated with this form of treatment for opioid dependence (discussed further in Appendix 1).

4.2.1. Usefulness of the NCIS for detecting naltrexone-related deaths

Unlike methadone and buprenorphine-related deaths, a naltrexone-related death is primarily identified by the lack of naltrexone, not its detection in the autopsy toxicology. The first stage in identifying a naltrexone-related death is searching for some mention of prior naltrexone treatment in the documents of a coronial case, including police reports, findings, autopsy or toxicology documents. Without an electronic keyword search capacity such as in the NCIS, this

would involve manually searching a great number of coronial files, which is not feasible on a national scale.

Information on a person's prior treatment history is vital in identifying naltrexone-related deaths. Unfortunately, this information is not consistently reported in coronial files. Information on the timing of the last dose received or the level of that dose is even more irregularly reported, making it difficult to assess any relationships between naltrexone treatment and death. Deaths related to a pharmacotherapy could occur within two weeks of the cessation of treatment. Deaths related to a pharmacotherapy occurring further away from the cessation of treatment are possible, but prior treatments is less likely to be noted as relevant in the coronial file, so the death is less likely to be considered related to the pharmacotherapy.

Not all drugs are routinely tested for in the case of a suspected drug-related death. In Victoria, for instance, methadone is routinely tested for in all suspected drug-related deaths, but buprenorphine and naltrexone are not. Less common drugs such as buprenorphine and naltrexone are only tested for where there is a reason to suspect its involvement in the death, such as a mention of the drug in police or autopsy reports, or if evidence of the drug was found at the death scene or victim's residence. This could have the effect of underestimating the mortality rate associated with naltrexone and buprenorphine in comparison with methadone.

The NCIS drugs module, implemented in 2001, aimed to improve the data collection on coronial cases where the death was wholly or partially, directly or indirectly, caused by one or more drugs, poisons and/or alcohol (Monash University National Centre for Coronial Information, 2000). The improvements have been incorporated into the NCIS, and make the task of determining deaths related to opioid pharmacotherapies much easier.

Spelling mistakes, possibly caused by a lack of knowledge of drug names, makes keyword searching imperfect. These errors occurred particularly in police reports, but also in all other documents. Spelling mistakes could only be discovered through keyword search if there was also a correctly spelt version of the word in the document, so coronial files with consistently incorrect spellings would not be detected by this search method. Spelling variations were more common with naltrexone, a less commonly prescribed drug, than with a more familiar drug such as methadone. Systematic misclassification such as this could lead to lower rate of naltrexone-related death and buprenorphine-related death in comparison to methadone-related death.

The quality of coronial records and speed of data entry into the NCIS system differs between jurisdictions. States such as Queensland only have police records uploaded onto NCIS, so we

lack details on the causes of death and toxicology results, resulting in much lower quality of data and difficulties in determining the relatedness of naltrexone, buprenorphine, or methadone to the death. This means it is inadvisable to compare mortality rates related to opioid pharmacotherapy across jurisdictions. Any differences could be the result of differences in data entry, coronial investigation procedures, state policies regarding maintenance pharmacotherapy dosing (such as provision of takeaway doses) or other factors influencing the observed mortality rates from the NCIS. Fortunately, for national comparisons in mortality rates between the different pharmacotherapies, any jurisdictional variations in quality of data are likely to be randomly allocated between patients receiving naltrexone, buprenorphine, and methadone - having minimal effect on the comparative mortality related to the different treatments.

4.2.2. Difficulties in classifying deaths as naltrexone-related

Assigning the level of causality of a particular pharmacotherapy to a death is always difficult, but it was more difficult with naltrexone than the other two pharmacotherapies. This is reflected in the lower proportions of "known" versus "probable" and "possible" for naltrexone than for methadone-related deaths.

In our calculations of mortality rates we have used results from all naltrexone, buprenorphine and methadone-related deaths, including "known", "probable" and "possible" related deaths. If we only consider the "known" related deaths, the mortality rate for naltrexone decreases from 10.1 to 4.7 per 1,000 treatment episodes, and for methadone this rate decreases from 2.7 to 2.5 per 1,000 treatment episodes. Due to the likelihood of a serious underestimate in the number of naltrexone-related deaths (see Appendix 1), we have decided to use all related deaths for our discussion and conclusions.

We do not know if naltrexone treatment *per se* contributed additional risk over and above the risk of death after a period of reduced opioid tolerance in an opioid-dependent person. The theory of opioid receptor hypersensitivity after naltrexone treatment has been put forward but this has little supporting evidence in humans. Further research studies in this field are recommended including monitoring of rates and causes of death in patients receiving naltrexone for opioid dependence.

While the mechanisms of naltrexone-related death are not fully understood, we cannot expect coroners, toxicologists and police officers to note factors such as the recent cessation of naltrexone treatment as a significant point to note in an opioid overdose. Without the recording

of these seemingly minor points of information, we can only give rough estimates of naltrexone-related mortality rates.

4.3. Other possibilities for calculating naltrexone-related deaths

Data from the NSW Division of Analytical Laboratories reports toxicology findings in drug-related death cases in NSW. This data could be used to give alternative estimates of methadone and buprenorphine-related deaths, as methadone and/or buprenorphine are typically found in toxicology results of related deaths. Unfortunately, this would not be appropriate for naltrexone-related deaths as it lacks any information on prior treatment status, and naltrexone is generally not found in toxicology results of related deaths.

If naltrexone was a scheduled drug, so that there were individual records of patients receiving the drug for opioid dependence, one might be able to use data linkage to trace the death records of all those people in naltrexone treatment. While naltrexone remains unscheduled, this is not feasible on a national level.

4.4. Conclusions

Identifying a naltrexone-related death is difficult as long as coronial databases do not systematically collect treatment data in a detailed fashion, so there remain a number of caveats around our estimates of naltrexone mortality. The mortality rate associated with naltrexone treatment also appears to be as high (during treatment), or higher (post treatment) than it is for opioid-dependent persons who are not in treatment; and our estimate is likely to be a conservative one. There is a need for future trials of the use of naltrexone, methadone and buprenorphine as treatments for opioid dependence to include monitoring of post-treatment mortality risk, that includes searches of death registries, for at least one month and preferably twelve months post-treatment exit.

Mortality rates associated with naltrexone implants were not able to be estimated in this study due to the lack of data on the number of people receiving naltrexone implants nationally. In our searches of oral naltrexone deaths, we incidentally discovered two naltrexone implant deaths. Research needs to be done to establish the efficacy of naltrexone implants in the treatment of opioid dependence, and it is recommended that careful attention be paid to establishing the rate of naltrexone implant-related mortality in Australia in any such studies.

The mortality rates associated with oral naltrexone are a cause for concern, and serious attention needs to be paid to the risks associated with naltrexone treatment (particularly the risks following cessation of treatment), considering that the majority of unselected opioid-dependent persons will return to opioid use after treatment with naltrexone. In order to more effectively monitor the use of this drug for the treatment of opioid dependence, it may be appropriate to consider naltrexone for scheduling because of its mortality risk.

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APPENDIX 1: MAJOR ASSUMPTIONS AND THEIR POTENTIAL TO BIAS ESTIMATES OF MORTALITY

Number of treatment episodes

1. Assumption that number of national treatment episodes for methadone and buprenorphine is accurate. Some jurisdictional differences will exist in the percentage of current episodes, and it is thought that states other than NSW might have lower percentages of current episodes. If this were to be the case, then there would be a relative underestimate of treatment episodes and so an overestimate of buprenorphine and methadone mortality rates.
2. Assumption that the mean length of methadone treatment nationally is 236 days - the mean retention calculated from NSW PSB data for the period 2000 to 2003. As NSW is the state with the highest number of methadone patients, this is likely to be a reasonable estimate.
3. Assumption that all private prescriptions for naltrexone were for the treatment of opioid dependence and all public prescriptions for naltrexone were for the treatment of alcohol dependence. It may be the case that a medical professional would write a public prescription for naltrexone for opioid dependence so that the patient could get the medication at a reduced price, particularly in the case where a patient has dual opioid and alcohol dependence. If a percentage of public naltrexone was prescribed for opioid dependence, the number of treatment episodes would increase, lowering the naltrexone mortality rate.

   Estimates of the rate of public naltrexone prescribing for opioid dependence in the absence of alcohol dependence are difficult to make because this would involve doctors self-reporting participation in a professionally inappropriate activity. However, levels of comorbid alcohol and opioid dependence are available. A sample of 222 Australian heroin injectors revealed that 49% also had current alcohol dependence (Darke & Ross, 1997). A British study of 735 subjects presenting for treatment of a drug-related problem (87% of which presented for opioid problems) who had had at least one drink in the previous three months had 37% of subjects endorse alcohol dependence items on the Severity of Dependence Scale (Gossop, Marsden, & Stewart, 2002). If one assumes that about half of patients presenting with opioid dependence also have alcohol dependence (the most generous estimate), then the number of treatment episodes is increased by 50%, effectively reducing the naltrexone mortality rate by a factor of two. The degree of underestimation of the number of naltrexone-related deaths (assumption 6) is likely to far outweigh this underestimate.
4. Assumption that clinical report of a mean length of a naltrexone treatment episode is approximately two months. It may be that the median number of prescriptions is smaller than this, and many patients may not return for a second prescription. However, the mean is expected to be greater than the median due to the small population of patients such as opioid dependent medical professionals, who have a high retention in treatment. The estimate of mean retention of two months is expected to be reasonably accurate.

Number of related deaths

5. Assumption that number of methadone and buprenorphine-related deaths is accurate. These estimates are likely to be accurate; however, it is possible that some deaths were missed due to spelling errors in the NCIS data. Buprenorphine-related deaths appear to be more prone to spelling errors than methadone, but due to the low numbers of buprenorphine-related deaths, it was not used as a primary comparator for naltrexone-related deaths.
6. Assumption that the number of naltrexone-related deaths is accurate. The number of naltrexone-related deaths captured by the NCIS is certainly a substantial underestimate. Known death series from Queensland and Western Australia do not appear in the naltrexone-related deaths identified in this study. From a case control study occurring between July 1997 and August 1999 in Western Australia, 21 fatal heroin overdoses were identified with prior exposure to naltrexone. In the period 2000-2003, we only identified 5 naltrexone-related deaths in this state. If numbers in Western Australia remained constant between 1997 and 2003, the NCIS only captured approximately 12% of the deaths in that state, implying that our national estimate of naltrexone mortality could be an 88% underestimate. Assuming this level of underestimation of deaths, the actual naltrexone mortality rate would be at least 7 times higher than the estimate produced in this study, more than enough to compensate for any overestimation of the mortality rate at assumption 3 above.

APPENDIX 2: DIFFERENT WAYS A METHADONE-RELATED DEATH WAS CODED IN VICTORIAN CORONIAL FINDINGS DOCUMENTS

Methadone toxicity
Toxic effects of methadone
Mixed drug toxicity
Combined drug toxicity
Combined toxicity to (list of drugs)
Toxicity to methadone
Toxicity to (list of drugs)
Effects of methadone
Narcotic toxicity
Toxicology consistent with drug overdose
Combined drug and alcohol toxicity
Multiple drug overdose
Overdose of methadone
Combination of drugs
Raised methadone level
Combined effects of (list of drugs)
Relates to the use of illicit drugs
Drug overdose
Synergistic respiratory depressant effect of methadone
Asphyxia, aspiration, drug overdose
Bronchopneumonia
Suffocation due to inhalation of vomitus
Pneumonia
Acute pulmonary oedema
Aspiration of gastric contents

APPENDIX 3: NALTREXONE, BUPRENORPHINE AND METHADONE-RELATED DEATH CASES

Table A1: Naltrexone-related death cases

Case Number	Cause of death	Naltrexone treatment history	Other notes	Toxicology
Known				
NSW1n	Acute narcotism	Coroner reports dangers of using excess heroin to get over naltrexone blockage		Naltrexone detected
NSW2n	Myocarditis, heart failure, naltrexone, morphine and methadone possibly contributed	Coroner reports naltrexone a possible contributing cause	On day of death, took naltrexone instead of methadone	Naltrexone detected
NSW3n	Heroin overdose	Last naltrexone supervised 24 hours prior (possible non compliance)		Naltrexone not tested
NSW4n	Heroin overdose	Last naltrexone 3 or 4 days prior	Appeared to have lower tolerance than friends	Naltrexone not detected
NSW5n	Heroin overdose	Left naltrexone treatment day before		Naltrexone not tested
NSW6n	Heroin overdose	Last naltrexone 2 days prior		Naltrexone not detected
NSW7n	Combined acute bronchopneumonia and drug intoxication	Appeared to be during attempt at home detoxification using naltrexone	Not in current naltrexone treatment	Naltrexone not tested
NSW8n	Multiple drug toxicity (cocaine, methadone, fluoxetine) and cardiac arrest	On day of death, took naltrexone instead of methadone		Naltrexone detected

Case Number	Cause of death	Naltrexone treatment history	Other notes	Toxicology
NSW9n	Mixed drug toxicity (methadone, temazepam, metoclopramide)	Last naltrexone within 1 week prior		Naltrexone not tested
NSW10n	Acute narcotism	Last naltrexone 2 days prior		Naltrexone not detected
QLD2n	Death due to external cause *(consistent with opioid overdose)*	Current naltrexone treatment, last dose unknown	Needle and white powder found on body	Naltrexone not tested
SA1n	Death due to external cause, death due to a product	Subject received naltrexone, then went home and died in bed		No details
WA2n	Death from external cause *(consistent with heroin overdose)*	On naltrexone program for last 3 weeks		No details
WA4n	Death due to external cause *(consistent with heroin overdose)*	Currently on naltrexone program	Opiates also taken, death occurred rapidly	Naltrexone detected
ACT1n	Cardiac and respiratory failure caused by combination of diazepam, heroin, sertraline and chlorpromazine and patchy pneumonia	Overdose appear to have occurred after naltrexone treatment was ceased	Coroner recommends warnings about naltrexone overdose risk be given*	No details
Probable				
NSW20n	Death due to external cause *(consistent with opioid overdose)*	Had been on naltrexone for last 3 months, last dose unknown	Injecting equipment found on body	No toxicology report
VIC1n	Combined drug toxicity (heroin, doxepin, diazepam)	Believed to be in current naltrexone treatment, not confirmed		Naltrexone not tested
VIC2n	Combined drug toxicity (heroin, codeine, sertraline)	Naltrexone treatment to avoid drinking (when would use heroin)		Naltrexone not tested
VIC4n	Heroin toxicity	Naltrexone treatment found		Naltrexone not tested

Case Number	Cause of death	Naltrexone treatment history	Other notes	Toxicology
		at home, last dose unknown		
Possible				
NSW12n	Pneumonia candidiasis	Death occurred soon after Rapid Opiate Detox (naltrexone)	Pneumonia was likely to be caused from a bacterial infection	Naltrexone detected
NSW13n	Heroin overdose	Naltrexone documentation found, unknown treatment status		Naltrexone not detected
NSW14n	Methadone toxicity	Treated with naltrexone, recency unknown		Naltrexone not tested
NSW15n	Alcoholic cardiomyopathy, combined effects of drugs may have contributed to respiratory depression	Naltrexone treatment a couple of weeks ago		Naltrexone not detected
NSW16n	Methadone and methamphetamine toxicity	Prescription for naltrexone found, treatment status unknown		Naltrexone not detected
NSW17n	Acute narcotism	Most recently on naltrexone program, treatment status unknown		Naltrexone not detected
NSW18n	Toxic effects of heroin in combination with temazepam, citalopram, methamphetamine	Entered naltrexone treatment 8 months before, treatment status unknown		Naltrexone not detected
NSW19n	Toxic effects of heroin and methamphetamine	Recently entered onto naltrexone treatment, further details unknown	Death during suicide attempt (by suffocation) but not due to this	Naltrexone not detected
VIC3n	Combined drug toxicity (narcotics, doxepin)	Was on naltrexone treatment prior to buprenorphine		Naltrexone not tested

Case Number	Cause of death	Naltrexone treatment history	Other notes	Toxicology
		treatment, last dose unknown		
WA3n	Death due to external cause *(consistent with heroin overdose)*	Previously on naltrexone, was about to restart program after relapse		Naltrexone not tested
WA5n	Death due to external cause *(consistent with multiple drug overdose)*	Naltrexone tablets found at home, no treatment details		Naltrexone not detected
WA6n	Combined drug toxicity (including alcohol effect) with vomit aspiration	Naltrexone tablets found at home, no treatment details		Naltrexone not detected
ACT2n	Heroin overdose	Had been on naltrexone treatment, details not known		Naltrexone not tested

* Text in finding document reads: *"I request the Minister for Health to consider requiring that a warning be given to persons for whom Naltrexone has been prescribed of the risks associated with its use if heroin is administered during the period Naltrexone is being taken and after the taking of Naltrexone has ceased".*

Table A2: Buprenorphine-related death case

Case Number	Cause of death	Buprenorphine treatment status	Other notes
Known			
WA1b	Combined respiratory depressant drug and alcohol toxicity	Uncertain if subject on buprenorphine treatment	Buprenorphine (unknown source) crushed and injected just before death. Buprenorphine, diazepam and alcohol detected at autopsy.

Table A3: Methadone-related death cases

Case Number	Cause of death	Methadone treatment status	Other notes
Known			
NSW1m	Combined effects of morphine, codeine, methadone, temazepam, oxazepam	Stopped MMT 4 years previously. No current MMT	
NSW2m	Methadone toxicity	Current MMT	
NSW3m	Methadone and benzodiazepine toxicity	Current MMT	
NSW4m	Acute toxicity due to alcohol and methadone	Unknown	
NSW5m	Multiple drug toxicity (opiates, methadone, benzodiazepines)	Previous MMT. Current treatment unknown	Coronary artery atheroma a contributing cause
NSW6m	Multiple drug (morphine, methadone) toxicity	Unknown	Intentional self-harm. Known HIV positive.
NSW7m	Multiple drug (methadone, diazepam) toxicity	Unknown	Recent internal injuries from sexual assault
NSW8m	Multiple drug toxicity (methadone, codeine, methamphetamines, tricyclic antidepressants)	Current MMT	
NSW9m	Combined effects of methadone and alprazolam	Current physeptone treatment	
NSW10m	Acute bronchopneumonia complicating methadone and oxazepam toxicity	Unknown	
NSW11m	Acute toxicity due to morphine and multiple other drugs	Unknown. Drugs from own pharmacy	Intentional self-harm
NSW12m	Methadone toxicity	Unknown	
NSW13m	Intracerebral haemorrhage, multiple drug ingestion	Unknown	
NSW14m	Toxicity of multiple drugs (opiates, methadone, tricyclic antidepressants) and alcohol	Unknown	First anniversary of child's death
NSW15m	Lobar pneumonia, multiple drug toxicity	Unknown	
NSW16m	Combined effects of pneumonia and opioid toxicity	Unknown	

Case Number	Cause of death	Methadone treatment status	Other notes
NSW17m	Consistent with hanging	Current MMT	Methadone and alcohol intoxication contributing causes, intentional self-harm. Methadone at fatal levels
NSW18m	Complications of multidrug toxicity	Current MMT	
NSW19m	Opioid toxicity	Current MMT	
NSW20m	Combined effects of heroin and methadone toxicity and acute myocardial infarction	Current MMT	Obesity, psychosis as contributing factors
NSW21m	Mixed drug toxicity (morphine, methadone, alcohol)	Unknown	Hepatitis C infection a contributing cause
NSW22m	Toxic effects of methadone and coronary artery atherosclerosis	Current MMT	
NSW23m	Combined effects of alcohol, methadone and diazepam	MMT history. Current treatment unknown	
NSW24m	Consistent with the consequences of multiple drug (methadone, methamphetamine) toxicity	None current	
NSW25m	Toxic effects of doxepin, methadone, doxylamine	Unknown	Presence of pethidine, citalopram, clonazepam derivative listed as contributing causes. Intentional self-harm
NSW26m	Methadone toxicity	Current MMT unknown, recent naltrexone treatment	Also listed as NSW14n (possible naltrexone-related death)
NSW27m	Pneumonia	Unknown	Methadone and methamphetamine toxicity as contributing causes
NSW28m	Toxicity due to methadone in a man with pilocytic astrocytoma of the cerebellum	MMT 10 months previously. None current	Was due to have brain operation soon
NSW29m	Multiple drug toxicity	Unknown	Methadone at fatal levels

Case Number	Cause of death	Methadone treatment status	Other notes
NSW30m	Gunshot wound to the head	Current MMT, recently enrolled	Effects of morphine, methadone and cannabinoids listed as contributing factors
NSW31m	Antidepressant and opioid drug toxicity	Current physeptone treatment	Also in treatment for pituitary tumour
NSW32m	Toxic effects of methadone	None current	
NSW33m	Combined effects of methadone toxicity and pneumonia	Current MMT but though to have bought additional illicit methadone	
NSW34m	Acute narcotism	Current MMT, in first week	
NSW35m	Acute narcotism and benzodiazepine toxicity	None current	Regular purchases of illicit methadone
NSW36m	Toxic effects of methadone	Current MMT	
NSW37m	Combined effects of incised wounds of the neck and elbows and combined drug (methadone and prozac) intoxication	Unknown	Intentional self-harm
NSW38m	Multiple drug toxicity (predominantly methadone)	None current	
NSW39m	Multiple drug (cocaine, methadone, fluoxetine) toxicity	Current MMT, but missed dose and took naltrexone on day of death	Also listed as NSW8n
NSW40m	Stab wound to back	Unknown	Methadone and alcohol intoxication listed as contributing causes. Methadone in therapeutic level.
NSW41m	Combined effects of airway obstruction and multiple injuries, multiple drug toxicity	Current MMT	Motorcycle accident
NSW42m	Overdose of methadone	Unknown	
NSW43m	Multiple drug toxicity (methadone, cocaine, benzodiazepines, alcohol)	Unknown	
NSW44m	Methadone and methamphetamine toxicity	Unknown	
NSW45m	Multiple drug toxicity due to methadone,	Unknown	Had been treated by ambulance for

Case Number	Cause of death	Methadone treatment status	Other notes
	aminoclonazepam, diazepam		two previous overdoses in days before death
NSW46m	Multiple drug toxicity due to temazepam, alcohol, methadone, zolpidem, sertraline	Current physeptone treatment	Intentional self-harm
NSW47m	Multiple drug (opioids, methamphetamine, benzodiazepine) toxicity	Unknown	
NSW48m	Multiple drug (methadone, doxepin, diazepam) toxicity	Current MMT	
NSW50m	Multiple drug (methadone, diazepam) toxicity	Current MMT, in first week of treatment	
NSW51m	Methadone toxicity	Unknown	
NSW52m	Methadone and amitriptyline toxicity	Current MMT	
NSW53m	Methadone toxicity	None current	
NSW54m	Gunshot wound to head	Current MMT	Multiple drug toxicity as contributing cause. Intentional self-harm
NSW55m	Acute toxicity due to multiple drugs	Unknown	
NSW56m	Mixed drug toxicity (morphine, methadone, codeine, dextropropoxyphene, benzodiazepines)	Unknown	
NSW57m	Acute toxicity due to multiple drugs	Unknown	
NSW58m	Toxicity of methadone and other drugs	Current MMT	Terminal pneumonia as contributing cause
NSW59m	Opioid toxicity (morphine and methadone)	Unknown	
NSW60m	Acute toxicity due to amitriptyline and methadone	Unknown	Coronary artery atherosclerosis as contributing cause
NSW61m	Multiple drug toxicity (methadone, benzodiazepines, cocaine)	Current MMT	

Case Number	Cause of death	Methadone treatment status	Other notes
NSW62m	Pneumonia and cerebral hypoxia, toxicity of amphetamine, methadone and alcohol	Unknown	Amphetamine not detected but listed as secondary cause
NSW63m	Combined drug (methadone, oxazepam) toxicity	None current	
NSW64m	Methadone toxicity	Unknown	
NSW65m	Pneumonia, subdural haemorrhage (operated)	None current	Clinical report of opiate toxicity as contributing cause
NSW66m	Hypoxic brain damage, combined drug intoxication (methadone, alcohol)	None current	
NSW67m	Inhalation of vomit (pre-terminal), toxic effects of methadone and cocaine	None current	
NSW68m	Multi-organ failure, multiple drug toxicity (morphine, methamphetamine, methadone)	Current MMT	Chronic hepatitis, hepatitis C virus infection, hepatic steatosis listed as contributing causes
NSW69m	Carbon monoxide poisoning, mixed drug toxicity (opiates, methadone, cocaine)	Unknown	Intentional self-harm
NSW70m	Combined effects of opiates, methadone and benzodiazepine toxicity	Previous MMT, current unknown	Parents had just taken out an AVO against person
NSW71m	Toxic effects of methadone	Current MMT	
NSW72m	Acute methadone toxicity	None current	
NSW73m	Toxic effects of methadone and diazepam	Unknown	
NSW74m	Multiple drug (methadone, methamphetamine, cocaine, benzodiazapine, alcohol) toxicity	Unknown	HIV infection listed as contributing cause
NSW75m	Opiate toxicity	Unknown	
NSW76m	Toxic effect of opiate (probably morphine), methadone and benzodiazepines	Unknown MMT status. Prescribed Panadeine forte and MS Contin	
NSW77m	Toxicity due to methadone	Current MMT	

Case Number	Cause of death	Methadone treatment status	Other notes
NSW78m	Combined effects of multiple drug (alcohol, methadone, methamphetamine) toxicity and cirrhosis	Current MMT	
NSW79m	Multiple drug toxicity	Unknown	Listed as intentional self-harm, but no evidence of this. Known HIV positive with no HIV treatment
NSW80m	Methadone toxicity	None current	
NSW81m	Multiple drug toxicity	Unknown	
NSW82m	Combined effects of immersion and multiple drug toxicity	Unknown	Renal cell carcinoma as contributing cause
NSW83m	Methadone and amitriptyline toxicity	Unknown	Cardiomegaly, Insulin dependent diabetes mellitus, chronic renal failure listed as contributing causes
NSW84m	Multiple drug (methadone, codeine, diazepam) toxicity	Current MMT	
NSW85m	Cardiac arrhythmias, toxic effects of methamphetamine	Current MMT	Toxic effects of methadone as contributing cause
NSW86m	Opioid toxicity (morphine and methadone)	Current MMT	
NSW87m	Opiate toxicity	Unknown	
NSW88m	Multiple drug toxicity	Unknown	
NSW89m	Methadone toxicity	Current MMT	
NSW90m	Acute bronchopneumonia complicating methadone and methamphetamine toxicity	Current MMT (unknown if continued from jail or recent new episode)	Released from jail in previous month
NSW91m	Methadone toxicity on a background of cirrhosis	Current MMT	
NSW92m	Multiple injuries	Current MMT	Methadone intoxication a contributing factor. Slipped off cliff

Case Number	Cause of death	Methadone treatment status	Other notes
NSW93m	Toxicity of methadone and benzodiazepines	Current MMT	Fatty change of liver as a contributing cause
NSW94m	Methadone toxicity	Current MMT	Had just received take-away methadone for long weekend
NSW95m	Pneumonia in a man with methadone toxicity	Current MMT	
NSW96m	Methadone toxicity	Unknown	
NSW97m	Methadone toxicity	None current	
NSW98m	Carbon monoxide poisoning	Current MMT	Opiate intoxication as contributing cause. Intentional self-harm
NSW99m	Pneumonia, methadone intoxication	Current MMT	
NSW100m	Acute toxicity due to multiple drugs and alcohol	Unknown	
NSW101m	Immersion in water in a man intoxicated with methadone and diphenhydramine	Unknown	
NSW102m	Complications of multi-drug toxicity (methadone, olanzepine, paroxetine)	None current	
NSW103m	Inhalation of vomit, toxicity of methadone and diazepam	Current MMT	
NSW104m	Multiple drug intoxication (alcohol, opiate, antidepressant, benzodiazepine)	Unknown	
NSW105m	Acute bronchopneumonia, methadone toxicity	Current MMT	Used saved up take-away doses
NSW106m	Multiple drug (opiate, methadone, doxepin, alcohol) toxicity	Current MMT	Intentional self-harm
NSW107m	Mixed drug toxicity (methadone, temazepam, metoclopramide)	MMT treatment unknown, recent naltrexone treatment	Also listed as NSW9n
NSW108m	Methadone and methamphetamine toxicity	Unknown	
NSW109m	Aspiration pneumonia complicating multidrug	Unknown	

Case Number	Cause of death	Methadone treatment status	Other notes
	toxicity		
NSW110m	Multiple drug (methadone, benzodiazepine) toxicity	Unknown	Released from psychiatric hospital 10 days earlier
NSW111m	Acute toxicity due to multiple drugs and alcohol	Current physeptone treatment	
NSW112m	Aspiration pneumonia, drug toxicity	Unknown. "Regular user of methadone"	Released from jail one month previously
VIC1m	Methadone toxicity	Current MMT	Coronary artery atherosclerosis a secondary cause
VIC2m	Toxic effects of methadone	None current	Diverted methadone in prison
VIC3m	Mixed drug toxicity (heroin, alcohol, methadone)	Unknown	Only trace methadone detected
VIC4m	Combined drug toxicity (heroin, methadone, diazepam)	Current MMT	Revived from earlier overdose that day
VIC5m	Combined drug toxicity (heroin, methadone, amitriptyline, oxazepam, nitrazepam)	Current physeptone treatment	
VIC6m	Combined toxicity to methadone, morphine and diazepam	Current MMT	
VIC7m	Combined drug toxicity (heroin, methadone, methylamphetamine, diazepam, oxazepam)	Current MMT, recently started	
VIC8m	Combined drug toxicity (methadone, alcohol, morphine, codeine, amitriptyline)	Unknown	Epilepsy a contributing factor
VIC9m	Pericardial tamponade, ruptured pulmonary vein, methadone toxicity	Current MMT	Injuries sustained in motor vehicle accident
VIC10m	Toxicity to methadone and doxepin	Current MMT	
VIC11m	Narcotic toxicity	Unknown	Possible effects of nitrous oxide inhalation a secondary cause
VIC12m	Unascertained *but coroner states "it cannot be ruled out*	Current MMT, in first week of	

Case Number	Cause of death	Methadone treatment status	Other notes
	that … died of methadone toxicity"	treatment	
VIC13m	Combined drug toxicity	Unknown	Found with needle still in vein
VIC14m	Methadone toxicity in an HIV positive person with multisystem organ failure	Current MMT	
VIC15m	Unascertainable from physical findings, toxicology consistent with drug overdose	Current MMT, in first week of treatment	
VIC16m	Mixed drug toxicity (methadone, codeine, paracetamol, amitriptyline, benzodiazepines)	None current. Illegally sold a bottle of returned methadone by pharmacist.	Coronary atherosclerosis a contributing factor
VIC17m	Methadone overdose	None current	Hypertensive heart disease a secondary cause
VIC18m	Combined drug toxicity (heroin and methadone)	Unknown	
VIC19m	Combined drug toxicity	Current MMT, started day before death	
VIC20m	Toxicity to methadone	Current MMT, took higher dose than prescribed	
VIC21m	Mixed drug toxicity (methadone, alcohol, valium, temazepam)	Unknown	Mild myocardial fibrosis a secondary cause
VIC22m	Combined drug toxicity	None current	
VIC23m	Hanging	None current	Combined drug and alcohol toxicity and pre-existing psychiatric illness secondary causes, intentional self-harm
VIC24m	Multiple drug overdose	Current MMT	Doctor was prescribing outside guidelines, multiple respiratory depressants prescribed
VIC25m	Combined drug toxicity including methadone,	Current MMT, in first week of	Focal bronchopneumonia a secondary

Case Number	Cause of death	Methadone treatment status	Other notes
	morphine, diazepam	treatment	cause, presented with breathing difficulties on second day of treatment
VIC26m	Methadone toxicity	None current	Had been treated for another overdose earlier that day and self-discharged from hospital
VIC27m	Carbon monoxide poisoning	Unknown	Combined drug toxicity a secondary cause, intentional self-harm
VIC28m	Combined drug toxicity	Unknown	Intentional self-harm
VIC29m	Combined drug toxicity	Current MMT, had recently been given 4 take-away doses	
VIC30m	Overdose of methadone and morphine	None current	
VIC31m	Combined drug toxicity (methadone, alcohol, oxazepam, clonazepam)	None current, took flatmate's methadone	
VIC32m	Consistent with epileptogenic brain seizure in a person with a previous brain injury	Unknown	Possible that a combination of drugs was contributing factor
VIC33m	Combined drug toxicity	Current MMT	
VIC34m	Bronchopneumonia	Current MMT, in first week of treatment	MMT started on a higher dose than usual
VIC35m	Combined drug toxicity (methadone, diazepam)	Current MMT	
VIC36m	Combined drug toxicity (methadone, diazepam, paracetamol, caffeine, theophylline)	Current MMT	Morbid obesity a contributing factor
VIC37m	Combined drug toxicity (methadone, thioridazine, benzodiazepines)	Current MMT but final methadone was illicit	Cardiomyopathy a contributing factor
VIC38m	Acute pulmonary oedema	None current	Methadone toxicity a secondary cause
VIC39m	Multiple injuries	Unknown	Motorcycle accident, methadone and alcohol would have both affected

Case Number	Cause of death	Methadone treatment status	Other notes
			riding ability
VIC40m	Methadone toxicity	Current MMT, in first week of treatment	
VIC41m	Suffocation due to inhalation of vomitus	None current	Probable methadone toxicity a secondary cause
VIC42m	Mixed drug toxicity (methadone, morphine, codeine, amitriptyline, diazepam, temazepam, oxazepam)	Unknown	Intentional self-harm
VIC43m	Mixed drug toxicity (methadone and chlorpromazine)	Current MMT, in the first week of treatment	
VIC44m	Toxicity to methadone and morphine	Unknown	
VIC45m	Pneumonia in a person with methadone toxicity	Current MMT	Chest pains, vomiting blood in week before death
VIC46m	Toxicity to methadone (combined drug toxicity)	None current, pills obtained from other hostel residents	
VIC47m	Mixed drug toxicity (methadone, codeine, diazepam)	Current MMT, recently started, dose recently raised	
VIC48m	Toxicity to methadone in a person with cardiomegaly and acute myocarditis	Current MMT, in first week of treatment	MMT commenced at high end of guidelines
VIC49m	Combined drug toxicity	None current	
VIC50m	Coronary artery atherosclerosis in a person with raised methadone level	Current MMT	
VIC51m	Combined drug toxicity, pulmonary congestion and bronchpneumonia	Current MMT, in early stages of treatment	
VIC52m	Combined drug toxicity	None current	Intentional self-harm
VIC53m	Toxicity to methadone	None current	
VIC54m	Combined drug toxicity (heroin and methadone)	Current MMT, in first weeks of	

Case Number	Cause of death	Methadone treatment status	Other notes
		treatment	
VIC55m	Acute pulmonary oedema, overdose of several drugs	Current MMT	Intentional self-harm
VIC56m	Combined drug toxicity	Current MMT	
VIC57m	Combined drug toxicity (methadone and propoxyphene)	Current physeptome treatment	
VIC58m	Mixed drug toxicity (morphine, codeine, methadone, doxylamine, amitrityline, paracetamol, theophylline, benzodiazepines)	Current MMT	Death followed MMT dose increase
VIC59m	Combined drug toxicity	Current MMT	
VIC60m	Combined drug toxicity (methadone, citalopram, benzodiazepines)	Unknown	
VIC61m	Methadone and alcohol toxicity and interaction	None current	
VIC62m	Asphyxia, aspiration, drug overdose	Unknown	
VIC63m	Methadone toxicity	None current	
VIC64m	Mixed drug toxicity (methadone, diazepam, dothiepin)	None current	
VIC65m	Multiple drug toxicity (methadone, oxycodone, morphine) in a person with epilepsy	Current physeptome treatment	
VIC66m	Combined drug toxicity	Current MMT, in first week of treatment	
VIC67m	Combination of bronchopneumonia and the synergistic respiratory depressant effect of methadone and benzodiazepines	Current MMT but likely that methadone last used was illicit	
VIC68m	Aspiration of gastric contents in a person who had recently commenced taking methadone and had levels of sedative drugs	Current MMT, in first week of treatment	

Case Number	Cause of death	Methadone treatment status	Other notes
VIC69m	Combined drug toxicity	Current MMT, in first week of treatment	Had changed from buprenorphine to methadone treatment in month before death
VIC70m	Mixed drug toxicity (heroin, methadone, oxazepam, doxepam, citalopram)	Current MMT, in first month of treatment	Intentional self-harm, child had just been taken from custody
VIC71m	Combined drug toxicity (morphine, oxycodone, methadone, venlafaxine), congestive cardiac failure (ischaemic heart disease), asthma, tracheobronchitis	None current	
VIC72m	Mixed drug toxicity (heroin, methadone, ethanol, codeine, oxazepam)	Current MMT	
VIC73m	Mixed drug toxicity (heroin, methadone, ethanol, diazepam)	Current MMT	
VIC74m	Cardiorespiratory arrest of indeterminate cause, possibly overdose of prescription medication including diazepam	None current	
VIC75m	Toxicity to methadone and diazepam in a person with coronary artery disease	Current MMT, in first week of treatment	Coronary artery disease a contributing cause
VIC76m	Combined drug toxicity (heroin, methadone, doxepine, oxazepam, temazepam)	Current MMT	
VIC77m	Combined drug toxicity (methadone and benzodiazepines)	Current MMT	
VIC78m	Combined effects of methadone and heroin	Unknown	
VIC79m	Combined drug toxicity (methadone, amitriptyline, diazepam) in association with olazepine use, hepatomegaly and steatosis	Unknown	
VIC80m	Combined drug toxicity (methadone, oxycodone, tramadol, codeine, alprazolam)	Unknown	

Case Number	Cause of death	Methadone treatment status	Other notes
VIC81m	Combined drug toxicity	Current MMT, in first week of treatment	
TAS1m	Methadone toxicity	None current	Active chronic hepatitis a contributing cause
TAS2m	Combined drug toxicity (methadone and benzodiazepines)	None current	
TAS3m	Bronchopneumonia from methadone and cannabis	None current	
TAS4m	Combined drug toxicity (salicylic acid, methadone, codeine, trimipramine, paroxetine, metoclopramide, diazepam)	Unknown	
TAS5m	Mixed depressant drug toxicity	Current MMT	Had emerging sepsis from hand infection
TAS6m	Multiple drug toxicity (alcohol, methadone, oxazepam)	Current MMT	
TAS7m	Inhalation of gastric material, drug overdosage (methadone, morphine, diazepam, 7-aminoflunitrazepam, nordiazepam)	Unknown	
TAS8m	Haemorrhagic bronchopneumonia, drug effect (methadone)	Current MMT	
TAS9m	Dry drowning, coronary heart disease	Current MMT	Hypertensive heart disease, depressant medication for chronic back pain (valproate, benzodiazepines, methadone, tricyclic antidepressants)
TAS10m	Bronchopneumonia, drug effect (methadone and alprazolam)	None current	
TAS11m	Combined drug (methadone, alcohol) intoxication	None current	
TAS12m	Respiratory depression induced by combination of	None current	

Case Number	Cause of death	Methadone treatment status	Other notes
	methadone, morphine, diazepam		
TAS13m	Combined drug intoxication (methadone, amitriptyline)	None current	Listed as intentional self-harm in NCIS, but accidental in coroner's report
TAS14m	Combined drug intoxication (alprazolam, methadone, morphine, diazepam)	None current, left methadone program 3 months previously	
TAS15m	Combined drug overdose (methadone and diazepam)	Unknown	Ischaemic heart disease as contributing factor
TAS16m	Combined drug overdose (methadone, temazepam, paracetamol)	Current MMT	Depression as contributing factor. Intentional self-harm
TAS17m	Drug effect (methadone, morphine, diazepam, nordiazepam)	None current, left methadone program 3 months previously	
TAS18m	Multiple drug effect (methadone, amitriptyline, 7-aminoflunitrazepam), bronchopneumonia, obstructive lung disease, narcotic drug addiction, depression	Current physeptome treatment	
TAS19m	Combined drug intoxication (methamphetamine and methadone)	Current MMT	Death followed a recent injection of ice or speed
TAS20m	Combined drug intoxication (methadone, benzodiazepine, methamphetamine, fluoxetine)	None current	Physeptome injected day of death
QLD1m	Death due to external causes *(consistent with opioid overdose)*	Current MMT, given 3 take-aways the day before	Methadone injection equipment found nearby. No toxicology
QLD2m	Death due to external causes *(consistent with methadone overdose)*	Unknown	Intentional self-harm. No toxicology
QLD3m	Death due to external causes *(consistent with methadone overdose)*	None current	Illicit methadone taken on day of death. No toxicology
QLD4m	Prescription drug overdose	Current MMT	Intentional self-harm. No toxicology

Case Number	Cause of death	Methadone treatment status	Other notes
QLD5m	Death due to external causes *(consistent with opiate overdose)*	Current MMT	8.5 months pregnant, HIV positive, depression. Both methadone dose and heroin taken. No toxicology
QLD6m	Death due to external causes *(consistent with methadone overdose)*	Current MMT, had recently collected take-aways for weekend	No toxicology
ACT1m	Overdose of methadone	Unknown	Citalopram may have contributed to respiratory depression, intentional self-harm
ACT2m	Toxic effects of multiple drugs including methadone, benzodiazepines, methamphetamine	Current MMT, had recently received 3 take-aways	Probably contributed to by asthma. Seen injecting methadone, immediately had breathing difficulties
ACT3m	Asphyxia caused by inhalation of vomit	Current MMT, recently started	Contributed to by a number of central nervous system depressant drugs including methadone and valium
ACT4m	Inhaled vomitus caused by high blood concentration of methadone	None current. Left MMT in last month	
ACT5m	Respiratory depression and drug overdose	None current	Methadone in toxic range
ACT6m	Drug overdose with methadone found in blood in toxic range	Current MMT but last methadone was illicit	
ACT7m	Septicaemia, acute bronchopneumonia, pulmonary oedema in combination with toxic levels of methadone in the blood	None current	
ACT8m	Drug overdose, carbemazepam at fatal levels, methadone and various benzodiazepines at close to or toxic levels	Current MMT	Had just received notification that would not be gaining back custody of children
NT1m	Acute methadone poisoning	Unknown	
NT2m	Carbon monoxide poisoning, acute narcotic	Unknown	Intentional self-harm

Case Number	Cause of death	Methadone treatment status	Other notes
	poisoning (heroin) and other drugs		
WA1m	Combined effects of injected drugs	Unknown	
WA2m	Acute combined respiratory depressant drug effect in association with aspiration pneumonitis	Current MMT, in first week of treatment	
WA3m	Aspiration of vomit associated with combined drug effect	Current MMT, in first week of treatment	
WA4m	Acute combined drug effect	Current MMT	Intentional self-harm
WA5m	Drug overdose (methadone)	Unknown	Intentional self-harm
WA6m	Acute combined drug and alcohol toxicity	Current MMT	
WA7m	Pneumonia and cardiac failure in a person with dilated cardiomyopathy, chronic opioid dependency and recent combined drug effect	Unknown	
WA8m	Acute combined drug toxicity	Unknown	
WA9m	Combined drug effect	Current MMT	
WA10m	Bronchopneumonia with combined drug effect	Current MMT	
WA11m	Acute combined toxic drug effect (methadone, heroin, amphetamines, benzodiazepines, cannabis)	Unknown	Intentional self-harm
WA12m	Combined effects of alcohol, methadone and cannabis	None current	
WA13m	Aspiration of vomit associated with combined drug effect	Current MMT	
WA14m	Acute combined drug toxicity including methadone	Current MMT	
WA15m	Pneumonia associated with combined drug effect	Unknown	
WA16m	Focal aspiration pneumonia associated with combined drug toxicity	Current MMT	
WA17m	Acute combined respiratory depressant drug effect	Current MMT	

Case Number	Cause of death	Methadone treatment status	Other notes
	(mirtazapine, benzodiazepines, methadone, cannabis)		
WA18m	Acute combined respiratory depression drug effect	None current	
WA19m	Acute combined multidrug toxicity (methadone, opiates, benzodiazepines, venlafaxine, moclobemide)	Current MMT	Intentional self-harm
WA20m	Acute combined respiratory depressant drug effect in a person with residual resolving pneumonia	Unknown	
WA21m	Aspiration of vomit associated with combined drug effect	Current MMT	
WA22m	Respiratory depression due to combined opiate and alcohol toxicity	Unknown	
WA23m	Acute combined respiratory depression drug effect in a person with status asthmaticus	Unknown	
WA24m	Consistent with opiate toxicity	Unknown	
WA25m	Aspiration associated with combined sedative effects of drugs	Unknown	
SA1m	Mixed drug toxicity (methadone, benzodiazepines)	Current MMT, in first week of treatment	
SA2m	Combined drug toxicity of butane, methadone, pethidine, alprazolam	Unknown	
SA3m	Methadone toxicity	Unknown	
SA4m	Methadone toxicity	Unknown	Intentional self-harm
SA5m	Methadone toxicity	Unknown	
Probable			
NSW113m	Methamphetamine toxicity	Current MMT	Methadone detected in high levels, ice taken just before death

Case Number	Cause of death	Methadone treatment status	Other notes
VIC82m	Unascertainable from physical findings, most likely relates to the use of illicit drugs (morphine)	Unknown	Methadone and morphine detected
VIC86m	Toxicity to heroin	Released from prison in previous week, where was receiving methadone. Uncertain when treatment ceased.	No methadone detected in toxicology
QLD7m	Death due to external causes *(Consistent with multiple drug toxicity)*	Current MMT	No toxicology
QLD8m	Death due to external causes *(Consistent with multiple drug toxicity)*	Unknown	Had dissolved benzodiazepines into methadone and injected it. No toxicology
Possible			
NSW49m	Combined drug toxicity	Current physeptone treatment	Only a trace methadone detected
NSW114m	Head injury	Unknown	Morphine toxicity, chronic hepatitis, hepatitis C virus infection as contributing causes. Insufficient sample for blood testing, methadone in urine.
NSW115m	Multiple injuries	Unknown	Cirrhosis of the liver as contributing cause. High level alcohol, low level methadone while driving
NSW116m	Multiple injuries	Unknown	Fell from high carpark
NSW117m	Multisystem organ failure, cardiac arrhythmia and cardiac arrest, toxicity due to amphetamine	Unknown	Injected amphetamine just before onset of heart pain.
NSW118m	Acute narcotism	Unknown	Overdose was primarily from heroin/ morphine, not methadone
NSW119m	Toxic effects of methamphetamine	Unknown	Methadone may have contributed
VIC83m	Drug overdose	Unknown	

Case Number	Cause of death	Methadone treatment status	Other notes
VIC84m	Multi-system organ failure	Current MMT	Likely to be related to cardiotoxic effects of IV amphetamine use. No toxicology. Had previously self-discharged from hospital, soon readmitted.
VIC85m	Unascertained	Current MMT, in first week of treatment	Advanced decomposition made diagnosis difficult
QLD9m	Death due to external causes *(Consistent with opioid overdose)*	Unknown	No toxicology. Used injecting equipment near body
QLD10m	Death due to external causes	Current methadone detoxification treatment	No toxicology. Two doses day before and one on day of death.
QLD11m	Death due to external causes *(Consistent with multiple drug overdose)*	Unknown	No toxicology
QLD12m	Death due to external causes *(Possible overdose)*	Current MMT, in first week of treatment	Intentional self-harm. No toxicology. Used injecting equipment near body
QLD13m	Death due to external causes *(Consistent with multiple drug overdose)*	Current MMT	No toxicology. Received methadone dose that morning, injected benzodiazepines and seizure followed.
QLD14m	Death due to external causes	Current MMT	No toxicology
ACT9m	Undetermined between natural causes and overdosage by methadone	Unknown	Larger weight heart could contribute to cardiac arrhythmia
NT3m	Acute hypertensive crisis, amitriptyline reaction	Current MMT	Was gurgling while sleeping just before death
WA26m	Unascertainable (due to delay between death and autopsy)	Unknown	

* Note: Methadone detected in the toxicology of all of the above cases except for one case from Victoria (VIC84m) and all cases from Queensland (QLD1m to 14m). Italic comments were written by the authors, not the coroner.